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Poster

455. Adult Neurogenesis: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 455.01/A1

Topic: A.02. Postnatal Neurogenesis

Support: the Kanae Foundation
the Miyata foundation bounty for pediatric cardiovascular research from the Miyata Cardiac Research Promotion Foundation
the Sumitomo Foundation
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Title: Identification of juvenility-associated long noncoding RNAs (JALNCs) as indispensable factors for the juvenile properties of the brain

Authors: *M. MORI, T. MORIMUNE, F. A. JAM, Y. KADOTA, A. TANO, Y. TANAKA, H. YUKIUE, S. AKAHANE, M. FUKUMURA
Shiga Univ. of Med. Sci., Shiga, Japan

Abstract: Inherent advantages of the young brain may be utilized for new therapeutics to combat with pediatric neurological diseases. The physiological properties of the younger brain include higher abilities for growth, learning, plasticity, regeneration and so on. Aiming at elucidating the molecular machineries for the juvenile properties of the brain, we performed transcriptome analysis with different tissues (brain, hepatocytes and cardiomyocytes) isolated from mice at different ages (postnatal days 1, 14 and 56). Thus, we identified the brain-specific transcripts that were expressed selectively at the younger ages. We call them as “juvenility-associated genes (JAGs)” of the brain. Further bioinformatics analysis revealed the brain JAGs were associated with cellular functions such as “secretion”, “glycosylation” and “extracellular matrix”, indicating an essential role of the brain JAGs for the construction of extracellular architecture during the postnatal brain development. We next sought to identify an indispensable therapeutic target for the juvenile properties. Noncoding RNAs are strong therapeutic targets because their functions are inhibited specifically via an antisense strategy using siRNA or antisense oligonucleotide (ASO). We established a pipeline for the bioinformatics analysis of the long noncoding RNAs (lncRNAs) and comprehensively identified the lncRNAs selectively highly expressed in the young brain as *j*uvenility-*a*ssociated *lnc*RNA*s* (JALNCs). Among the JALNCs, we identified Gm14230 that is evolutionary conserved and expressed highly selectively in the young brain. Gm14230 shuttles from cytosol to nucleus and is engaged in the transcriptional regulation in

cooperation with Ezh2, a histone methyltransferase. siRNA-mediated suppression of Gm14230 significantly deteriorates cell growth and perturbs the expression of genes associated with the extracellular architecture. Furthermore, loss of Gm14230 leads to the cellular senescence, indicating the juvenile-selective Gm14230 safeguards the neuronal cells from the premature senescence. Thus, our transcriptome-wide analysis leads to the identification of the factor that is indispensable for the juvenile physiology of the brain.

Disclosures: M. Mori: None. **T. Morimune:** None. **F.A. Jam:** None. **Y. Kadota:** None. **A. Tano:** None. **Y. Tanaka:** None. **H. Yukiue:** None. **S. Akahane:** None. **M. Fukumura:** None.

Poster

455. Adult Neurogenesis: Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 455.02/A2

Topic: A.02. Postnatal Neurogenesis

Support: Grant-in-Aid for Young Scientists (B)

Title: Role of endoplasmic reticulum quality control in the adult hippocampal neurogenesis

Authors: *N. MURAO, H. NISHITOH
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Abstract: The endoplasmic reticulum (ER) has a quality control mechanism that ER resident stress sensors recognize unfolded or misfolded (malfolded) proteins and trigger the unfolded protein response (UPR). The UPR mediates the proper folding or degradation of malfolded proteins and the translational attenuation to inhibit the further production of ER proteins. A collapse of the ER quality control mechanism contributes to the onset and deterioration of several neurological disorders associated with impaired learning and memory. Adult neurogenesis is the process to generate new neurons from adult neural stem/precursor cells in restricted brain regions. Neurogenesis in the adult hippocampal dentate gyrus plays an important role in learning and memory formation, and its homeostasis is disrupted in several neurological disorders associated with memory impairment. ER quality control and adult neurogenesis are thought to be closely related to the mechanisms of learning and memory, whereas the physiological relevance among them remains to be elucidated. In the present study, we found that the disturbance of ER quality control by deletion of an ER membrane protein in the central nervous system (CNS) leads to a chronic ER stress state without cell death and impairs hippocampal neurogenesis. Our findings suggest that ER quality control mechanism in the CNS may play an important role in maintaining homeostasis of adult hippocampal neurogenesis and learning and memory.

Disclosures: N. Murao: None. **H. Nishitoh:** None.

Poster

455. Adult Neurogenesis: Molecular Mechanisms

Location: SDCC Halls B-H

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Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant R15NS092026-01A1

Title: Akt drives cell cycle entry in the subventricular zone

Authors: *J. E. MARKS[1], F. LICAUSI[2], A. FOSTER[2], N. W. HARTMAN[2]
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Abstract: Neural stem cells in the subventricular zone (SVZ) continually generate new daughter cells that migrate to the olfactory bulb (OB), differentiating into neurons. SVZ stem cells need to integrate extracellular signals to properly divide, differentiate and migrate. Downstream of growth factor and amino acid signaling are the Akt and mammalian target of rapamycin (mTOR) pathways. The Akt pathway is important for cellular growth, proliferation and differentiation. While there are many downstream targets of Akt, activation of this molecular cascade through mTORC1 has been proposed to increase cellular differentiation and protein translation. It is unclear whether Akt and mTOR play roles independent of each other in NSC development. Here, we show that a constitutively active form of Akt resulted in a threefold increase in the number of newly born neurons in the OB. In contrast to driving mTOR alone, Akt activation did not result in apparent aberrant migration in the SVZ or OB. Akt activation increased dendritic length and complexity; however, mTORC1 inhibition did not rescue total dendritic length. In the SVZ, inhibition of Akt decreases proliferation of stem cells. Whereas, activation of the Akt pathway drives NSCs into cell cycle progression and differentiation. Blockade of downstream mTORC1 targets inhibited differentiation, but did not alter the number of proliferative cells in the SVZ. These data suggest that Akt controls NSC differentiation via mTOR, but may exert proliferative effects on NSCs independently.

Disclosures: J.E. Marks: None. **F. Licausi:** None. **A. Foster:** None. **N.W. Hartman:** None.

Poster

455. Adult Neurogenesis: Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 455.04/A4

Topic: A.02. Postnatal Neurogenesis

Support: NIDCR K99/R00 DE027706
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Title: TGFbeta signals regulate afferent innervation in the developing tooth

Authors: *S. PETERS, C. BARKLEY, K. NGUYEN, R. SERRA
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Abstract: Teeth require a high degree of sensory innervation to detect noxious input to protect the tooth and organism throughout their lifetime. Tooth innervation research remains in its elementary stages despite the fact that tooth decay and its associated pain responses are currently the most chronic disease in the United States. During postnatal development, sensory nerve fibers from the trigeminal nerve ganglia (TG) extend toward tooth germs and penetrate the dental pulp (DP) coincident with odontoblast differentiation and dentin deposition. Previous studies indicate the DP cells secrete neurotrophic factors to guide tooth innervation. Transforming growth factor β (TGFβ) is known to play an important role in bone and tooth development. The **objective** of this study was to investigate the role of Tgfbr2 in regulating paracrine signals from the DP guiding afferent innervation. **Methods and Results:** Our laboratory established a mouse model in which Tgfbr2 was conditionally deleted in odontoblast-producing mesenchyme using an osterix promoter driven Cre recombinase ($Tgfbr2^{cko}$). These mice survived postnatally with significant defects in bones and teeth. We performed an mRNA-Seq analysis using RNA from postnatal day 7 (P7) DP from control and mutant mice and found that neuronal pathways in development and function were highly regulated. Immunofluorescent images of neuronal marker, β3 tubulin, verified significantly reduced innervation throughout the DP and odontoblast region in P7 $Tgfbr2^{cko}$ mice. We co-cultured TG neurons in Transwell filters overlying primary $Tgfbr2^{f/f}$ DP and infected the DP with Adenovirus-Cre recombinase to knockdown Tgfbr2 in the DP. Large immunofluorescent images of entire filters were acquired with confocal microscopy and assembled with NIS-Elements 4.6 software. Pixel intensity of autothresholded images was quantified with Image J and indicated a significant reduction in neurite outgrowth when Tgfbr2 was knocked down in DP. **Conclusions:** These results suggest Tgfbr2-guided paracrine signals from the DP and/or odontoblasts of the tooth guide innervation. Research into this cross-talk is likely to provide information that will help plan preventative, therapeutic and regenerative strategies and improve the preservation of teeth.

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Poster

455. Adult Neurogenesis: Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 455.05/A5

Topic: A.02. Postnatal Neurogenesis

Title: PSA-NCAM upregulation and differential expression after telencephalic lesions in turtles

Authors: *A. J. NAPOLI[1], A. S. POWERS[2]
[1]State Univ. of New York At Stony Brook, Stony Brook, NY; [2]Psychology, Stony Brook Univ., Stony Brook, NY

Abstract: Adult neurogenesis in mammals is found only in discrete regions, and this restricted localization means that it plays a limited role in CNS repair. Non-mammalian vertebrates such as reptiles, however, demonstrate adult neurogenesis throughout the telencephalon, as well as migration, maturation, differentiation, and integration of cells. These processes can be harnessed for repair and have been demonstrated to restore the cytoarchitecture and functionality of lesioned telencephalic regions in reptiles.
PSA-NCAM is a critical modulator of both developmental and reparative processes in the CNS. It facilitates the multifaceted processes of neurogenesis and circuit building and thus allows for the establishment of brain architecture as well as its reorganization after injury. We hypothesized that PSA-NCAM expression would be upregulated in the brains of lesioned animals in order to facilitate reparative processes. To determine the expression of PSA-NCAM in reptilian brains, we studied it in painted turtles, *Chrysemys picta*, with telencephalic lesions and compared them to non-lesioned controls. We observed the expression level, characteristics, and locations of PSA-NCAM expression after different survival periods ranging from 1 week to several months, using immunohistochemical labeling of PSA-NCAM along with BrdU to determine the role of new cells, and NeuN to distinguish cells as neurons.
PSA-NCAM expression is markedly upregulated in the brains of *C. picta* after lesioning, as is the generation of new neurons. Furthermore, there is differential expression over time, with early labeling found primarily on cell bodies within the ependyma and parenchyma, and most robustly in regions near the lesions. Later survival times demonstrate continued upregulation, but expression is shifted primarily to neuronal and radial glia processes throughout the tissue. Widespread generation and functional integration of new neurons in the adult telencephalon was probably a trait present in ancestral vertebrates, but was lost in mammals. Therefore, appreciation of non-mammalian vertebrates as ancestral to mammals is critically important in understanding the conservation or loss of traits that dictate neurogenesis and integration, and to the elucidation of the mechanisms that drive, or fail to drive, the process. Deficiency of

permissive signals for polysialylation of the NCAM molecule may be at the root of the limited reparative capabilities of the adult mammalian brain. This study is the first to qualify and quantify PSA-NCAM expression, and to examine its expression after lesioning of the telencephalon, in turtles.

Disclosures: A.J. Napoli: None. **A.S. Powers:** None.

Poster

455. Adult Neurogenesis: Molecular Mechanisms

Location: SDCC Halls B-H

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Topic: A.02. Postnatal Neurogenesis

Support: National Natural Science Foundation of China Grant 81571095
Hubei Natural Science Foundation Grant 2016CFB501

Title: The fmrp/icam5 mrna interaction uncovers a new mechanism of modulating dendritic spine development in fragile x syndrome

Authors: *Z. YAN, Y.-P. PEI, Y.-Y. WANG, Y.-S. CHEN
Wuhan Univ. of Sci. and Technol., Hubei, China

Abstract: The absence of fragile X mental retardation protein (FMRP) results in fragile X syndrome (FXS), the most common form of inherited intellectual disability and the leading monogenic cause of autism spectrum disorders (ASD). Here, we report that FMRP regulates the synthesis of intercellular adhesion molecule 5 (ICAM5), a cell adhesion molecule that belongs to the Ig superfamily. In *Fmr1* KO mice, a preclinical model of FXS, lack of FMRP results in excessive production of ICAM5 protein, which leads to aberrant dendritic spines and abnormal behaviors. Genetic reduction of ICAM5 corrects dendritic spine abnormality in *Fmr1* KO mice, and ameliorates defective behaviors including social interaction, fear memory and anxiety. Moreover, we found that FMRP directly binds with ICAM5 mRNA, and interacts with its coding sequence that affects spine maturity through regulating ICAM5 expression. The knockdown of *Fmr1* mRNA can increase levels of ICAM5 protein expression as well as correlated impairments in dendritic spine morphology. Overexpression of FMRP decreases ICAM5, consistent with a repressive role for FMRP. Taken together, our results demonstrated that FMRP regulates synthesis of ICAM5 through direct interaction with ICAM5 mRNA, and lack of FMRP in *Fmr1* KO mice results in excessive ICAM5 production that leads to impairments in dendritic spine morphology and behaviors. To our knowledge, this is the first study to provide a functional link for ICAM5 with deficient neuronal morphology and cognitive impairment in FXS.
Keywords: Fragile X syndrome; fragile X mental retardation protein; intercellular adhesion molecule 5; dendritic spine development; FMRP/ICAM5 mRNA interaction

Disclosures: Z. Yan: None. **Y. Pei:** None. **Y. Wang:** None. **Y. Chen:** None.

Poster

455. Adult Neurogenesis: Molecular Mechanisms

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Topic: A.02. Postnatal Neurogenesis

Support: AcRF Tier 1 (2016-T1-001-010), Ministry of Education, Singapore

Title: Identification of genes regulated by short term environmental enrichment during a critical period for the survival of new neurons in the adult dentate gyrus

Authors: *C. C. CHANG, A. TASHIRO
Sch. of Biol. Sci., Nanyang Technol. Univ., Singapore, Singapore

Abstract: Environmental enrichment promotes the survival of new neurons in the adult dentate gyrus of the hippocampus. This effect is dependent on the age of new neurons, and a maximal effect has been observed on neurons during a critical period around the second week after their birth. However, the molecular mechanism underlying this experience-dependent survival during the critical period is not well understood. Here, we established a method to isolate mRNA from new neurons at a specific neuronal age in the dentate gyrus and performed microarray analysis to identify genes the expressions of which are affected by exposure to enriched environment. To label newly-generated cells at a specific age, we used a retroviral vector expressing fluorescent protein. Further, to distinguish new neurons from other types of newly-generated cells, we visually identified new neurons based on their morphology under a fluorescence microscope and selectively harvested them with laser capture microdissection. Using genetic materials obtained with this method, we performed a DNA microarray analysis for new neurons at a specific neuronal age. We exposed a group of adult female mice to enriched environment, which consisted of a large cage (W100×D100×H60 cm) with enriching materials (9 tunnels, 2 shelters and 1 running wheel) housing 10 mice per cage. We started this exposure 7 days after retroviral injection and collected the genetic materials of new neurons at 11 days after the injection. Thus, these mice were exposed to enriched environment for 4 days during the critical period for neuronal survival. We compared gene expression in these enriched mice with control mice housed always in a standard cage (W31×D16×H16 cm) housing 5 mice per cage without enriching materials. Each sample for the microarray analysis was mRNA pooled from >300 fluorescent new neurons in at least 3 mice. From this analysis, we identified 63 coding genes, 16 microRNAs and 3 ribosomal proteins that were up- or down-regulated by 4-day enrichment. Thus far, we have been able to verify the effects on some of these genes using real-time PCR. We are examining roles of these verified genes in enrichment-induced neuronal survival using retroviral vectors for overexpression or knockdown of the genes. Preliminary data indicate some

of these genes support neuronal survival. Thus, we established the method to isolate mRNA from new neurons at a specific age and identified genes regulated by 4-day enrichment during the critical period. The results from this study would provide the basis for understanding the molecular mechanism involving in experience-dependent regulation during the critical period for neuronal survival in the adult brain.

Disclosures: C.C. 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.; Ayumu Tashiro. **A. Tashiro:** None.

Poster

455. Adult Neurogenesis: Molecular Mechanisms

Location: SDCC Halls B-H

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Topic: A.02. Postnatal Neurogenesis

Support: Norwegian Research Council, NO.32198
China Postdoctoral Science Foundation Project, No. 2017M623152

Title: Histone modifications define neural stem cells subtypes in mouse subventricular zone

Authors: *Z. ZHANG[1,2], A. MANAF[1], S. PEÑA PEREZ[1], R. SUGANTHAN[1], M. BJØRÅS[1], J. ARNE DAHL[1], A. KLUNGLAND[1,3]
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Abstract: Neural stem cells (NSCs) persist in the mammalian brain throughout life and can be activated in response to the physiological and pathophysiological stimuli. Therefore, understanding the dynamic regulation of NSCs might help develop novel therapeutic strategy for stroke and other brain diseases. Defining the epigenetic features of neural stem cells may be critical for formulating a rational strategy for the therapeutic intervention of stem cell dysfunction. Therefore, we aimed at defining different subtypes of NSCs by individual histone modifications. At first, we found high levels of Histone H3 lysine 4 trimethylation (H3K4me3), histone H3 lysine 27 trimethylation (H3K27me3) and Histone H3 lysine 36 trimethylation (H3K36me3) in neurogenesis based on their co-staining with NSCs marker SOX2 during neural development. Then, CD133 (a quiescent NSCs marker), ID1 (an active NSCs marker) and DCX (a neuroblast NSCs marker) immunostaining were used to define different subtypes of NSCs. At early development, P10, 51.7% ± 11.7% high level H3K27me3 cells expressed CD133. On the contrary, just 15.8% ± 4.1% high level H3K36me3 cells and 4.8% ± 2.2% high level H3K4me3 cells co-stained with CD133. For the active NSCs, 56.9% ± 4.8% high level H3K36me3 cells co-

stained with ID1, significantly higher than H3K27me3 (28.0% ± 11.7%) and H3K4me3 (6.6% ± 2.6%). For neuroblast NSCs, 86.1% ± 3.5% of high level of H3K4me3 co-stained with DCX, significantly higher than H3K27me3 (11.7% ± 2.7%) and H3K36me3 (21.6% ± 5.0%). These results indicated that high level of H3K27me3 could be considered a quiescent NSCs marker, high level of H3K36me3 is an active NSCs maker and high level of H3K4me3 mark neuroblasts. Our results indicate different features of histone modifications subtypes of NSCs. This research may reveal novel insight into the onset of neurodevelopment and provide an innovative epigenetic signature for discovery and characterization of key regulatory genes for neurogenesis. However, whole genome analysis need be conducted to gain insight on the role for individual histone modifications domains in neurodevelopment.

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Poster

455. Adult Neurogenesis: Molecular Mechanisms

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Program #/Poster #: 455.09/A9

Topic: A.02. Postnatal Neurogenesis

Support: Sigma Xi Grant-in-Aid of Research, G2017031574228171

Title: Exercise increases caspase-3 expression in hippocampal astrocytes and radial glia-like cells

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Abstract: Exercise induces plasticity in the hippocampus, which includes increases in neurogenesis, the proliferation of new neurons, in the subgranular zone of the dentate gyrus (DG), and angiogenesis, the sprouting of new capillaries from preexisting blood vessels. Following exercise, astrocytes also undergo morphological changes, paralleling the events occurring in the neurovascular system. There have also been reports of increased apoptosis following aerobic exercise. In our experiment, cleaved caspase-3, a terminal protein in the apoptotic cascade, was initially used to identify apoptotic cells in the hippocampus after rats completed an acute bout of exercise. Following exercise, we found caspase-3 expression was increased in CA1 and DG. Because caspase-3 expression was elevated in DG, a region where new neurons proliferate, we wanted to identify whether newly birthed or adult neurons disproportionally expressed caspase-3 and, in turn, were undergoing apoptosis following exercise. Interestingly, caspase-3 was not highly expressed in neuronal populations, and

expression was not increased in these cells post exercise. However, caspase-3 was predominantly expressed in astrocytes. Furthermore, following exercise, caspase-3 expression was elevated in these astrocytes in DG and CA1, and in the radial glia-like cells present in the subgranular zone. To determine whether caspase-3 expression in these glial cells was associated with apoptosis, we completed a TUNEL assay as a second measure of apoptotic cell death. TUNEL staining was negligible in all groups and did not mirror the pattern of caspase-3 labeling. This suggests cleaved caspase-3 expression is non-apoptotic in these hippocampal astrocytes and radial glia-like cells. Future experiments aim to determine the non-apoptotic role of caspase-3 in these cell populations.

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Poster

455. Adult Neurogenesis: Molecular Mechanisms

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Topic: A.02. Postnatal Neurogenesis

Support: NIH/NIDCD Grant DC012425

Title: Endogenous BDNF regulates spine development in adult-born olfactory granule cells

Authors: B. MCDOLE[1], *K. M. GUTHRIE[2]
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Abstract: The olfactory bulb (OB) undergoes continuous, adaptive circuit remodeling as resident interneurons are gradually replaced by adult-born cells produced in the forebrain subventricular zone. New GABAergic granule cells (GCs) constitute the largest population. Following their migration to the OB, GCs elaborate dendrites and spines as they mature and functionally integrate. During this process, GCs receive inputs from centrifugal afferents, and on their apical dendrites, develop spine-located dendrodendritic synapses with glutamatergic bulb mitral and tufted cells. New GCs that fail to stably integrate undergo apoptosis within a few weeks of their birth. Multiple mechanisms regulate the incorporation of these new interneurons, with neural activity known to play a major role. Sensory deprivation by naris occlusion impairs spine and synapse development in adult-born GCs and increases their apoptotic loss. Brain-derived neurotrophic factor (BDNF) has a well-established role in activity-dependent spine and synapse maturation and maintenance. Using transgenic mice over-expressing BDNF in the OB, we previously showed with Golgi staining that BDNF increased overall spine density, and the prevalence of mature spines, on established populations of GCs. How increases in endogenous BDNF levels impact the maturation of adult-born GCs has not been determined. Using viral-mediated labeling of adult-born GCs in these mice, followed by neuronal reconstruction and

morphometric analyses, we followed GC maturation from 12-60 days post-infection (dpi) to test for developmental BDNF effects. While increased BDNF had no effect on dendrite growth or branching, effects on spine morphology and density were evident as early as 12 dpi. By 22 dpi, total spine density was 11% higher in transgenic mice relative to controls, and included a 28% increase in the density of headed spines. By 35 days, the latter value reached 38%, remaining stable to 60 days (42%). Despite increases in spine numbers and density, potentially indicating successful integration, numbers of surviving GCs, measured by BrdU+ cell counts, not differ from that of controls. These results establish that endogenous BDNF can shape the connectivity of adult-born GCs within dynamic olfactory circuits that process odor information.

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Poster

455. Adult Neurogenesis: Molecular Mechanisms

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Núcleo UNAB DI-4-17/N (BvZ, LVN)

Title: PSD-95 modulates adult-born neuron maturation in mouse hippocampus

Authors: *M. D. MARDONES[1], P. V. JORQUERA[1], A. HERRERA-SOTO[1], F. J. BUSTOS[2], B. VAN ZUNDERT[1,3], L. VARELA-NALLAR[1]
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Abstract: The generation of new neurons in the dentate gyrus of adult mouse hippocampus is a process that involves proliferation of neural stem cells, neuronal fate commitment, differentiation, neuronal maturation and integration of new neurons into the hippocampal network. PSD95 is a major scaffold postsynaptic protein and has been tightly associated to synaptic development and maturation of hippocampal neurons. Here we evaluate the function of PSD95 in the different steps of adult hippocampal neurogenesis. Retroviruses (MMLV) expressing a control shRNA or an shRNA targeting PSD95, and the ZsGreen reporter protein were stereotaxically injected into 2-month-old mouse dentate gyrus. Animals were sacrificed after 2, 4 and 6 weeks post injection (wpi). Neuronal differentiation was evaluated by double immunostaining for ZsGreen and the immature neuronal marker DCX. Morphological

maturation was assessed by total dendritic length, average branch order, and total number of intersections. PSD95 knockdown did not affect differentiation of newborn cells into neurons nor migration of adult-born neurons through the granule cell layer. At 4 wpi PSD95 deficient neurons expressing the mature neuronal marker NeuN showed no changes in total dendritic length, but there was a significant increase in the total number of intersections and average branch order, suggesting that PSD95 controls dendritic development of adult-born granule neurons. Moreover, at 6 wpi mature neurons deficient in PSD95 showed a decrease in dendritic spine density indicating the relevance of this scaffold protein controlling spinogenesis in adult-born neurons.

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Poster

455. Adult Neurogenesis: Molecular Mechanisms

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Topic: A.02. Postnatal Neurogenesis

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American Epilepsy Society Postdoctoral Fellowship 412212

Title: A critical period for aberrant neurogenesis rewires hippocampus circuitry to cause epilepsy

Authors: *Z. R. LYBRAND[1], J. ZHU[2], K. RAJASEKARAN[2], M. AKTAR[2], L. ZHANG[2], P. VARMA[1], K. CHO[3], S. GE[4], J. HSIEH[1]
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Abstract: Stem cells in the adult mammalian brain give rise to adult-born granule cells (GCs) that help maintain an inhibitory feedback circuit within the dentate gyrus thought to be very beneficial for brain health. However, disruption of the dentate gyrus circuitry causes spontaneous recurrent seizures (SRS), which often leads to acquired epilepsy. Although adult-born (GCs) are part of an inhibitory feedback circuit within dentate gyrus critical for a range of cognitive processes, whether they are involved in SRS and epileptogenesis remains elusive. Here we

identified a critical window that excessive activity drives aberrant maturation of adult-born GCs that is sufficient to disrupt hippocampus circuitry. We found these aberrant GCs developed an abnormal morphology and migration pattern, became hyper-excitable, and resulted in spontaneous seizures. Importantly, silencing of a restricted cohort of aberrant adult-born GCs in a temporal lobe epilepsy model prevented abnormal development and SRS, thereby restoring the protective function back to the dentate gyrus. Furthermore, silencing aberrant neurogenesis prevented recurrent CA3 back-projections and restored proper cortical connections to the hippocampus circuitry. Our results demonstrate that despite their limited number, adult-born GCs have a tremendous, unlimited pathological capacity to disrupt hippocampus circuitry. Therapeutic strategies to target these few new neurons can restore normal brain function possibly in a broad spectrum of neurological disorders.

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Poster

455. Adult Neurogenesis: Molecular Mechanisms

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Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant RO1NS093992
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Title: Targeting aberrant neurogenesis in a clinically-relevant window leads to transient but not persistent seizure reduction

Authors: *P. VARMA[1], R. R. BRULET[2], L. ZHANG[3], J. HSIEH[4]
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Abstract: Mesial temporal lobe epilepsy (mTLE), the most common form of medically refractory epilepsy in adults, emerges from the hippocampus and accounts for nearly 80% of all the temporal lobe seizures. Adult-born granule cells from the dentate gyrus born prior to an epileptic injury, for example status epilepticus (SE), contribute to epileptogenesis making them promising therapeutic targets, either genetically or pharmacologically, to prevent the formation of chronic seizures. However, current studies aiming to do so are limited in their clinical relevance as they target neural stem cell populations prior to an epileptic insult, a clinically irrelevant time period for preventing epilepsy development. Therefore, we aim to determine if

adult-born granule cells born after SE can suppress epilepsy. Using pilocarpine-induced SE model of mTLE in mice, we show for the first time that ablation of aberrant neurogenesis for eight weeks specifically after SE can reduce the formation of spontaneous recurrent seizures (SRS) by 65%. Further, we show that this effect is dependent upon the reduction of aberrant neurogenesis below a critical threshold as four weeks of blocking of seizure-induced neurogenesis was not sufficient to affect chronic SRS. However, this effect is transient and does not have a long-term impact on the reduction of seizures. These findings provide evidence that aberrant neurogenesis when targeted optimally in a clinically relevant therapeutic window, has the potential to suppress the epileptogenic process at least transiently.

Disclosures: P. Varma: None. **R.R. Brulet:** None. **L. Zhang:** None. **J. Hsieh:** None.

Poster

455. Adult Neurogenesis: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 455.14/A14

Topic: A.02. Postnatal Neurogenesis

Title: Olfactory perception and newborn neurons integration in a mouse with reduce number of projection neurons

Authors: *L. SANCHEZ[1], B. WANG[2], C. LOIS[2]
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Abstract: The early olfactory system comprises the olfactory epithelium and the olfactory bulb (OB). Olfactory sensory neurons placed in the olfactory epithelium send their axons to the OB where they make synapses with the main projection neurons, mitral and tufted cells (M/T cells), which send their axons to cortical areas. The activity of the M/T cells in the OB is modulated by local interneurons that are incorporated into it daily. Every day, hundreds of newborn interneurons are produced in the subventricular zone and migrate rostrally to integrate into a pre-establish neuronal circuit in the OB. It is thought that projection neurons are necessary for the integration and survival of newborn interneurons, in addition, to decode the identity of the odors. Conditional cell ablation is a strategy broadly used in the brain to reveal the importance of a specific cell type during development. Here, we used a transgenic mouse line for tissue-specific genetic ablation of the main projection neurons in the olfactory bulb (OB). We induced diphtheria toxin expression in the M/T cells during development stages. Then, we analyzed how the lack of M/T cells affects the newborn interneurons integration, the olfactory bulb organization, and its operationality. We found that only 1-3 % of the main projection neurons remained in the OB while the structural organization of the OB was mostly maintained. The production of newborn interneurons was not drastically affected by the lack of M/T cells but their survival after the critical period was significantly reduced. However, the morphology of

these newborn neurons, once they are integrated into the circuit, was very similar to the interneurons of wild-type mice. Surprisingly, behavior analyses showed that mice with few M/T cells were able to detect odors as well as discriminate between two different odors. In addition, we noted that females mated and exhibited normal maternal behavior, while males were not able to mate and showed an inadequate behavior in presence of an intruder male.

Disclosures: L. Sanchez: None. **B. Wang:** None. **C. Lois:** None.

Poster

455. Adult Neurogenesis: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 455.15/A15

Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant R00 NS089938
Chronic Brain Injury Initiative at OSU

Title: Characterization of adult neural stem cell potential for paracrine signaling based therapies

Authors: *J. K. DENNINGER[1], X. CHEN[2], L. WALKER[2], R. BUNDSCHUH[3], P. YAN[4], E. D. KIRBY[1]
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Abstract: Stem cells are currently being studied as potential therapeutic agents for a variety neuropathologies. Although direct cell replacement is an obvious method for regeneration, using stem cells as sources of paracrine signaling factors that can modify injury outcome is an interesting alternative. In order to identify the factor(s) secreted by neural stem cells (NSCs) both at baseline and during injury, we have generated transcriptomes of NSCs in the adult mouse dentate gyrus (DG). Located in the hippocampus, the DG is an important neurogenic niche that is critical for proper cognitive function. Unfortunately, the DG is exquisitely sensitive to different types of injury such as seizures and concussions. Despite its vital function, the DG is actually a small structure, making the study of its various cell populations extremely difficult. Using a novel low-cell number RNA sequencing (lcRNASeq) protocol and Coverage-Based Limited-Cell Experiment Analysis for RNA-Sequencing (CLEAR) algorithm, we have confirmed the feasibility of accurately characterizing these NSCs on a population level from individual mice. Due to the high degree of heterogeneity between individual NSCs, the ability to obtain faithful transcriptomes from a sample of the population is key to understanding what NSCs do as a whole. For several cytokines and growth factors that are highly transcribed by NSCs according to our lcRNASeq dataset, we have confirmed synthesis and secretion of these proteins in NSC

conditioned media with a commercially available cytokine antibody array. By implementing lcRNASeq and CLEAR to obtain transcriptomic profiles of NSCs in the adult dentate gyrus at baseline and during injury, we can study changes in gene expression on a population level, allowing for the development of a comprehensive list of injury-modifying NSC-derived paracrine factors which could then be refined with further study of individual factors. Generation of such an injury-modifying NSC secretome will lead to more successful therapeutic applications of NSCs in the future.

Disclosures: J.K. Denninger: None. **X. Chen:** None. **L. Walker:** None. **R. Bundschuh:** None. **P. Yan:** None. **E.D. Kirby:** None.

Poster

455. Adult Neurogenesis: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 455.16/A16

Topic: A.02. Postnatal Neurogenesis

Support: NIH/NINDS Grant R00NS089938

Title: Hippocampal neural stem cells clear extracellular glutamate via excitatory amino acid transporters

Authors: *J. D. RIESKAMP, V. VALENTINI, J. P. BRUNO, E. D. KIRBY
Psychology, The Ohio State Univ., Columbus, OH

Abstract: Neural stem cells (NSCs) persist in the neurogenic niche of the rodent hippocampus throughout life. Adult NSCs contribute to hippocampal cognition by generating new granule neurons, a process that is highly sensitive to niche-derived neurotransmitter, growth factor, cytokine, and morphogen signaling. While early work focuses on NSCs as recipients of niche-derived signaling, recent studies suggest this communication is bi-directional, and NSCs influence the niche via growth factor and cytokine secretion.
Here we investigate whether NSCs have the potential to influence neighboring cells by regulating glutamate signaling via excitatory amino acid transporters (EAATs). Decades of research suggest that astrocytes and neurons use EAATs to shape neurotransmission and protect vulnerable cells from glutamate-induced excitotoxicity. However, whether NSCs similarly regulate glutamate signaling is unknown.
To address this question, we used RNA-sequencing to profile EAAT gene expression in NSCs isolated from the dentate gyrus (DG) of 2 month old mice by fluorescence activated cell sorting. We detected expression of both EAAT1 and EAAT2 mRNA. We confirmed using qPCR that NSCs *in vitro* express EAAT1 and EAAT2, with about 100-fold greater expression of EAAT1. To determine whether NSCs can clear extracellular glutamate, we exposed NSCs cultured from

the adult DG to 5 μM glutamate in the extracellular media. In the presence of NSCs, glutamate declined to 22.8% (SEM ± 3.1%, n = 3 independent replicates) of the initial concentration over 20 minutes, an effect that was completely blocked by the pan-EAAT inhibitor TFB-TBOA. Using a combination of specific EAAT inhibitors, we determined that EAAT1 is responsible for the majority of NSC glutamate transport while the contribution of EAAT2 only becomes apparent when EAAT1 is impaired.
We conclude that hippocampal NSCs exhibit the capacity to substantially alter extracellular glutamate concentrations. Furthermore, NSC glutamate transport is comparable to that reported for astrocytes *in vitro*, suggesting that NSCs could impose physiologically relevant regulation over glutamate signaling. We are currently testing this question *in vivo* using a Cre-dependent lentiviral shRNA expression vector to knock-down EAAT1 specifically in NSCs. Future work will investigate whether NSC glutamate transport has therapeutic value in the context of excitotoxic disease.

Disclosures: J.D. Rieskamp: None. **V. Valentini:** None. **J.P. Bruno:** None. **E.D. Kirby:** None.

Poster

455. Adult Neurogenesis: Molecular Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 455.17/A17

Topic: A.02. Postnatal Neurogenesis

Support: R00 NS089938

Title: Adult neural stem cells require VEGF intracrine signaling for stem cell maintenance in the dentate gyrus neurogenic niche

Authors: J. K. DENNINGER, *E. D. KIRBY
Ohio State, Columbus, OH

Abstract: Neural stem and progenitor cells (NSPCs) mediate neurogenesis in homeostasis as well as disease states. In the adult hippocampal neurogenic niche, Vascular Endothelial Growth Factor (VEGF) is highly expressed by astrocytes and newly discovered to be highly synthesized and secreted by adult NSPCs. While VEGF is a known growth factor of stem cell maintenance, proliferation, and migration in other stem cells, such as hematopoietic stem cells, how NSPC-synthesized VEGF influences stemness in adult hippocampal NSPCs is unknown. This study elucidates a novel intracrine mechanism of VEGF signaling within neural stem cells that is critical to maintaining the stem cell population. We show using cultured adult hippocampal NSPCs that blocking intracellular VEGF signaling with the chemical VEGF receptor 2 (VEGFR2) inhibitor SU5416 diminished VEGFR2 phosphorylation as well as the phosphorylation of downstream mediator Akt while antibody-mediated neutralization of

extracellular signaling did not. Functionally, intracellular inactivation of VEGF signaling with either VEGF RNA interference or SU5416 led to markedly diminished neurosphere number, indicating depletion of the stem cell population. Importantly, exogenous recombinant VEGF had no impact on phosphorylation of VEGFR2 or Akt. Immunofluorescent staining and confocal microscopy indicate that VEGFR2 activation by VEGF may occur in intracellular compartments such as endosomes, further supporting the idea that an intracrine mechanism of VEGF signaling is the primary mechanism of VEGF-mediated preservation of the stem cell compartment. Altogether, our data uncovers a novel intracrine mechanism of VEGF signaling in adult hippocampal NSPCs that is critical to preservation of stemness.

Disclosures: J.K. Denninger: None. **E.D. Kirby:** None.

Poster

456. Autism: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 456.01/A18

Topic: A.07. Developmental Disorders

Support: NIH Grant MH101209

Title: Atypical excitatory-inhibitory balance in feedforward and feedback circuits in autism

Authors: *I. TRUTZER[1,2], B. ZIKOPOULOS[2]
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Abstract: Interactions between excitatory and inhibitory elements in neural circuits are crucially altered in autism and contribute to its central symptoms. Functionally and neurochemically distinct classes of inhibitory neurons, which express the calcium-binding proteins calbindin (CB), calretinin (CR), and parvalbumin (PV), are distributed differentially between different cortical areas and cortical layers. These neurons modify the influence of the excitatory pathways, carried by myelinated axons, that project to those layers. Excitatory connections that terminate in the middle or deep cortical layers behave similarly to the feedforward pathways that are defined in sensory areas, and provide driving input to the cortex. Pathways that terminate in superficial layers behave as feedback pathways and modulate the activity of the cortex. In order to study excitatory-inhibitory balance in the human cortex we studied the distribution of the three classes of inhibitory neurons and the density of myelinated axons in post-mortem tissue from medial, cingulate, and lateral prefrontal cortices of typically developing individuals and individuals with autism. We separately studied superficial and middle/deep cortical layers in order to distinguish changes that influence feedback and feedforward pathways. Adults with autism had a significant reduction in the density of CR-expressing inhibitory neurons in both superficial and middle/deep cortical layers in lateral prefrontal cortices. There was a similar trend in medial prefrontal

cortices in adults with autism. CR-expressing inhibitory neurons in superficial cortical layers serve a disinhibitory role while those in deep layers may provide modulatory inhibition. We found no significant change in the density of PV-expressing or CB-expressing interneurons in adults with autism in these regions. In individuals with autism there was also a steeper rate of increase in the density of small myelinated axons, which are representative of short-range pathways, across layers during development. These parallel structural changes likely produce opposite functional effects: enhanced short-range feedback pathways terminate in an environment with increased inhibition, while enhanced short-range feedforward pathways terminate in an environment with reduced inhibition. Together, these changes in laminar structure may significantly affect information processing in the prefrontal cortex in autism.

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

Poster

456. Autism: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 456.02/A19

Topic: A.07. Developmental Disorders

Support: NIH Grant MH101209

Title: Balance of excitation and inhibition in orbitofrontal cortex and potential for disruption in autism

Authors: *X. LIU, J. BAUTISTA, E. LIU, B. ZIKOPOULOS
Boston Univ., Boston, MA

Abstract: The human orbitofrontal cortex (OFC) is involved in assessing the emotional significance of events and stimuli, emotion based learning, allocation of attentional resources, and social cognition. Little is known about the structure, connectivity and excitatory/inhibitory circuit interactions underlying these diverse functions in human OFC. To fill this gap we used high resolution microscopy, followed by quantitative tracing analysis, to characterize the morphology and distribution of myelinated axons across cortical layers in human OFC at the single axon level, as a proxy of excitatory pathways. In the same regions, we also examined the laminar distribution of neurochemically- and functionally-distinct inhibitory neurons that express calcium-binding proteins parvalbumin (PV), calbindin (CB), and calretinin (CR). Associations of myelinated axons with distinct inhibitory neurons changed across layers and provided a proxy for the study of the excitatory/inhibitory ratio in OFC. We found that density of myelinated axons increased consistently towards layer VI, while average axon diameter did not change significantly. Inhibitory CR-positive neurons were mostly found in layer II, the layer with the lowest density of myelinated axons. CB-positive inhibitory neurons were most dense in layer II

and upper layer III. PV-positive inhibitory neurons were mostly found in the middle/deep layers, especially lower layer III, among a dense plexus of myelinated axons, some of which also expressed PV, presumably coming from the thalamus. The balance between excitation and inhibition in OFC is at the core of OFC function. The OFC gets an overview of the sensory environment through feedforward cortical inputs and assesses the emotional significance of events, based on robust feedback input from the amygdala, in processes that are disrupted in autism spectrum disorder (ASD). We previously showed that in individuals with ASD, excitatory OFC pathways exhibit overall thinning of the myelin sheath of axons, which likely affects conduction velocity and neurotransmission. This suggests laminar-specific changes in the ratio of excitation/inhibition in OFC of individuals with ASD, and may provide the anatomic basis for disrupted transmission of signals for emotions.

Disclosures: X. Liu: None. **J. Bautista:** None. **E. Liu:** None. **B. Zikopoulos:** None.

Poster

456. Autism: Cellular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 456.03/A20

Topic: A.07. Developmental Disorders

Support: NIH Grant MH103398

Title: ASD/ID related de novo mutations in the TRIO-Rac1 pathway alter synaptic function

Authors: *C. TIAN[1,2], Y. KAY[1,2], A. SADYBEKOV[3,4], S. RAO[1,2], V. KATRITCH[3,2,5], B. HERRING[2]
[1]Neurosci. Grad. Programe, [2]Dept. of Biol., [3]Dept. of Chem., [4]Chem. Grad. Program, [5]the Bridge Inst., USC, Los Angeles, CA

Abstract: The Rho guanine nucleotide exchange factor (RhoGEF) Trio promotes actin polymerization by directly activating the small GTPase Rac1. Growing evidence suggests that disruption of the Rac1 signaling pathway at glutamatergic synapses contributes to Autism Spectrum Disorder/Intellectual disability (ASD/ID)-related behaviors seen in animal models of ASD/ID. Here, in humans, we discover a large cluster of ASD-related de novo mutations in Trio's Rac1 activating domain, GEF1. In accordance with pathological increases or decreases in glutamatergic neurotransmission observed in animal models of ASD/ID, we find that these mutations result in either reduced synaptic AMPA receptor expression or enhanced glutamatergic synaptogenesis. Rac1, activated by Trio's GEF1 domain, has recently been identified as an ID risk gene. Similar to hypofunctional ASD-related mutations in Trio, an ID-related de novo missense mutation in Rac1 results in a reduction in synaptic AMPAR expression. Additionally, this mutation prevents the induction of LTP, the cellular mechanism underlying

learning and memory formation. Together, our findings implicate both excessive and reduced Trio/Rac1 activity and the resulting synaptic dysfunction in ASD/ID-related pathogenesis, and point to the Trio-Rac1 pathway at glutamatergic synapses as a possible key point of convergence of many ASD/ID-related genes.

Disclosures: C. Tian: None. **Y. Kay:** None. **A. Sadybekov:** None. **S. Rao:** None. **V. Katritch:** None. **B. Herring:** None.

Poster

456. Autism: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 456.04/A21

Topic: A.07. Developmental Disorders

Support: CONACYT Grant 621770

Title: Modifications in cytoskeletal and astrocytic proteins content in prefrontal cortex, hippocampus and cerebellum of the murine model of autism C58/J strain

Authors: *I. C. BARON-MENDOZA[1], O. GARCIA[2], A. GONZÁLEZ-ARENAS[3]
[1]Inst. De Investigaciones Biomédicas, Ciudad DE Mexico, Mexico; [2]Facultad de Psicologia, UNAM, Mexico, D.F., Mexico; [3]Inst. De Investigaciones Biomedicas, Mexico D.F., Mexico

Abstract: Autism Spectrum Disorder (ASD) is characterized by an impairment of social interaction and communication, and restricted and repetitive behaviours. Alterations in elongation of axons and dendrites, and greater spine densities in ASD patients, particularly found in brain structures as prefrontal cortex, hippocampus and cerebellum, besides a reported synaptic gene dysfunction, suggest disturbances in plasticity in the autistic brain. The cytoskeleton has a pivotal role in regulating the structure and dynamics of dendrites, spines and axons. As well astrocytes-secreted proteins are essential for synaptic connections stabilization. Hence, some modifications of cytoskeletal and astrocyte components could be involved at molecular level in neurite alterations. The objective of this research was to analyse changes in the content of cytoskeletal and astrocytic proteins in the brain of an autistic animal model corresponding to the C58/J mice strain. Prefrontal cortex (pCx), hippocampus (Hc) and cerebellum (Cer) from C58/J and C57 BL/6 (WT) mice were dissected. Samples were processed for Western Blot technique. Results were statistically analysed by one-way ANOVA test. α-tubulin content showed no change in pCx, neither Hc nor Cer between both strains. But microtubule-associated proteins as MAP2A and Tau presented differences. We observed six Tau isoforms (20-100 kDa) in pCx, Hc and Cer of WT mice strain. Four Tau isoforms disappear in autistic brain areas; 80 and 60 kDa isoforms were detected in both strains. The 80 kDa Tau isoform content in pCx, Hc and Cer of autistic mice was not different compared to the WT strain, but the 60 kDa isoform and its

phosphorylated form showed a decrease in the autistic pCx and Hc. Furthermore the MAP2A protein content was lower only in pCx of autistic mice compared to WT strain. The content of β-actin was uniform in the studied brain areas between both strains. The content of phosphorylated actin-binding protein cofilin showed a decrease in the autistic pCx and an increase in autistic Cer. Besides, synaptopodin content, another actin-binding protein enriched in dendritic spines neck, was diminished only in Hc of autistic mice. Finally, the protein content of astrocyte-secreted protein thrombospondin-1 showed a decrease in pCx and Hc of autistic mice, although the GFAP protein content was not different between both strains. Our work showed important brain structure-dependent changes in protein content of 60 kDa Tau/phospho-Tau isoform, MAP2A, phosphorylated-cofilin and synaptopodin, as well as differences in the astrocyte-secreted protein thrombospondin-1 content in pCx, Hc and Cer of autistic animals compared to WT mice.

Disclosures: I.C. Baron-mendoza: None. **O. Garcia:** None. **A. González-Arenas:** None.

Poster

456. Autism: Cellular Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 456.05/A22

Topic: A.07. Developmental Disorders

Support: Jerome Lejeune Foundation

Title: Analysis of mutant delta-catenin haploinsufficiency in altering synaptic pathology and autism-associated behavior changes

Authors: *K. NIP, H. SCOTT, T. GARVER, J. SHOU, S. KIM
Colorado State Univ., Fort Collins, CO

Abstract: δ-catenin is a neuron specific catenin with known implications in cognitive function and synaptic plasticity. The association of this protein with AMPA receptor (AMPAR)-binding protein (ABP) and the related glutamate receptor-interacting protein (GRIP) via association with PSD95 contributes to the structural integrity of the GluA2 AMPA receptor subunits within synaptic membranes. Loss of δ-catenin function is strongly associated with severly affected autism spectrum disorder (ASD) patients. Given the key links between the synaptic adhesion complex and δ-catenin, it is not surprising that δ-catenin regulates synaptic densities and architecture in neurons. Structural plasticity of spines is important for proper synapse development, maturation, and function. Alterations in spine dynamics resulting in abnormal spine morphology and density are proposed to contribute to aberrant synaptic transmission in ASD.
Many genetic disorders are caused by haploinsufficiency, in which having only one copy of the

wild-type (WT) allele is not sufficient to produce the WT phenotype when the other allele is a loss-of-function mutation or deleted. Indeed, δ-catenin haploinsufficiency induces ASD and learning disabilities in humans. δ-catenin homozygous knockout (KO) mice have not been used to determine neurobiological mechanisms underlying ASD-associated synaptic and behavioral deficits. Moreover, the precise effects of δ-catenin haploinsufficiency on pathophysiology are a major gap in our understanding in ASD. Here, we showed that δ-catenin haploinsufficiency was sufficient to impair synaptic structures and autism-related behavioral alteration. This suggests that δ-catenin heterozygous KO mice can be a useful model of δ-catenin haploinsufficiency-induced ASD.

Disclosures: K. Nip: None. **H. Scott:** None. **T. Garver:** None. **J. Shou:** None. **S. Kim:** None.

Poster

456. Autism: Cellular Mechanisms

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Topic: A.07. Developmental Disorders

Support: Ministry of Science and ICT Grant 17-BR-02, 17-BR-04
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Title: Investigation of cortical synaptic structures in microglia-specific eif4e overexpressing mouse using serial block-face sem

Authors: *G. KIM[1], Z. XU[2], S.-H. LEE[1], N. DO[1], C. LEE[1], S. KWON[3], B. XU[2], K. LEE[1]
[1]Korea Brain Res. Inst., Daegu, Korea, Republic of; [2]The Scripps Res. Inst., Jupiter, FL; [3]Catholic Univ. of Daegu, Daegu, Korea, Republic of

Abstract: Imbalance of synaptic excitation to inhibition (E/I) is thought to cause autism spectrum disorders (ASDs). The mammalian target of rapamycin (mTOR) pathway is strongly associated with ASDs by means of its upstream and downstream regulatory mechanisms. Dysregulated activity of Eukaryotic translation initiation factor 4E (eIF4E) promotes the excitatory synaptic transmission by enhancing translation of neuroligin and triggers autistic-like behavioral phenotypes including impaired social interactions and repetitive/stereotyped behaviors. However, specific cell types of eIF4E translational control and structural correlates of impaired E/I balance are poorly understood. Using serial block-face SEM and three-dimensional reconstruction of synaptic connectivity, here we show that eIF4E overexpression selectively in microglia leads to the altered ratio of excitatory and inhibitory synapses in the layer 2 pyramidal neurons of prelimbic area in the medial prefrontal cortex (mPFC). Intriguingly, the increased dendritic spines in eIF4E knock-in mice exhibited to have the reduced spine volume and PSD

surface area compared to those in wild-type animals. In contrast, the number and size of synapses in the dendritic shaft and cell soma were not different between groups. Additionally, further tracing of the presynaptic axonal segments of somatic synapses revealed that their synaptic contacts with neighboring neurons were significantly decreased in the mutant mice. Together, these results demonstrate that disrupted translational activity of eIF4E in microglia results in hyperconnectivity of excitatory synapses as well as abnormal inhibitory circuitry in layer 2 pyramidal neurons of mPFC, suggesting a structural correlates of impaired E/I balance and autistic-like behaviors.

Disclosures: G. Kim: None. **Z. Xu:** None. **S. Lee:** None. **N. Do:** None. **C. Lee:** None. **S. Kwon:** None. **B. Xu:** None. **K. Lee:** None.

Poster

456. Autism: Cellular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: 456.07/A24

Topic: A.07. Developmental Disorders

Support: Ministry of Science and ICT(18-BR-01-01)

Title: Assessment of autophagy in autism induced cell

Authors: *H. CHOI[1,2], M. JUNG[3], J. MUN[2]
[1]Eulji Univ., Gyeongido, Korea, Republic of; [2]Korea Brain Res. Inst., Daegu, Korea, Republic of; [3]Dept. of Convergence Med., Asan Med. Ctr., Seoul, Korea, Republic of

Abstract: Autophagy is highly conserved as a lysosomal degradative process which plays an important role in maintaining cytoplasmic homeostasis. As well, autophagy is involved in a cellular pathway, can lead to cell death, possibly through activating apoptosis. Despite the accumulation of evidence that autophagy is involved in cell death, there is controversy as to whether autophagy affects in cell death. Autophagy and apoptosis are interlocked in an extensive crosstalk with each other. It has recently been the focus of numerous human diseases such as neurodegeneration. Many types of neurodegenerative diseases are accompanied by the accumulation of aggregated and ubiquitinated protein. As well the inhibition of constitutive autophagy induces to the neurodegeneration in neuronal system. It is important to keep balance between autophagosome formation and autophagic degradation. Thus, the accumulation of autophagosome, disruption in the autophagic process of neurons, and decrease of autophagy is associated with neurodegenerative diseases. Until now, because there is not enough protein marker to detect every single autophagic subtypes, there is a limitation to analyzing 'autophagic flux' using light microscopy. TEM is essential to observe the specific type of autophagy because it is the most accurate method of correlating between protein degradation and the volume

fraction of autophagic vacuoles, and it is possible to do classification of autophagosome and autolysosome. It is well known that factors affecting autophagy include amino acid, insulin, and chemicals. Here we analyzed the structural changes of autophagy by several different TEM techniques to study the specific stage of autophagy that are more tightly linked with the mechanisms of autophagy dysfunction.

Disclosures: H. Choi: None. **M. Jung:** None. **J. Mun:** None.

Poster

456. Autism: Cellular Mechanisms

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Topic: A.07. Developmental Disorders

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BR was also supported by the János Bolyai Research Fellowship of the Hungarian Academy of Sciences

Title: Ultrastructural abnormalities of the prefrontal cortex in the CNTNAP2 model of autism

Authors: *B. L. RACZ[1], M. T. LAZARO[2], G. M. MARCELLO[1], P. SOTONYI[1], P. GOLSHANI[3,4,5,6]
[1]Univ. of Vet. Med., Budapest, Hungary; [2]Dept. of Neurology,, David Geffen Sch. of Medicine, UCLA., Los Angeles, CA; [3]UCLA Dept. of Neurol., Los Angeles, CA; [4]Icahn Sch. of Med. at Mount Sinai, Dept. of Neurosci., New York, NY; [5]ntellectual Develop. and Disabilities Res. Center, UCLA, Los Angeles, CA; [6]West Los Angeles VA Med. Ctr., Los Angeles, CA

Abstract: Alterations in synaptic connectivity and imbalance of excitation and inhibition have long been thought to underlie autism spectrum disorder (ASD). Recessive truncating mutations in the CNTNAP2 gene, cause a syndromic form of ASD and Cntnap2 knock-out (KO) mice recapitulate core ASD deficits. However, the anatomical effects of this mutation at the cellular and ultrastructural level remain elusive. To gain a better insight into the phenotype, we used quantitative electron microscopy to determine whether the synaptic structure is modified in the prelimbic medial prefrontal cortex of CNTNAP2 knockout mice, focusing on the neuropil of layers 2/3. Mice lacking CNTNAP2 exhibited alterations in the morphology of their synapses:

we observed a decrease in dendritic spine density, a reduction of both excitatory and inhibitory synapses and multi-synaptic boutons, longer and more complex postsynaptic densities, while dendritic complexity remained unchanged. These findings suggest a profound autism-related alteration in synaptic morphology and a critical role for CNTNAP2 in establishing normal synaptic architecture in the rodent forebrain.

Disclosures: B.L. Racz: None. **M.T. Lazaro:** None. **G.M. Marcello:** None. **P. Sotonyi:** None. **P. Golshani:** None.

Poster

456. Autism: Cellular Mechanisms

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Topic: A.07. Developmental Disorders

Support: CIHR MOP-125985
CRC 950-231066

Title: Conditional knock-out of TSC1 in MGE-derived inhibitory interneurons upregulates mTORC1 activity, impairs hippocampal synaptic inhibition and alters contextual and spatial memory

Authors: N. HAJI[1], I. RIEBE[1], A. AGUILAR VALLES[2], J. ARTINIAN[1], I. LAPLANTE[1], *J.-C. LACAILLE[1]
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Abstract: An imbalance in excitation-inhibition has been proposed as a major factor in neurodevelopmental disorders, including autism spectrum disorders (ASD). However, synaptic inhibition in ASD-linked structures involves complex local circuits composed of multiple types of interneurons and how different interneurons are affected in ASD remains largely unknown. Multiple ASD syndromes are caused by mutations in genes implicated in control of mechanistic target of rapamycin complex 1 (mTORC1) signaling pathway, including the repressor TSC1/TSC2. mTORC1 regulates cell proliferation, survival, growth, and metabolism, and in neurons is important for synaptogenesis and translation-dependent synaptic plasticity. mTORC1 hyperactivation results in impaired synaptic structure, function and plasticity, but these effects have been mainly studied in forebrain excitatory cells.
Here we asked whether inhibitory cell types in forebrain circuits are affected by TSC1 knockout to result in cell type specific synaptic or behavioral phenotypes. We investigated conditional knockout of TSC1 in MGE-derived inhibitory cells by crossing $Nkx2.1^{Cre/Cre}$ mice with $TSC1^{f/f}$ mice. We detected cell-specific increased phosphorylation of ribosomal protein S6 in

Nkx2.1$^{Cre/wt}$;TSC1$^{f/wt}$ mice, indicating upregulated mTORC1 signaling. At the behavioral level, Nkx2.1$^{Cre/wt}$;TSC1$^{f/wt}$ mice exhibited intact contextual fear memory and impaired contextual fear discrimination. Also, Nkx2.1$^{Cre/wt}$;TSC1$^{f/wt}$ displayed intact spatial learning but impaired reversal learning in the Barnes maze, indicating a deficit in spatial working memory. Whole cell voltage clamp recordings in acute hippocampal slices showed that miniature excitatory and inhibitory synaptic transmission were unaffected. Using optogenetic activation of Nkx2.1 interneurons in slices of Nkx2.1$^{Cre/wt}$;TSC1$^{f/wt}$ mice we found that synaptic inhibition of principal cells was decreased. Chronic but not acute treatment with mTORC1 inhibitor rapamycin reversed the impairment in synaptic inhibition by Nkx2.1 interneurons.
Our results indicate that TSC1 haploinsufficiency in MGE-derived inhibitory cells upregulates mTORC1 activity in these interneurons, reduces hippocampal GABAergic transmission and alters contextual fear discrimination and spatial working memory. Thus selective dysregulation of mTORC1 function in specific subtypes of inhibitory cells is sufficient to impair synaptic inhibition and contribute to hippocampus-dependent cognitive deficits in the TSC1 mouse model of ASD.

Disclosures: N. Haji: None. **I. Riebe:** None. **A. Aguilar Valles:** None. **J. Artinian:** None. **I. Laplante:** None. **J. Lacaille:** None.

Poster

456. Autism: Cellular Mechanisms

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Program #/Poster #: 456.10/A27

Topic: A.07. Developmental Disorders

Support: DOD TSCRP

Title: Conditional loss of the tuberous sclerosis gene, Tsc1, results in altered cortical GABAergic interneuron development and physiology

Authors: *R. MALIK[1], E. L.-L. PAI[1], A. M. STAFFORD[2], J. T. NGUYEN[2], J. L. RUBENSTEIN[1], V. S. SOHAL[1], D. VOGT[2]
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Abstract: Tuberous sclerosis (TS) is a multi-systemic disorder caused by mutations in *Tsc1* or *Tsc2 genes*. These genes encode proteins that form a complex, which indirectly inhibits the activity of the mammalian target of rapamycin complex 1 (mTORC1). Notably, the biology underlying the high rate of neurological symptoms in individuals with TS, including autism spectrum disorder (ASD), intellectual disability and epilepsy, is poorly understood. Moreover, accumulating evidence suggests that some ASD symptoms and associated comorbidities may be

caused due to abnormalities in cortical GABAergic interneuron (CIN) function and connectivity, which could lead to compromised neural circuitry. While the role of mTORC1 signaling and *Tsc* genes on excitatory neurons has been studied for some time, relatively little is known about their roles in CIN development and function. CINs consist of morphologically and functionally diverse subclasses of neurons that modulate cortical output, shape cortical oscillations and perform crucial roles in development of cortical circuitry. Parvalbumin (PV)-expressing and somatostatin (SST)-expressing CINs constitute two major subgroups, with substantially different morphological and physiological properties. Specifically, PV+ CINs exhibit fast-spiking firing properties and synapse onto soma/axons of excitatory neurons. By contrast, SST+ CINs have regular-spiking firing properties and target distal dendrites of excitatory neurons. Whether the development and cell-fate of these CINs is affected in TS and other syndromes with high rates of ASDs has not been examined in depth. Due to our previous findings in a *Pten* deletion model (Vogt et al., 2015. *Cell Rep*. 11:944-56), we hypothesized that aberrant signaling downstream of *Tsc1* might affect the development and function of PV and SST CINs. To test this prediction, we generated *Tsc1* conditional mutant mice where *Tsc1* was either deleted in all MGE progenitors or only in post-mitotic SST-lineage CINs. Using a combination of fluorescent imaging and *ex vivo* electrophysiological recordings, we found that *Tsc1* plays an important role in regulating the development and excitability of MGE-derived CINs. Notably, *Tsc1* deletion also resulted in unique phenotypes compared to *Pten* deletion, suggesting novel roles during CIN development. Overall, we predict that these findings may underlie symptoms in several neuropsychiatric disorders (like ASD and schizophrenia) that are linked with deficits in CIN development and function.

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Poster

456. Autism: Cellular Mechanisms

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Topic: A.07. Developmental Disorders

Support: NIH Grant T32MH065214
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Title: Perineuronal nets in the hippocampus are atypical in mouse models of autism spectrum disorder

Authors: *E. C. COPE[1], A. D. ZYCH[2], N. J. KATCHUR[2], C. Y. PARK[2], S. MURTHY[2], B. A. BRIONES[2], E. GOULD[2]
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Abstract: Autism spectrum disorder (ASD) is characterized by social impairments, communication deficits, and repetitive or restricted interests/behaviors. Many individuals with ASD also suffer from excessive anxiety and intellectual disabilities. Neuroimaging studies of humans with ASD have identified atypical structure in the hippocampus, a region that supports cognition, anxiety, and social behavior. Abnormalities in perineuronal nets (PNNs), a specialized extracellular matrix that enwraps certain types of neurons and limits synaptic plasticity, have been linked to other neuropsychiatric conditions, but have not been investigated in ASD. In the current work, we explored PNNs in the hippocampus in two mouse models of ASD, the BTBR idiopathic model and Cntnap2-/- transgenic model compared to C57 controls. Because the hippocampal CA2 region has been linked to spatial and contextual processing as well as social memory, we focused our analyses on this area, along with hippocampal subregions that are connected with CA2 neurons. Using Wisteria floribunda agglutinin to label PNNs, we found increased PNN+ cross sectional area in the CA2 of both BTBR and Cntnap2-/- mice compared to controls. BTBR mice also had robust increases in PNN intensity in the CA2 that coincided with increased OTX2 expression, a transcription factor associated with PNN formation. We next investigated whether PNNs in the dorsal dentate gyrus and CA3, subregions that project to CA2 neurons, differed between ASD mouse models and controls. We found decreased PNN intensity in the dorsal CA3 of both BTBR and Cntnap2-/- mice compared to controls. We also found PNN intensity changes in the dorsal and ventral CA1, brain regions that receive input from the CA2. Both mouse models showed consistent increases in PNN intensity in the dorsal CA1, whereas in the ventral CA1 BTBR mice showed an increase in PNN intensity and Cntnap2-/- mice showed a decrease in PNN intensity. While relative PNN differences between these models might reflect heterogeneity of symptoms seen with ASD, our data overall suggest that PNN abnormalities might contribute to behavioral deficits associated with ASD. Ongoing studies will determine whether changes in PNNs in the hippocampus are causally linked to ASD-related behaviors.

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Poster

456. Autism: Cellular Mechanisms

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Title: Functional characterization of a de novo mGlu7 mutation associated with autism spectrum disorder

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Abstract: Metabotropic glutamate receptor 7 (mGlu7) is an inhibitory heterotrimeric G-protein-coupled receptor that modulates neurotransmitter release and synaptic plasticity at presynaptic terminals in the CNS. mGlu7 is also involved in a variety of neuropsychiatric disorders such as epilepsy, depression, and anxiety. Recent studies have revealed that many de novo mutations in synaptic receptors and scaffold proteins regulating development and function of synapses are associated with autism spectrum disorder (ASD). It has also been shown that exaggerated post-synaptic signaling through mGlu5 can explain the pathogenesis of Fragile X syndrome (FXS), the leading cause of inherited mental retardation and ASD. However, there is no evidence for the role of presynaptic mGlu7 in mediating ASD-related phenotypes. A recent whole exome sequencing study has identified a de novo missense mutation of mGlu7 (Arg622Gln) possibly associated with ASD. In this study, using biochemistry and confocal imaging technology, we evaluate the function of ASD-related mGlu7 Arg622Gln mutation by focusing MAPK signaling, spine morphology, localization, and surface trafficking of mGlu7 in HEK293T cells and rat cultured neurons. This approach will help to understand the etiology of ASD and to provide potential therapuetic targets.

Disclosures: J. Song: None. **Y. Suh:** None.

Poster

456. Autism: Cellular Mechanisms

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Title: Increase aggression in ube3a transgenic model of 15q autism

Authors: *Y. NONG[1], D. STOPPEL[1], M. JOHNSON[1], J. TODOROVIC[1], X. ZHOU[1], M. NADLER[1], M. BOILLOT[1], I. NAGAKURA[1], E. KASPER[2], M. ANDERSON[1]
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Abstract: Individuals with autism spectrum disorder (ASD) are prone to behavioral difficulties including excessive tantrums, irritability, and self-injurious aggressive behaviors that often require medical treatment. Maternal 15q11-13 triplication, a common and penetrant genetic cause of ASD, triples the neuron-expressed dosage of *UBE3A* that encodes an E3 ubiquitin ligase and transcriptional co-regulator. Here we report that the transgenic mouse model of maternal 15q11-13 triplication *(Ube3a2x* mice), with increased copies of the *Ube3a* gene, displays increased aggression behaviors while display impaired sociability and increased repetitive self-grooming. To map the neuronal circuits where increased UBE3A elevates aggression, we developed "*LoxTBUbe3a*" transgenic mice whereby UBE3A can be selectively increased in specific neuronal cell types and brain areas when combined with specific Cre driver mouse lines. Male mice with selective increases of UBE3A in glutamatergic neurons displayed elevated aggression (*VGluT2Cre*). In contrast, selective increases of UBE3A in GABAergic (*VGATCre*) or serotoninergic (*ePetCre*) neurons did not affect indices of aggression. Recent work has shown that glutamatergic neurons in the VMHvl can drive attack behavior in male mice. To evaluate the role of VMH neurons in UBE3A-elevated aggression, *LoxTBUbe3a-2x* (homozygous for *LoxTB-Ube3a*) alleles were combined with the *Sf1-Cre* allele (steroidogenic factor 1 [*Sf1*,*Nr5a1*], which expresses mainly in VMH). These male mice also displayed elevated aggression. We increased *Ube3a* selectively in glutamatergic neurons of the VMHvl by stereotactically injecting *AAV-hSyn-DIO-Ube3a* into VMHvl of *VGluT2-Cre* mice. These mice displayed heightened aggression compared with WT littermate male mice injected with control AAV. These results indicate that increasing UBE3A in glutamatergic neurons of VMHvl is sufficient to elevate aggression in a manner not contingent on developmental effects.

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Poster

456. Autism: Cellular Mechanisms

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COMPETE
UID/NEU/04539/2013-2020

Title: Glutamate/GABA- glutamine cycle imbalance in a mouse model of autism spectrum disorder: Relationship to glial reactivity

Authors: *J. T. GONÇALVES[1,2,3], I. R. VIOLANTE[4], J. SERENO[1,2,3], R. A. LEITÃO[2,3,5], Y. CAI[6], A. ABRUNHOSA[1], A. SILVA[2,3,5], A. J. SILVA[6], M. CASTELO-BRANCO[1,2,3]
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Abstract: It has been reported that changes in the glutamine/glutamate ratio and imbalance between excitation and inhibition signaling could be possible neural mechanisms underlying autism spectrum disorders (ASD). An association between GABA/glutamate imbalance (affecting glutamine levels) and neuroinflammation in autistic patients has been previously postulated. Here, we used neurofibromatosis type 1 (NF1) mouse as a monogenic model to study mechanisms of autism spectrum disorders to investigate these pathological mechanisms. Using magnetic resonance spectroscopy, we observed that cortical γ-aminobutyric acid (GABA)/glutamate ratio was increased compared with wild-type animals, while we observed no differences in the hippocampus. However, both cortical and hippocampal glutamine/glutamate ratios were augmented. Since this ratio has been used as an indicator of neuronal-glial interactions, we investigated the effect of *Nf1*$^{+/-}$ mutation on glia cells. Although, our studies revealed an increase of reactive astrogliosis and glial fibrillary acidic protein (GFAP) in both regions, while microglia activation (Iba-1-positive cells) was only detected in *Nf1*$^{+/-}$ hippocampus. To investigate the known relation between glial activation and blood-brain barrier (BBB) dysfunction we investigated changes in BBB permeability. We analyzed the levels of serum albumin in the brain since this protein is undetectable or present at very low levels in the brain parenchyma under physiological conditions. Hippocampal expression of albumin was dramatically increased, while prefrontal cortex showed a slight augment of this protein. Overall, these results support the hypothesis that autism spectrum disorders are synaptic disorders showing concomitant excitation/inhibition imbalance and an abnormal neuroinflammatory response.

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Poster

456. Autism: Cellular Mechanisms

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Topic: A.07. Developmental Disorders

Support: Ricerca Finalizzata PE-2013-02355126

Title: Altered expression of mGlu5 receptor and its regulatory proteins in several autism spectrum disorders

Authors: *M. CATANIA[1], C. M. BONACCORSO[2], A. ARENA[3], J. J. ANINK[3], S. D'ANTONI[1], M. SPATUZZA[2], E. ARONICA[3]
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Abstract: Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by impaired social interaction and stereotyped behaviours. Increasing evidence suggests that a convergence on signaling pathways involved in protein translation and triggered by the activation of group I metabotropic glutamate (mGlu) receptors can be common to different ASDs. A dysregulation of mGlu5 receptor-mediated signaling has been reported in different animal models of ASD, including animal models of Fragile X syndrome (FXS) and Angelman Syndrome (AS). In this context, we have found that the interaction between mGlu5 receptor and its scaffolding protein Homer is abnormal in mouse models of FXS and AS (Giuffrida et al., J. Neurosci., 2005; Pignatelli et al., J. Neurosci, 2014). Thus, we are currently investigating if mGlu5 alteration is involved in other neurodevelopmental disorders associated with intellectual disability and Autism, such as Tuberous Sclerosis Complex (TSC) and Down Syndrome (DS). To this aim, we have studied protein expression of mGlu5 receptor and its endogenous regulators of cell surface localization, intracellular trafficking and signaling, such as Homer, Preso1, Tamalin and Norbin, on brain tissue of patients affected by these different pathologies. We have found a different pattern of expression of these proteins in these different pathologies. We observed that mGlu5 receptor, Homer1bc and Tamalin levels are increased in neurons of TSC patients, whereas a reduction is detected in Preso1 and Norbin levels. No difference was observed in mGlu5 receptor expression levels of AS patients; in contrast, a reduction is shown in Homer1bc levels. In addition, our data highlighted a reduction of Homer1bc and mGlu5 receptor in neurons of DS patients. Our findings provide strong support for the hypothesis that alteration

in mGlu5 receptor expression is common to different ASDs and that a dysregulation of its regulatory proteins might have possible consequences for its activity.

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Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

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Program #/Poster #: 457.01/A33

Topic: A.07. Developmental Disorders

Support: NIH Grant

Title: Understanding dysphagia through 22q11.2 deletion syndrome mediated changes in murine laryngeal motorneurons

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Abstract: Pediatric dysphagia, difficulty in swallowing and feeding, is one of the most common problems associated with various developmental disorders, and is especially prevalent in patients with 22q11.2 Deletion Syndrome (22q11DS). The act of swallowing is largely regulated through vagal innervation to the larynx from laryngeal motor neuron cell bodies located within the medullar portion of the brainstem. Two laryngeal structures in particular, the vocal folds and the epiglottis, are especially important as they work to seal off the trachea during active swallowing, preventing aspiration into the lungs. Using a large deletion (LD) mouse model for 22q11DS, the objective of this work aims to establish and characterize changes in the electrophysiological properties of laryngeal motor neurons that occur in LD animals. The spontaneous firing, evoked firing, voltage-gated currents, as well as both excitatory and inhibitory synaptic neurotransmission to laryngeal motor neurons recorded from the LD animals was quantified and compared to those from wild-type (WT) littermates. Preliminary data suggests that laryngeal neurons from LD animals possess a higher spontaneous action potential (AP) firing frequency than those from WT animals. Additionally, while excitatory postsynaptic currents (EPSCs) appear to occur at the same frequency in both LD and WT laryngeal motor neurons, the spontaneous excitatory events are reduced in amplitude in the LD neurons compared to those from the WT animals. Our overall goal is to determine the different electrophysiological properties of laryngeal neurons from LD animals compared to WT littermates. This work aims to provide the foundation needed to later identify therapeutic targets and hopefully develop novel treatments to restore laryngeal activity, as well as future possible treatment strategies for pediatric dysphagia associated with 22q11DS.

Disclosures: H.L. Caudill: None. **D.S. Mendelowitz:** None. **A. LaMantia:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

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Topic: A.07. Developmental Disorders

Support: Nipissing University

Title: Exposure to alcohol alters behavioural recovery as a function of single or group housing during regeneration in planaria

Authors: *M. J. SAARI[1], L. GOODRIDGE[2], R. VERNESCU[3], A. STILLAR[4]
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Abstract: Planaria, *Dugesia dorotocephala*, may be a suitable tool for the study of FASD because of their remarkable ability to grow a completely new body, including neural tissue, from even a small fraction of body tissue. This ability is mediated by the presence of totipotent somatic stem cells. In previous studies we have shown that planaria are sensitive to social isolation and we hypothesized that the social condition (isolated or group housing) may influence regeneration and possibly interact with the effects of alcohol exposure during regeneration. The purpose of this study was to explore activity and body morphology of planaria as they regenerate a new head region while exposed to two different social environments: isolated or group housed in either in an ethanol or the standard salt solution (Montjuic analog). Following removal of the head region, the planaria were placed in either individual or group housing in their respective solutions for 30 days. During the next six days all planaria were removed from their respective solution, and placed into the standard salt solution. Video of the worms was captured every 2nd day with water changes occurring on alternate days. Analyses of the videos (WormLab; MBF Bioscience) revealed significant differences in recovery between the alcohol and salt conditions and the social environment as well as behavior during and after the alcohol exposure. Significant reduction in the duration of the “scrunch reflex” (Longitudinal Body Contraction) suggests weakening of inhibitory control in planaria exposed to alcohol during regeneration. Negative phototaxis did not appear to be significantly altered by the alcohol, however. These results suggest that the effects of post-bisection head region regeneration are sensitive to the social conditions and ethanol exposure during regeneration in planaria.

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Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

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Program #/Poster #: 457.03/B1

Topic: A.07. Developmental Disorders

Support: Conacyt 332502/232728

Title: Neurodevelopmental and behavioral alterations after conditional deletion of type 2 cannabinoid receptors in dopamine neurons

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Abstract: Our recent report revealed that DAT-*Cnr2* mutant mice with selective deletion of type 2 cannabinoid receptors (CB2Rs) in dopamine neurons exhibit a hyperactive phenotype characterized by hyper-locomotor activity compared to the wild type (WT) mice (Liu et al, Sci Rep. 2017 ; 7(1):17410). The endocannabinoid and dopaminergic systems play pivotal roles in a number of behavioral functions in the central nervous system such as motor control, emotion and reward. CB2Rs are expressed in the postsynaptic somatodendritic area of dopaminergic neurons and modulate midbrain dopamine neuronal activity and dopamine-related behavior in mice. In this study, we evaluated the neurodevelopmental and behavioral alterations after cell-type specific deletion of CB2Rs in dopamine neurons in DAT- *Cnr2* conditional knockout (cKO) mice. We investigated and tested the hypothesis that the DAT-*Cnr2* cKO mice may represent a model of attention deficit hyperactivity disorder (ADHD). Ultrasonic vocalizations (USVs), physical development, and reflex activities of the DAT-*Cnr2* cKO and WT male and female pups from postnatal day 1 (PND1) to the weaning day (PND21) were analyzed. Other behavioral tests including spontaneous locomotor activities and performances in the plus maze test of the animals were determined from PND 22 to 25. A separate group of DAT-*Cnr2* cKO and WT adolescent mice (PND 30±2) were treated acutely with amphetamine 2.0 mg/kg ip and their performances in the open field were accessed. We report that the DAT-*Cnr2* cKO pups started crawling and walking sooner than the WT mice. USV rates at 60-80 hertz were higher in the DAT-*Cnr2* cKO mice than in the WT mice. The DAT-*Cnr2* cKO mice gained weight more slowly than WT mice. The most important difference between the animals is that the DAT-*Cnr2* cKO mice displayed hyperactivity in the open field and plus-maze tests. When 2.0 mg/kg amphetamine was administered, it produced a significant increase in motor activity in the WT, and in contrast, a significant reduction in motor activity in the DAT-*Cnr2* cKO mice in the open

field test. Taken together, the data obtained suggests that DAT-*Cnr2* cKO mice show signs of ADHD -like phenotype, as the hyperactivity was diminished with the dose of amphetamine used. It was concluded the DAT-*Cnr2* cKO mice may be a useful model for the investigation of the components of the endocannabinoid system as possible therapeutic targets in ADHD.

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Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

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Program #/Poster #: 457.04/B2

Topic: A.07. Developmental Disorders

Support: Wellcome 204580/Z/16/Z

Title: Effects of acute and chronic DISC1 disruption on plasticity and morphology in the prefrontal cortex

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Abstract: DISC1 has been identified as a schizophrenia risk factor and plays an important role in brain development. Various DISC1 models have been studied to address the role of DISC1 in neurodevelopment and brain function, but the relevance of many of the models is debatable as many have little similarity to the original DISC1 translocation. We have studied two DISC1 mouse models, one with inducible disruption of c terminus DISC1 signalling via tamoxifen injections and one with a constitutive disruption of DISC1 using the first accurate mouse model of the t(1;11) translocation (Der1, K Millar & M Didier (Sanofi)) . Transient disruption of DISC1 signalling at P7 (in the inducible model) resulted in schizotypic behaviour in the mice (Li *et al*, 2007) and a complete loss of experience dependent plasticity and LTP in adult layer 2/3 barrel cortex (Greenhill et al 2015). Schizophrenia has been strongly linked to dysfunction in the prefrontal cortex with both functional and structural prefrontal deficits implicated. We therefore set out to investigate whether following transient P7 disruption of DISC1 signalling, synaptic plasticity is occluded in the adult prefrontal cortex as it is in the barrel cortex and also to determine whether chronic disruption of DISC1 has a comparable effect to transient DISC1 disruption. We observed only a partial occlusion in prefrontal cortex LTP following transient DISC1 disruption (a 50% reduction in LTP magnitude ($p<0.01$ compared to WTs, DISC1 LTP still at significant levels), but a total blockade of LTP following chronic DISC1 disruption ($p<0.001$). This total blockade of LTP following chronic DISC1 disruption was accompanied by alterations in STP ($p<0.01$). In addition to this, we observed deficits in dendritic complexity in

adult mice following chronic DISC1 disruption (26% reduction, $p<0.001$ including a 36% reduction in basal complexity ($p<0.001$) and a 10% reduction in apical complexity (ns) but no deficit in dendritic complexity following acute DISC1 disruption (ns). In addition, after chronic DISC1 disruption we observed a reduction in spine density on basal dendrites (10%, $p<0.05$), but also an increase in spine density on apical dendrites (14%, $p<0.01$) which was via a significant increase in thin spines ($p<0.05$). The enhanced spine density on apical dendrites was also observed following acute P7 DISC disruption (24% increase, $p<0.001$). Thus, the constitutive DISC1 model exhibits more deficits, both functional and structural, than the inducible DISC1 model following disruption of DISC1 at P7. However, P7 disruption does produce some deficits suggesting possibly an extended critical period in the prefrontal cortex compared to the barrel cortex.

Disclosures: N.R. Hardingham: None. **C.M. Hilldrup:** None. **K.D. Fox:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 457.05/B3

Topic: A.07. Developmental Disorders

Support: University of Scranton, Start-up funding

Title: Differing effects of hypoxia on developmental dopaminergic neurons in the developing zebrafish brain

Authors: T. M. BIELINSKI[1], J. N. MACDONALD[1], M. R. BARRETT[1], M. SEID[1], J. BONKOWSKY[3], *J.-H. SON[2]
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Abstract: Hypoxic injury to the developing human brain from prematurity may increase the risk of lifelong behavioral and intellectual deficits, including autism spectrum disorders, cerebral palsy, depression, bipolar disorders, epilepsy, and intellectual disabilities. However, the mechanisms of hypoxia-induced injury to the developing nervous system are poorly understood. Previously, we have demonstrated that hypoxic injury resulted in connection errors of telencephalic neurons in the vertebrate nervous system using the embryonic zebrafish (*Danio rerio*) (Stevenson et al., 2012). Here, we have studied the effects of hypoxia on the diencephalic dopaminergic (DA) neurons (1-5% of pO_2, from 24-96 hours post-fertilization (hpf)). Our results demonstrate that developmental hypoxia had differing effects on DA neurons depending on the timing and level of hypoxic exposure. Early exposure to hypoxia (24 to 48 hpf, 1% of pO_2) led to reduced DA neuron proliferation (20-30% of control normoxic group, 21% of pO2). In contrast,

later hypoxia (48 to 72 hpf, 3% of pO_2) led to an increase in developmental cell death. Interestingly, while later hypoxia exposure (72 to 96 hpf, 5% of pO_2) led to a 15-30% decrease in DA tissue content, it did not affect DA pathfinding or extension to motor neurons of the spinal cord. Our findings have important implications for understanding normal DA development and function in the vertebrate nervous system, and the pathophysiology associated with prematurity-associated hypoxia diseases.

Disclosures: T.M. Bielinski: None. **J.N. MacDonald:** None. **M.R. Barrett:** None. **M. Seid:** None. **J. Bonkowsky:** None. **J. Son:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 457.06/B4

Topic: A.07. Developmental Disorders

Support: NSERC Discovery Grant

Title: Acute effects of early seizures on hippocampal interneurons in the immature brain

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Abstract: The neonatal period is characterized by a critical period of synaptogenesis and plasticity, in part mediated by a physiological imbalance between excitation and inhibition, and this imbalance is thought to contribute to the enhanced susceptibility of the immature brain to seizures and epileptogenesis. Previous studies have shown that early life seizures induce acute enhancement of AMPAR function in hippocampal CA1 pyramidal neurons. Glutamatergic inputs from pyramidal neurons mediate Ca^{2+} influx in the interneuron dendrites and determine the functional maturation of the interneurons. However, little is known about whether early seizures will activate hippocampal interneurons. Here, we aim to investigate the acute effects of early life seizures on different interneuron populations in developing hippocampus. Early seizures were induced in c-Fos-tTA/c-Fos-GFP mice by single dose of PTZ (60mg/kg, i.p.) at P10, with saline-injected littermates used as controls. We revealed that no co-labeling of GFP and GAD65/67 following PTZ seizures (n=6), confirming that GABAergic interneurons are not activated during acute early seizures in the immature hippocampus. Using whole-cell patch-clamp recordings, CA1 interneurons were identified according to their morphology and distinctive electrophysiological properties. We found that intrinsic membrane properties were unchanged in both fast-spiking interneurons and non-fast spiking interneurons at 1h post-seizures compared with controls (n=7-11, $p>0.05$). Moreover, AMPAR-mediated sEPSC amplitude in both fast-spiking (20.8±2.0 pA, n=16) and non-fast-spiking interneurons (19.7±2.0 pA, n=14) from 1h

post-seizure mice were not different from littermate controls (fast-spiking interneurons 23.9±1.4 pA, n=18, p>0.05; non-fast-spiking interneurons 23.8±2.4 pA, n=13, p>0.05). However, AMPAR sEPSC frequency in fast-spiking interneurons from 1h post-seizure mice (0.29±0.06 Hz; n=16) was significantly lower than controls (1.27±0.19 Hz; n=18, p<0.05), while no significant changes of AMPAR sEPSC frequency were observed in non-fast-spiking interneurons from 1h post-seizure mice (1.10±0.29 Hz; n=14) compared with controls (0.69±0.14 Hz; n=13, p>0.05). Our data support that early seizures differentially regulate excitatory inputs to hippocampal pyramidal and interneurons, which may represent a potential synaptic mechanism mediating neuronal circuit reorganization in early life epilepsy.

Disclosures: T. Wang: None. **H. Sun:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 457.07/B5

Topic: A.07. Developmental Disorders

Support: Novo Nordisk - Hallas-Møller Investigator

Title: Differential outcomes of schizophrenia-associated genetic and environmental risk factors on interneuron development

Authors: *B. SANZ MORELLO[1], N. A. VASISTHA[1], M. PARDO-NAVARRO[1], J. GASTHAUS[1], D. D. WEIJERS[1], N. W. HANSEN[2], U. PFISTERER[1], A. THAKUR[1], S. DEMHARTER[1], K. S. HOUGAARD[3], I. KORSHUNOVA[1], J.-F. PERRIER[2], K. KHODOSEVICH[1]
[1]Biotech Res. and Innovation Ctr. (BRIC), Kobenhavn N, Denmark; [2]Dept. of Neurosci., Fac. of Hlth. Sciences, Univ. of Copenhagen, Kobenhavn N, Denmark; [3]The Natl. Res. Ctr. for the Working Envrn., Kobenhavn O, Denmark

Abstract: Schizophrenia is a complex psychiatric disorder where both genetic and environmental factors contribute to the disease development. Thus, schizophrenia risk factors include single gene mutations and copy number variations as genetic, and maternal inflammation, drug abuse and stress as environmental factors. In recent times, mouse models have been generated that recapitulate some of these risk factors. Importantly, although these mouse models show some similar phenotypic characteristics, there are also significant differences in morphological and behavioural schizophrenia-associated impairments between the models. This also resembles closely the human disorder, since schizophrenia patients have a spectrum of positive and negative symptoms that might vary from patient to patient. Substantial evidence from human studies show that the cognitive decline in schizophrenia might result from

an imbalance between excitation and inhibition in the brain due to impaired activity of interneurons. We highlight that development of interneurons is differentially affected in several genetic and environmental mouse models of schizophrenia. We show widespread vulnerability of interneurons in response to various schizophrenia-associated “hits”, affecting all stages of interneuron development - neurogenesis, migration and maturation. Looking at subtypes of interneurons derived from medial and caudal ganglionic eminence, we find higher vulnerability of specific subtypes in comparison to others. At the same time, each schizophrenia-associated risk factor has a distinct effect on interneuron development, thus affecting only a subset of interneuron subtypes while sparing the others. Such differential impairment of interneuron subtypes might explain the phenotypic differences observed in schizophrenia as well as provide novel cellular targets for interventional therapies.

Disclosures: B. Sanz Morello: None. **N.A. Vasistha:** None. **M. Pardo-Navarro:** None. **J. Gasthaus:** None. **D.D. Weijers:** None. **N.W. Hansen:** None. **U. Pfisterer:** None. **A. Thakur:** None. **S. Demharter:** None. **K.S. Hougaard:** None. **I. Korshunova:** None. **J. Perrier:** None. **K. Khodosevich:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 457.08/B6

Topic: A.07. Developmental Disorders

Support: NIH 1F32HD094625

Title: The role of asparagine synthetase in brain development

Authors: *X. YAO[1], D. B. GOLDSTEIN[3], Y.-H. JIANG[2]
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Abstract: Asparagine Synthetase Deficiency (ASNSD) is a recently identified rare autosome recessive neurological disease characterized by severe microcephaly, developmental delay, intellectual disability, cerebral atrophy and intractable seizures. ASNSD is caused by mutations in the ASNS gene encoding asparagine synthetase (ASNS). ASNS is believed to catalyze the biosynthesis of asparagine (ASN), a non-essential amino acid in humans, from aspartate and glutamine in an ATP-dependent manner. However, very few investigations have followed this lead and the exact physiological relevance related to the function of ASNS in ASN synthesis remains elusive. Remarkably, nothing is known about the pathogenesis of ASNSD and the function of ASNS in brain development and there is no treatment available. TO determine the specific role of ASNS in brain development and delineate the mechanism underlying the

neuropathogenesis of ASNSD, we generated *Asns* conventional knockout (KO) mouse and brain specific conditional KO mouse to investigate the consequence of *Asns* loss in brain development. We found that conventional Asns-KO results in perinatal lethality and significantly reduced brain mass. Brain-specific Asns-KO mice by Nestin-Cre ($Asns^{NS-/-}$) nicely recapitulate core features of ASNSD. $Asns^{NS-/-}$ mice have smaller brain mass, and display growth retardation and high penetrance for spontaneous seizures and lethality at postnatal days 15-22 (P15-22). Interestingly, the primary cultured cortical neuron from conventional Asns-KO shows significant growth defect and this defect can be rescued by supplementing extra asparagine. Our results demonstrate that ASNS plays critical roles in early brain development. Phenotypes observed in *Asns* KO mice mimics clinical features of ASNSD, suggesting that *Asns* KO mouse is a valid model to study the mechanisms underlying neurological impairment in ASNSD and to test potential strategies for clinical interventions.

Disclosures: X. Yao: None. **D.B. Goldstein:** None. **Y. Jiang:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

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Program #/Poster #: 457.09/B7

Topic: A.07. Developmental Disorders

Support: NIH Grant NS097534

Title: Rapid evaluation of ciliopathy patient-derived ZNF423 variants by genome editing in mice

Authors: *B. A. HAMILTON
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Abstract: Ciliopathies are disorders that share defects in primary cilia, most often due to mutations that disrupt proteins localized to cilia. *ZNF423* encodes a transcriptional regulator with 30 zinc fingers, conserved among vertebrates, that forms alternative complexes with a variety of lineage-selective or signal-responsive transcription factors and with DNA damage response factors. Rare mutations in *ZNF423* are reported in patients with cerebellar vermis hypoplasia, Joubert Syndrome (JBTS19), or nephronophthisis (NPHP14) and other brain malformations. Patient sequencing more frequently returns variants of unknown significance, often in heterozygous state, some of which have been proposed to act dominantly. Null mutations in mouse *Zfp423* recapitulate brain malformation aspects seen in human patients, including hypoplasia or agenesis of the cerebellar vermis. To determine the impact of patient-derived variants, we used CRISPR/Cas9-mediated genome editing with synthetic components to rapidly introduce ~30 distinct mutations in *Zfp423* in mouse embryos with a uniform genetic background (FVB/NJ). Protein truncating alleles uniformly result in recessive severe ataxia with gross

malformations. Substitution alleles, even at strongly conserved sites, rarely produce strong phenotypic consequences. Surprisingly, in-frame deletions that remove or disable some zinc fingers did not produce strong effects.

Disclosures: B.A. Hamilton: None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 457.10/B8

Topic: A.07. Developmental Disorders

Support: NIH/NIAAA RO1 AA022460
NIH/NIAAA R37 AA007789

Title: Beneficial impacts of minocycline administration following prenatal alcohol exposure

Authors: *T. S. BODNAR, S. SARKAR, A. CHAO, S. BAGLOT, P. HOLMAN, J. WEINBERG
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Abstract: Prenatal alcohol exposure (PAE) has a significant impact on immune function, resulting in an increased risk of infections, alterations in immune organ development, and disturbances to immune cell populations. We have shown previously that following PAE, cytokine levels are increased during the early postnatal period, a critical window for both brain and immune system development. Based on these findings, here it was hypothesized that administration of an anti-inflammatory agent during early-life could have a beneficial impact on the immune system following PAE.
To test this hypothesis, pregnant Sprague-Dawley rat dams were assigned to: PAE – ad libitum access to liquid ethanol diet; or Control (C) – ad libitum access to control diet. Next, offspring were administered minocycline during either lactation or during adolescence. Immune organs and brain tissue were collected following minocycline administration to assess cytokine levels. In adulthood, the response to lipopolysaccharide (LPS) challenge was assessed and, due to the modulatory role of the neuroimmune system on cognition and learning and memory, adults were tested in the Barnes Maze (spatial learning/memory task).
Results indicate that PAE males show deficits in the Barnes Maze task, specifically in the reversal phase, and that minocycline administration during lactation or adolescence appears to normalize performance. In addition, preliminary data indicate that PAE animals have a heightened cytokine response to LPS, with both sexes showing elevated levels of IL-5, along with elevated IL-13 in females and TNF-α in males. Notably, minocycline administration during lactation or adolescence also normalized the cytokine response to LPS in PAE animals.

Taken together, as altered immune function/neuroimmune signaling may underlie some of the long-term effects of PAE, findings from this ongoing study may have implications for understanding the long-lasting deficits associated with FASD and support further investment into immune-based intervention strategies.

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Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 457.11/B9

Topic: A.07. Developmental Disorders

Support: NIH Grant HD080910

Title: The ontogeny of cognitive, behavioral and metabolic deficits in creatine transporter deficiency

Authors: *K. C. UDOBI, N. DELCIMMUTO, A. KOKENGE, Z. ABDULLA, M. PERNA, M. SKELTON
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Abstract: Creatine (Cr) transporter (CrT) deficiency (CTD) is a leading cause of X-linked intellectual disability (XLID). CTD is characterized by moderate to severe intellectual disability, epilepsy, and autistic-like symptoms. On occasion CTD patients also exhibit muscular and skeletal symptoms like hypotonia, and microcephaly. Animal models of CTD exhibit cognitive and behavioral deficits, mimicking the disorder. While it is clear that Cr is essential for proper cognitive and metabolic function as evidenced by neurological and metabolic deficits resulting from the loss of cellular Cr, it is still unknown if these deficits are caused by changes in brain development due to a lack of Cr or if the loss of Cr leads to disruptions in neuronal function. To understand the role of Cr in brain development, we eliminated the Crt during two distinct life stages using mice that express a tamoxifen-inducible Cre recombinase (UBC-cre/ERT2) crossed with $Crt^{flox/y}$ mice. To understand the role of Cr in a normally developed brain, the Crt was knocked out in adult animals. The effect of Cr on brain development was examined by deletion of the Crt in neonatal mice, a period analogous to third trimester brain development in humans. Tamoxifen was administered from postnatal day (P) 5-10 in the neonatal group (P5-KO) and from P60-65 for the adult mice (P60-KO). Brain CrT transcripts were undetectable 5 days following Cre recombinase induction. Both groups of KO mice had a significant reduction in body weight compared with control (CONT) mice. Both P5-KO and P60-KO mice were hyperactive in the open-field test. Cognitive function was assessed based on deficits observed in

previous CrT knockout mice, representing three distinct types of learning to assess global cognitive function. Spatial learning was assessed in the Morris water maze (MWM). During visible platform testing, P10-KO mice had an increased latency to the platform compared with controls. The P60-KO mice show differences compared with CONT mice. In the acquisition and reversal phases, P5-KO mice had an increased in latency and path length compared with CONT. No differences were observed in P60-KO mice in the MWM. Both groups of cKO showed no deficits in object recognition or fear memory when compared with CONT mice. Both groups of cKO mice showed increases in whole-body metabolism, consistent with ubiquitous KO mice. In addition, increased brain mitochondrial respiration was observed in both groups of mice. The results of this study suggest that the loss of Cr in the adult brain is not sufficient to induce cognitive deficits, suggesting that the deficits observed are due to changes in brain development.

Disclosures: K.C. Udobi: None. **N. Delcimmuto:** None. **A. Kokenge:** None. **Z. Abdulla:** None. **M. Perna:** None. **M. Skelton:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

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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 JRJ
UD OGPE University Doctoral Fellowship to ZHG
Private Anonymous Gift to AYK

Title: Early postnatal alcohol exposure increases microglia density in the rat cerebellum that can be offset by voluntary exercise in adolescence

Authors: *A. Y. KLINTSOVA, J. R. JOHANSSON, Z. H. GURSKY
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Abstract: During development, precise function of brain neuroimmune system is required for maintenance of extracellular space, refinement of synapses, and clearance of apoptotic neurons. Microglia (MG), the resident immune cells of the brain, colonize the brain from the periphery in the first half of prenatal development in both humans and rodents. MG are sensitive to teratogenic effect of alcohol during brain development. The current study examines the distribution and morphology of MG in rat cerebellum following early postnatal ethanol exposure. Male and female Long Evans rats underwent one of 3 experimental postnatal treatments on postnatal days (PD) 4-9: exposure to 5.25 g/kg/day of ethanol via intragastric intubation

(alcohol-exposed, AE), intubation without any liquid (sham-intubated, SI), or undisturbed (suckle control, SC). On PD 30, animals were placed (2-3 same-sex in a cage) in one of 2 adolescent housing conditions: social housing in standard cage (socially-housed, SH), or social housing with free access to a running wheel (wheel-running, WR). On PD42, brains were fixed with 4% paraformaldehyde. Cerebelli were sectioned parasagittally at 40µm and immunohistochemically labeled for Iba-1, a MG-specific protein. Images of systematically-selected serial sections were acquired using Stereo Investigator (MBF Bioscience) for densitometry analysis of Iba-1 using ImageJ software. To assess morphology of individual MG, serial random sampling was used to acquire z-stacks within lobules (L) 1-4 and L9-10 of cerebellum, and MG morphology was analyzed using Neurolucida (MBF Bioscience).
In L1-4, there were main effects of postnatal treatment (AE>SI, AE>SC) and adolescent housing (WR<SH) on density of MG material. There was a main effect of postnatal treatment on volume (AE<SI, AE<SC), and a main effect of housing on MG material (WR<SH). In L9-10, there were main effects of postnatal treatment (AE>SI, AE>SC) and housing (WR<SH) on density of MG material, similar to the pattern observed in L1-4. WR increased the volume of L9-10 (WR>SH), suggesting that changes in volume contributed to changes in MG density. This data indicates that WR counteracts the long-term alterations in MG density following AE. In both L1-4 and L9-10, there was exclusively a main effect of adolescent housing on the average territory of individual MG (WR<SH). Reduction in cell territory is often associated with MG activation and increased cell size, which suggests that WR-induced changes in MG density in both L1-4 and L9-10 are likely driven by reductions in number of MG cells rather than altered MG morphology.

Disclosures: A.Y. Klintsova: None. **J.R. Johansson:** None. **Z.H. Gursky:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 457.13/B11

Topic: A.07. Developmental Disorders

Support: American Epilepsy Society Pre-doctoral Fellowship

Title: A mouse model for GNAO1-associated movement disorder

Authors: *H. FENG[1], Y. YUAN[2], C. L. LARRIVEE[2], R. R. NEUBIG[2]
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Abstract: Rationale: The heterotrimeric protein G_o, whose α subunit is encoded by *GNAO1*, regulates ion channel function, neurotransmitter release, and neurite outgrowth. Mutations in *GNAO1* have been identified in children with either epileptic encephalopathy (EIEE17) or neurodevelopment disorder with involuntary movements (NEDIM). The mechanism underlying

the complex clinical spectrum of these *GNAO1* encephalopathies is poorly understood. Previously, we discovered a genotype-phenotype correlation on patients mutations with an *in vitro* functional assay. *De novo GNAO1* mutations have both GOF and LOF biochemical function with the former associated with seizures and the latter with movement disorder. We also reported a *Gnao1* GOF knock-in mutant (*Gnao1*$^{G184S/+}$) with a mild seizure phenotype in C57Bl/6J mice. In the current study, we assessed behavioral characteristics and electrophysiology properties and morphological changes in the cerebellum of *Gnao1* mutant mouse models to explore the pathophysiology of *GNAO1*-associated movement disorders and to further validate our model associating *GNAO1* GOF mutations with movement disorder.
Methods: *Gnao1*$^{G184S/+}$ (GOF) and *Gnao1*$^{-/+}$ (HetKO) animals of both sexes (age 8 to 14 weeks) were analyzed. Spontaneous inhibitory (sIPSCs) and excitatory postsynaptic currents (sEPSCs) in Purkinje cells in cerebellar slices were measured using whole cell patch-clamp recording techniques. Morphology was assessed with Nissl staining. Motor capabilities were assessed using a battery of behavioral tests.
Results: Compared to *Gnao1* WT mice, GOF mice showed a number of behavioral abnormalities related to movement including open field, rotarod, stride length, paw angle variability, and grip strength. HetKO mice were relatively normal in motor functions. Cerebellar slices from GOF mice showed reduced sIPSC frequency but relatively normal EPSCs. Cerebella from GOF mice also had reduced lobule number but molecular layer thickness was unchanged.
Conclusions: The *Gnao1* GOF mutant mice, as with human *GNAO1* GOF patients show a pronouced movement disorder. This may be related to altered inhibitory signaling in the cerebellum.
Funding: Supported by an American Epilspsy Association Predoctoral Fellowship (to H.F.)

Disclosures: H. Feng: None. **Y. Yuan:** None. **C.L. Larrivee:** None. **R.R. Neubig:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 457.14/B12

Topic: A.07. Developmental Disorders

Support: NIH Grant

Title: The role of interleukin-6 expression in maternal gut bacteria and the alternation of mouse offspring brain development

Authors: *V. PEÑA-GARCIA[1], A. OYETUNDE[2], B. TENG[2], D. BANNER[2]
[1]Biol., California State University, Northridge, Alhambra, CA; [2]Biol., California State University, Northridge, Northridge, CA

Abstract: There is a wealth of emerging information displaying a connection between maternal health and fetal brain development. One of the primary causes of neurodevelopmental abnormalities is mediated through an activated maternal immune system. The maternal immune system may be activated by many different environmental factors, one being exposure to a high-fat diet (HFD). Rates of maternal obesity have increased in proportion to weight increases seen in the general population. The National Vital Statistics System reported that in 2015 maternal pre-pregnancy obesity rates were greater than 25%, and rates of obesity in women aged 20-39 years is more than 34%. The mechanisms by which maternal obesity leads to neurodevelopmental disorders in the offspring remains unclear but recent research has found that changes in inflammatory cytokines may be a contributing factor. Increases in the cytokine interleukin (IL)-6 has been shown to be required for the behavioral deficits seen in offspring born to mice with an activated immune system. One of the ways that IL-6 could modulate neurodevelopment may be through the maternal microbiome. Recent evidence has shown that following maternal immune activation, neurodevelopmental disorders in offspring result from microbiome-induced increases in IL-17 that is mediated, in part, by IL-6. To address the role of IL-6 in neurodevelopmental deficits seen in maternal obesity we used IL-6 knockout (KO) mice exposed to a high-fat diet to better understand the role of IL-6 and gut microbiota in mouse fetal brain development. Preliminary results show that there is a decrease in the relative abundance of Firmicutes to Bacteroidetes for IL-6 KO mice in the pre-pregnancy and post-pregnancy stages. These decreases were not seen in the C56BL/6 mice. Analyses are ongoing, we will characterize changes to the gut microflora during pregnancy by 16S rRNA gene sequencing for bacterial identification. By comparing the gut microbiome with the absence of IL-6 and increase or decrease in other inflammatory cytokines, we will help delineate the association of maternal IL-6 and neurodevelopmental abnormalities in offspring.

Disclosures: V. Peña-Garcia: None. **A. Oyetunde:** None. **B. Teng:** None. **D. Banner:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

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Program #/Poster #: 457.15/B13

Topic: A.07. Developmental Disorders

Support: NIH/NIGMS COBRE: The Delaware Center for Neuroscience Research Grant 1P20GM103653-01A1 to AYK

Title: State of cholinergic neurons in the nucleus basalis of meynert (NBM) of adult rats following alcohol exposure during the brain growth spurt (PD 4-9)

Authors: *K. MILBOCKER, Z. H. GURSKY, A. Y. KLINTSOVA
Univ. of Delaware, Newark, DE

Abstract: Prenatal alcohol exposure is known to impact CNS development in humans and rodents, resulting in neurocognitive deficits associated with learning and memory. A period of substantial brain maturation, the brain growth spurt occurs prenatally in humans during the last trimester of pregnancy (Dobbing & Sands, 1979) and during the first two postnatal weeks in rodents (Bonthius & West, 1990). Previous studies suggest that cholinergic neurons in the forebrain-cortical circuitry could be a target in prenatal alcohol exposure leading to alterations in the innervation of the cortex and resulting in behavioral deficits in executive functioning tasks and object recognition (Robinson-Drummer et al. 2017; Kleiber et al. 2014). Our study examines the long-term effects of binge-like alcohol exposure (AE) during the brain growth spurt in a rat model of Fetal Alcohol Spectrum Disorders (FASD) on cholinergic cell number and soma volume in the NBM, as well as the overall volume of the NBM. On PD 4-9, Long-Evans rats were exposed to ethanol (5.25 g/kg/day) via intragastric intubation twice a day in milk substitute. Two control groups were sham-intubated (SI) rats that were not given any liquids and suckle-control (SC) rats. Rats were weaned and housed in same-sex groups of three at PD23. Animals were sacrificed on PD72 and forebrain tissue was collected and sectioned horizontally at 40 µm. An immunohistochemical staining of cholinergic neurons was performed on every eighth section using anti-choline acetyltransferase (ChAT) antibody. Unbiased stereology was used to estimate the total number of ChAT+ neurons in the NBM and their volumes. A one-way ANOVA was conducted to compare the effect of neonatal binge-like AE on cholinergic cell count and soma volume. A similar analysis was used to measure the effect of treatment on structural volume of the NBM. There was no significant main effect of alcohol exposure on ChAT+ cell number and NBM volume ($F(2, 9) = 0.696$, $p=0.524$ and $F(2, 9) = 0.816$, $p=0.472$; respectively). However, we did observe a main effect of treatment on the soma volume of ChAT+ neurons when comparing AE animals to SC ($F(2, 9) = 6.867$, $p=0.016$) which suggests an increase in NBM cholinergic neuronal volume following alcohol exposure during the brain growth spurt. To check the hypothesis that density of cholinergic projections from NBM to the cortex is also increased in AE animals, we are using an unbiased stereological estimate of the axonal number and length. It is shown that alcohol exposure during the brain growth spurt alters the central cholinergic system in a rat model of FASD which may result in deficits of higher order cognition.

Disclosures: K. Milbocker: None. **Z.H. Gursky:** None. **A.Y. Klintsova:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 457.16/B14

Topic: A.07. Developmental Disorders

Support: NIH Grant R01 AA012446
NIH Grant R01 AA022460

NIH Grant R37 AA007789

Title: Choline alters hippocampal development: Implications for the treatment of fetal alcohol spectrum disorders

Authors: *K. R. BREIT[1], T. S. BODNAR[3], J. WEINBERG[4], J. D. THOMAS[2]
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Abstract: Prenatal alcohol exposure disrupts development, leading to a variety of behavioral and cognitive problems, referred to as fetal alcohol spectrum disorders (FASD). Some behavioral problems depend on the functional integrity of the hippocampus, a brain area vulnerable to alcohol's teratogenic effects. Supplementation with the essential nutrient choline can reduce the severity of behavioral deficits associated with prenatal alcohol exposure. Specifically, choline can improve performance on tasks that depend on hippocampal function, even when administered after alcohol exposure has ceased. Consistent with behavioral improvements, we have found that early postnatal choline supplementation can alter hippocampal structure and function, including cholinergic functioning, DNA methylation and neurotrophic factors. Recently, we found that choline mitigates ethanol-related increases in ceramide, which may suggest that choline protects against neuroinflammation. In fact, the hippocampus has the highest density of cytokine receptors in the brain. The present study examined whether choline modifies immune function in the hippocampus of subjects exposed to alcohol during early development. Sprague-Dawley rats were intubated with either 5.25 g/kg/day alcohol or sham intubated from postnatal days (PD) 4-9, a brain development period equivalent to the human third trimester of pregnancy. Subjects were then injected with either 100 mg/kg/day of choline chloride or saline from PD 10-30. Thus, this study included a 2 (ethanol, sham) x 2 (choline, vehicle) x 2 (male, female) design with n's 9/group. Hippocampal tissue was dissected on PD 35 and cytokine levels measured using the Meso Scale Discovery proinflammatory panel. Choline reduced levels of the anti-inflammatory cytokines IL-4 and IL-10 in males, and IL-5 in males and females, in both alcohol-exposed and control subjects. These data suggest that choline may modify neuroimmune function in the hippocampus. Although alcohol did not alter cytokine levels, further studies are required to determine if choline protects against alcohol-related increases in cytokines during immune challenges. These data suggest that choline may protect against alcohol-related damage, in part, by altering neuroimmune function, findings that have important implications as choline is explored as a treatment for fetal alcohol spectrum disorders.

Disclosures: T.S. Bodnar: None. **J. Weinberg:** None. **J.D. Thomas:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 457.17/B15

Topic: A.07. Developmental Disorders

Support: NIH Grant 5R01NS088378

Title: A mouse model of X-linked intellectual disability protein PHF6 associated with impaired neuronal maturation

Authors: *C. CHENG[1], P.-Y. DENG[1], C. YUEDE[1], Y. IKEUCHI[2], N. RENSING[1], D. LI[1], J. HUANG[1], T. WANG[1], M. WONG[1], D. WOZNIAK[1], V. KLYACHKO[1], A. BONNI[1]
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Abstract: Mutations in PHF6 are implicated in Börjeson-Forssman-Lehmann syndrome (BFLS), an X-linked intellectual disability (XLID) characterized by mental impairment, developmental delay and seizures. However, the mechanisms by which mutations of PHF6 contribute to the pathogenesis of BFLS remain poorly understood. Here, we report a novel patient-specific PHF6 mutation mouse of BFLS. PHF6 C99F knock-in mice display deficits in memory and adaptive behaviors as well as reduced threshold to seizures. Electrophysiological studies reveal increased neuronal intrinsic excitability, providing a basis for susceptibility of BFLS mice to seizures. Transcriptomic analysis of the cerebral cortex in C99F knock-in mice and PHF6 knockout mice show that PHF6 promotes the expression of neurogenesis genes and concomitantly suppresses the expression of synaptic genes. Remarkably, PHF6-regulated genes overlap with autism spectrum genes and autism-regulated gene modules. These findings advance our understanding of BFLS pathogenesis and offer new links between BFLS and autism spectrum disorders.

Disclosures: C. Cheng: None. **P. Deng:** None. **C. Yuede:** None. **Y. Ikeuchi:** None. **N. Rensing:** None. **D. Li:** None. **J. Huang:** None. **T. Wang:** None. **M. Wong:** None. **D. Wozniak:** None. **V. Klyachko:** None. **A. Bonni:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 457.18/B16

Topic: A.07. Developmental Disorders

Support: Department of Anatomy postgraduate funds

Title: Long term effects of binge alcohol exposure during development on the cingulate cortex. Cell numbers and preliminary investigations using serial block face scanning electron microscopy

Authors: *R. M. NAPPER, H. KIM, P. SHOEMACK, C. JONES
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Abstract: Background: Binge drinking during pregnancy can result in permanent brain damage and brain dysfunction without external markers of damage. Animal studies have shown that the cingulate cortex (CgC), important in a range of cognitive skills, suffers acute cell death but we have little information on whether this results in long-term cell deficits or changes in synaptic interactions. This study investigated the acute and long-term effects of a single ethanol binge on total cell number in the CgC. We also undertook preliminary investigations of the morphology of synapses in the superficial CgC layers using serial block face scanning electron microscopy (SBF-SEM). Methods: Long-Evans rat pups were exposed to either alcohol (E) at a daily dose of 6.0g/kg ethanol via intubation as two feeds two hours apart, or a sham intubation (IC) on PN6. The brains were studied either 12 hours post ethanol (apoptotic cell death) or when adult (permanent cell number). Animals were perfused and brain tissue processed for light and electron microscopic studies. The optical fractionator method was used to estimate the total number of apoptotic cells (PN6) or neurons (adult) within the cingulate cortex. SBF-SEM was used to quantify aspects of synaptic connectivity. Results: On PN6, alcohol exposed animals had significantly more apoptotic cells within the CgC than controls ($P = 0.0029$): the total number of apoptotic cells in the CgC was 6,518 (±11,326) in IC (n=7) and 64,523 (±43,098) in AE (n=5) (mean±sd). There was a significant effect of location on acute cell death, with the upper CgC showing a significantly more apoptotic cells than the lower zone ($P < 0.0001$). There was a permanent deficit of neurons in the adult CgC, AE < IC ($P < 0.01$). The effect of neuronal loss on the synapses in upper cell layers of CgC was determined by 3D reconstruction of images from SBF-SEM stacks. Discussion: This study shows that the rat cingulate cortex exhibits long-term neuronal deficits following a single binge ethanol exposure and due to the complex networks within which the CgC is involved, this will impact on function. The SBF-SEM data provides an indication of how the brain synaptic connectivity is adjusted to accommodate developmental cell loss. This indicates that a single binge drinking episode during late pregnancy may result in a long-term change in brain structure and must be considered when the risks of drinking in pregnancy are assessed. It also shows that SBF-SEM is a valuable tool in understanding how cell loss contributes to brain dysfunction.

Disclosures: R.M. Napper: None. **H. Kim:** None. **P. Shoemack:** None. **C. Jones:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 457.19/B17

Topic: A.07. Developmental Disorders

Support: AA025425

Title: Developmental cannabinoid exposure alters the effects of early alcohol exposure on behavioral development

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Abstract: Cannabis is the most commonly used illicit drug among pregnant women, and over half of pregnant women who report cannabis use also consume alcohol. Prenatal alcohol exposure, by itself, can lead to fetal alcohol spectrum disorders, including a variety of behavioral deficits; however, the consequences of combined prenatal alcohol and cannabis exposure on fetal development are not well understood. Using the cannabinoid receptor agonist CP-55,940 (CP), the current study examined behavioral development following exposure to CP and/or ethanol (EtOH) during postnatal days (PD) 4-9, a period of brain development equivalent to the human 3rd trimester. Sprague-Dawley rat pups received CP (0.4 mg/kg/day, i.p.) or vehicle, as well as EtOH (5.25g/kg/day) or sham intubation, utilizing a 2 (CP, Vehicle) x 2 (EtOH, Sham) x 2 (male, female) design. Peak blood alcohol concentrations (BAC) were analyzed (PD 6) to examine if CP altered blood alcohol levels during exposure. Following CP and/or EtOH exposure, all subjects performed a battery of behavioral tasks examining motor development (grip strength and hindlimb coordination, PD 12-20), motor coordination (parallel bar motor balance and coordination, PD 30-32), activity levels (open field, PD 18-21), and spatial learning (Morris water maze, PD 40-47). Developmental CP exposure exacerbated ethanol-related mortality, reductions in body growth and increased peak BAC levels. Motor development was advanced by CP exposure yet delayed by EtOH exposure, and performance of subjects exposed to the combination of CP and EtOH was intermediate. However, long-term motor coordination was not altered by developmental CP exposure, although CP exposure exacerbated long-lasting motor impairments related to EtOH exposure, specifically in females. Separately, both CP and EtOH exposure increased activity levels in the open field, but the combination produced more severe impairments in habituation than either exposure alone. Lastly, while only development EtOH exposure impaired spatial learning, both EtOH and CP independently increased thigmotaxis in the Morris water maze, with more severe increases observed following combined exposure. Thus, developmental exposure to CP or EtOH disrupted behavioral development in

unique ways, but the combination produced the most severe effects within specific behavioral domains. Importantly, these data suggest that prenatal cannabis exposure disrupts development and that effects may be more severe when combined with alcohol, which has important implications for public health policy.

Disclosures: C. Rodriguez: None. **K.R. Breit:** None. **J.D. Thomas:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 457.21/B19

Topic: A.07. Developmental Disorders

Support: NIH R01
LouLou Foundation Grant
IFCR Grant
NIH NRSA F31

Title: Modeling CDKL5 disorder in mice

Authors: *B. TERZIC, S. TANG, I.-T. WANG, K. SIZOV, Y. CUI, Z. ZHOU
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Mutations in the X-linked gene encoding cyclin-dependent kinase-like 5 (CDKL5) cause the childhood epileptic encephalopathy known as CDKL5 disorder. The disease is characterized by a heterogeneous array of clinical symptoms including early-onset seizures, and severe cognitive and motor disability. There has been a steady increase in the rate of diagnoses each year, and mutations in *CDKL5* appear to be enriched in populations of patients with epilepsy or autism spectrum disorders. This suggests that the disorder may be more prominent than currently understood, and emphasizes the necessity of understanding the pathophysiology of CDKL5 in the aforementioned conditions. To determine the genetic causality of CDKL5 disorder, we generated the first *Cdkl5* knockout (KO) mouse and found that they mirror several hallmark symptoms of the human disease, including autistic-like behaviors, impaired motor control, and poor learning and memory. Given that CDKL5 is expressed in multiple tissues with the highest level in the forebrain, we next generated *Cdkl5* conditional KO mouse, ablating Cdkl5 expression predominantly from the central nervous system (Nestin-cKO). We found that these mice largely resemble *Cdkl5* constitutive KO mice, supporting the theory that CDKL5 disorder is caused by CDKL5 dysfunction within the nervous system. Our recently developed knock-in mouse modeled after a patient missense mutation, R59X, also manifests several of the phenotypes observed in *Cdkl5* KO mice, providing us with a reliable proxy to identify pathogenic mechanisms underlying CDKL5 disorder. Currently, we have expanded our genetic

approach to dissect the function of CDKL5 in different cell types in the brain, and to identify the signal transduction pathways regulated by CDKL5, particularly with regards to synapse development and function. These studies will be critical for the development of more targeted therapeutics for patients.

Disclosures: B. Terzic: None. **S. Tang:** None. **I. Wang:** None. **K. Sizov:** None. **Y. Cui:** None. **Z. Zhou:** None.

Poster

457. Developmental Disorders: Animal Models of Neurodevelopmental Disease II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 457.22/B20

Topic: A.07. Developmental Disorders

Support: Duke University Superfund Research Center (ES010356)

Title: Behavioral consequences of retinoid disruption during embryonic development in the zebrafish

Authors: *A. B. HAWKEY[1], C. L. DEAN[1], S. KULLMAN[2], E. D. LEVIN[1]
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Abstract: A variety of environmental contaminants are known to cause neurobehavioral toxicity after developmental exposure(s), although more work is needed to define the relevant adverse outcome pathways. Our previous work with the zebrafish model suggest the importance of retinoic acid (RA) signaling in neurodevelopment and behavioral impairment, offering one such mechanism for linking neurotoxic chemical exposures to disruptions in brain development and behavioral dysfunction. We have previously shown that embryonic excess of vitamin A (retinol) or exposure to valproic acid (VPA) which disrupts RA, alters behavioral function in larval zebrafish and into adulthood. Recent screening of TOX21 compounds has identified a number of chemicals that have the potential to transactivate the retinoic acid receptor, including select pesticides. However, additional work is needed to link their putative retinoid activity to relevant adverse behavioral outcomes. The present study measured the behavioral effects of embryonic exposure to these compounds using the larval motility assay. Zebrafish embryos were exposed to vehicle (DMSO), chlorothalonil (CTN, 10-100μM), imazalil (IMZ, 0.1-1μM) or buprofezin (BPF, 0.3-3μM) from 5-120 hours post-fertilization (hpf). Doses were selected to fall below the threshold for overt dysmorphogenesis or toxicity. Larval motility was assessed at 144hpf. This testing consisted of 10 minutes acclimation in the dark followed by two alternating light and dark phases at 10 min each. For each of the three compounds, the highest dose reduced locomotor activity. For CTN and IMZ, this pattern appeared under both lit and dark conditions. For CTN,

this pattern was limited to dark conditions. At lower doses, the pattern was more unique for each compound. The lowest dose of CTN reduced activity, but only during the dark phases, as with the highest dose. IMZ, by contrast, showed a non-monotonic dose-response function, whereby the lowest dose produced locomotor hyperactivity rather than hypoactivity under both lit and dark conditions. The present data show that compounds with retinoid activity dose-dependently alter larval activity. To complete this analysis, future tests in adulthood will assess locomotor, affective and cognitive functions following these embryonic exposures. This work was supported by the Duke University Superfund Research Center (ES010356).

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Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.01/B21

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

Support: Rockefeller University Graduate Student Fellowship
New York Neuroscience Foundation

Title: Glutamatergic hindbrain and motor neurons develop different patterns of network activity *in vitro*

Authors: *A. BUBNYS[1], H. KANDEL[1], G. N. REEKE[3], L.-M. KOW[1], D. W. PFAFF[3], I. TABANSKY[2]
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Abstract: Multielectrode arrays (MEAs) are emerging as powerful tools for studying the development and dynamics of neuronal networks noninvasively over weeks and months. One prominent feature of neurons cultured on MEAs is the development of robust network bursts that recruit many recording electrodes and may persist over many months. This kind of activity has been detected in cultures of cortical, hippocampal, and motor neurons, among others. However, the mixed excitatory/inhibitory nature of these cultures has made dissecting the neuronal components that contribute to network bursts challenging. We have developed a system to culture homogeneous populations of murine excitatory spinal motor neurons derived from a GFP reporter cell line and primary hindbrain V2a neurons developmentally expressing the transcription factor Chx10 on MEAs for up to 30 days using flow cytometry to separate the cell types of interest on the basis of fluorescent reporter expression. Both glutamatergic cell types were able to generate spontaneous bursts in the absence of inhibitory interneurons when cultured on a layer of astrocytes. However, these bursts were qualitatively different between cell types.

The motor neurons developed tonic spiking that sometimes organized itself into bursts, while the V2a hindbrain neurons developed very strong network bursts that generated signals sufficient to deflect the MEA recording channel baselines over a timescale of seconds. These results indicate that spinal motor and V2a hindbrain neurons are able to generate network bursts in the absence of inhibitory interneurons and that cell type determines network burst morphology and dynamics. The tendency of V2a hindbrain neurons to generate such robust network bursts supports their hypothesized role as the pacemaker neurons required for regulating respiratory rhythm in newborn mice.

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Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.02/B22

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

Title: Promoter capture Hi-C reveals the genome-wide chromatin interactome and Zic1/4 cis-regulatory elements in cerebellar granule cell precursors

Authors: *K. L. RIEGMAN[1], C. GEORGE[2], R. KADO[1], C. MOHAN[1], B. J. P. HUNTLY[3], D. SIMS[2], C. OSBORNE[1], M. A. BASSON[1]
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Abstract: Cerebellar granule cells are the most numerous neuronal subtype. Granule cell development follows a strict temporal schedule to coordinate the development of the granule cell progenitor (GCp) pool that underlies the vast expansion and foliation of the cerebellar structure. The gene-regulatory mechanisms that control GCp development remain incompletely understood. Chromatin conformation capture techniques may provide insight into long-range gene-regulatory mechanisms as they provide information on the physical proximity of DNA sequences in the nucleus. To identify *cis*-regulatory elements that may control cerebellar growth, we performed Promoter Capture Hi-C (PCHi-C) in undifferentiated, proliferating mouse GCps. This approach identified ±80,000 promoter interacting regions (PIRs) of >18,000 gene promoters. PIRs were further characterized by a combination of ATAC-seq and ChIP-seq to identify active regulatory elements. These analyses identified approximately 19,000 PIRs as putative enhancer elements that harbour the histone modification mark H3K4me1. Of these, 4,200 appear to be ‘active’ as they were accessible, as determined by ATAC-seq, and also marked by H3K27ac. Interestingly, *Zic1/4* had several of the most statistically significant PIRs among the ±80,000 identified in our data-set. *Zic1* and *Zic4* are known to be essential for the

proliferation of GCps and also remain expressed in differentiated GCs. *Zic1/4* mutation or heterozygous deletion is responsible for Dandy-Walker malformation, a syndrome characterized by cerebellar hypoplasia. Yet, how *Zic1/4* expression is regulated in GCps is not understood. *In vitro* luciferase assays confirmed that some of these *Zic1/4* PIRs are capable of 'enhancer-like' activities. Further validation is in progress. Together, these findings provide mechanistic insights into the complex nature of *Zic1/4* gene regulation in GCps.

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Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.03/B23

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

Support: CCXDP grant
NINDS grant

Title: Nr4a1 promotes maturation of striatal striosome neurons and regulates the dopamine D1 receptor signaling pathway

Authors: *M. D. CIRNARU[1], C. MELIS[1], T. FANUTZA[1], S. NAPHADE[2], B. S. MUNTEAN[3], K. MARTEMYANOV[3], L. M. ELLERBY[2], M. E. EHRLICH[1]
[1]Neurol., Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]The Buck Inst. for Res. on Aging, Novato, CA; [3]Neurosci., The Scripps Res. Inst., Jupiter, FL

Abstract: The GABAergic medium-sized spiny neuron (MSN), the striatal output neuron, may be classified into striosome, i.e. patch, and matrix, based on neurochemical differences between the two compartments. The patches comprise ~15% of the striatal volume, receive limbic inputs and contain D1 and D2 dopamine receptor direct and indirect pathway MSNs. Striosome MSNs express the mu opioid receptor (*OPRM1*), substance P (SP), calretinin, and the transcription factor Nr4a1 (nuclear receptor subfamily 4, group A, member1). Activity imbalance between striosomes and matrix is hypothesized to contribute to several movement disorders, including dystonia and levodopa-induced dyskinesias, but little is known regarding the developmental regulation of the two compartments. Nr4a1 function has been studied primarily in its role as an immediate early gene. In the *Nr4a1*-null mouse, multiple aspects of the dopamine (DA) system are dysregulated, including turnover and response to DA degeneration. We sought to determine the effects of Nr4a1 genetic, constitutive overexpression and knockout in the development and function of the MSN dopaminoceptive system. Using the Nr4a1-EGFP (GENSAT) which has 2X normal *Nr4a1* mRNA and the *Nr4a1*-null (JAX Nr4a1tm1Jm1) mouse lines, and *in vitro* viral

transduction in primary striatal neurons and differentiated iPSCs, we sought to determine whether Nr4a1 is necessary and/or sufficient for striosome development. In the presence of *Nr4a1* overexpression *in vivo*, we also examined the integrity of the striatal dopaminoceptive system, MSN excitability and plasticity, and locomotor and signal transduction response to acute and chronic cocaine. In the absence of *Nr4a1*, *Oprm1* mRNA is decreased, as are the number and size of Nr4a1-identified striososmes. With *Nr4a1* overexpression, *Oprm1* mRNA increases *in vivo*, in primary striatal neurons, and in differentiated iPSCs. Locomotor response to acute cocaine (20 mg/kg, ip) is normal but induction of pERK is diminished, as is sensitization to chronic cocaine. Moreover, *Nr4a1* overexpression reduces long-term potentiation (LTP) and dysregulates multiple mRNAs of the dopaminoceptive signal transduction system. In the resting state, the adenylyl cyclase V (AC5) system is not perturbed, but the ability of AC5 to be activated by D1R and adenosine A2A receptor (A2AR) GPCR inputs in direct and indirect MSNs is diminished. **Conclusion:** Our results indicate that Nr4a1 promotes the maturation of the striatal patch medium spiny neurons and its constitutive overexpression alters the D1 receptor signaling pathway.

Disclosures: M.D. Cirnaru: None. **C. Melis:** None. **T. Fanutza:** None. **S. Naphade:** None. **B.S. Muntean:** None. **K. Martemyanov:** None. **L.M. Ellerby:** None. **M.E. Ehrlich:** None.

Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.04/B24

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

Title: Proper spatiotemporal formation of the striatal direct pathway is required for appropriate formation of corticofugal axon trajectories

Authors: *J. M. EHRMAN[1,2], P. MERCHAN-SALA[1], B. CHEN[3], K. CAMPBELL[1]
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Abstract: The striatum is the principle output nucleus of the basal ganglia; a group of subcortical nuclei best known for their role in regulating voluntary movement. Recent studies show that they also contribute to aspects of cognitive and social behavior. Malformed or malfunctioning striatal circuitry is therefore implicated in the motor, social, and cognitive deficits characteristic of several neuropsychiatric diseases of childhood, such as obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, and autism. The axons of the striatal direct pathway and descending corticofugal axonal trajectories form in close proximity to each other from mid to late gestation, suggesting that signaling between these pathways may

help to guide their outgrowth. However, the interdependence of these two axonal pathways during development remains unclear. Using murine BAC transgenic reporter lines that mark the developing striatal direct pathway (Sox8-GFP) and corticofugal pathway (Fezf2-tdTomato) we are examining the spatiotemporal relationships between these two pathways at several embryonic timepoints. Combining these reporters with genetic manipulations of these pathways allows us to interrogate their dependence upon one another for proper formation. Selective disruption of direct pathway axon outgrowth, as observed in Sox8 knockout (KO) mice, leads to mistargeting of the corticofugal pathway axons. Conversely, our preliminary findings indicate that disruption of the corticofugal pathway, as seen in Fezf2 KO mice, does not appear to disrupt striatal direct pathway formation. Thus, we hypothesize that axons of the direct pathway are required for the proper guidance of the descending corticofugal trajectories though the diencephalon and midbrain during early circuit formation. Our findings suggest an avenue by which disruptions in striatal direct pathway formation can impair the normal development of corticofugal circuitry and contribute to the motor deficits seen in childhood brain disorders.

Disclosures: J.M. Ehrman: None. **P. Merchan-Sala:** None. **B. Chen:** None. **K. Campbell:** None.

Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.05/B25

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

Support: Cal-PT Fund Research Grant

Title: Variability of leg movements across seven days during early infancy

Authors: *W. DENG, B. A. SMITH
Div. of Biokinesiology and Physical Therapy, USC, Los Angeles, CA

Abstract: Background: Infants with or at risk of developmental disabilities tend to have different movement patterns and characteristics. Early intervention aims to provide beneficial motor experience for infants at risk and promote neuromotor development. To detect infants' typical movements patterns in the natural environment, we are using wearable sensors to measure the characteristics of leg movements infants produce across days and relate movement experience to skill development.
Purpose: To determine whether one day is sufficient to represent an infant's typical performance, or more days are needed.
Methods: We used wearable sensors to collect 7 consecutive days of full-day leg movement activity, 7-13 hours per day, from 10 infants with typical development between the ages of 1-5

months. We identified each leg movement's average acceleration, peak acceleration and duration.
Results: Absolute difference between the average of first two days and the standards (average of seven days) of average acceleration, peak acceleration and duration dropped below 5% of the standard(3.8%, 4.4% and 3.3%). Wilcoxon signed rank test shows there is no significant different between the average of first two days and standards across all measurements (p=0.51, 0.80, 0.88).
Conclusions: The variability of leg movement kinematic data across seven days is visually within a limited range in infants with typical development. The results suggest it is better to collect data for two consecutive days. Our results will inform the clinical measurement of full-day infant leg movement for neuromotor assessment and outcome measurement purposes.
Research Supported by: Cal-PT Fund Research Grant (PI: Smith).

Disclosures: W. Deng: None. **B.A. Smith:** None.

Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.06/DP01/B26

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

Support: NINDS K08NS099502
Project ALS
NIGMS, 5-T32-GM007748
NHLBI, 5-T32-HL007627

Title: Genetic mapping of diversity among developing brainstem motor neuron subtypes at single cell resolution

Authors: *M. F. ROSE[1], A. GELBER[2], M. A. TISCHFIELD[2], A. P. TENNEY[2], A. N. COWAN[2,3], A. A. NUGENT[2], P. ANG[2], S. IZEN[2], M. R. BAUER[2], W. HUANG[2], R. SATIJA[4], O. ROZENBLATT-ROSEN[5], A. REGEV[5], E. C. ENGLE[2]
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Abstract: The brainstem ocular motor neurons (OMNs) mediate eye movements and are differentially affected compared with other motor neuron (MN) groups in some disorders. Specific subsets of OMNs show disrupted or aberrant innervation in congenital cranial dysinnervation disorders (CCDDs). In contrast, OMNs continue to function in Amyotrophic Lateral Sclerosis (ALS), while spinal and other brainstem MNs degenerate. We aim to define the unique developmental gene expression patterns among OMNs, and generate a toolbox of genetic

markers to help study these disorders. We first used Islet-1:GFP and Hb9:GFP mice to isolate and compare seven distinct MN pools on embryonic days E10.5 and E11.5, via microdissection and fluorescence-activated cell sorting (FACS): the three ocular motor nuclei (CN3, CN4, CN6) and the other primary MN types (CN5, CN7, and CN9/10/12 in the brainstem, and spinal cord MNs). Pooled RNA-seq analysis was performed on each with Genesifter and DESeq2. Second, we evaluated the subpopulations within CN3, CN4, and CN6 across their embryonic development time course (E9.5 to E18.5) with single cell RNA-seq and the SEURAT analysis package. Gene expression was validated with database analysis and in situ hybridization. We co-labeled for BrdU/EdU after injection on different developmental days (E8.5-E11.5) to correlate the gene expression differences with cell age. Each MN population showed unique gene expression patterns, including novel markers of OMNs, providing a genetic fingerprint of developing MNs for future studies. Spatially- and temporally-distinct subpopulations were identified within the ocular motor nuclei, including a late-born caudal CN3 population that crosses the midline and may give rise to the superior division of the oculomotor nerve, selectively affected in some CCDDs. These data uncover distinct developmental gene expression patterns and markers of the various cranial motor neurons and provide new tools to study their selective vulnerability in the CCDDs.

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

Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.07/B27

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

Support: NINDS R01 NS089585 (NIH)
NIDCD R01 DC015799 (NIH)

Title: Examination of intrinsic and extrinsic programmed cell death in the superior cervical ganglion

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Abstract: During development, as many as half of all neurons produced in the peripheral nervous system undergo apoptosis. It is well established that competition for neurotrophic factors secreted by targets of innervation results in the death of unnecessary neurons during defined

developmental periods of programmed cell death (PCD). An extensive amount of research on the molecular mechanisms underpinning PCD has been performed on sympathetic neurons of the superior cervical ganglion (SCG) of mice and rats. The SCG is composed of neurons that are noradrenergic, express TrkA, and require NGF for target-dependent survival. The vast majority of PCD studies in the SCG examined total cell counts as a measure of PCD, concluding that cell death occurs between embryonic day 19.5 (E19.5) to postnatal day 3 (P3) in mice. However, to what extent these total cell counts compare to direct measurements of apoptotic neurons *in vivo* has not been well characterized. In this study we intend to establish a detailed time course of PCD, as well as neurogenesis, in the SCG. In C57/bl6j mice, we are counting tyrosine hydroxylase (TH) positive cells to measure the total number of neurons in the SCG, in addition to quantifying the number of apoptotic and mitotic neurons by measuring the number of cleaved caspase-3 (CC3) and Ki67 labeled neurons, respectively. These measurements will be performed from shortly after the SCG has fully coalesced at E17.5 through adulthood. Surprisingly, there is an extensive amount of PCD embryonically before the reported decline in SCG neurons, and a significant amount of apoptosis continues to occur postnatally after what is traditionally thought of as the period of PCD. Interestingly, neurogenesis continues into postnatal ages, potentially obscuring the total neuronal cell loss that has been reported in other studies. More recent investigations of SCG developmental cell death have pointed to the role of pro-apoptotic receptor mechanisms, raising the possibility that PCD occurs via both intrinsic pathways typically thought to underlie apoptosis through loss of trophic factor support, as well as extrinsic apoptotic cascades regulated by death receptors. By examining caspase-8, caspase-9 and Bax mutant mice as described above, we are determining to what extent intrinsic and extrinsic death pathways contribute to PCD in the SCG. Taken together, by utilizing multiple strains of mutant mice with cellular markers for PCD and neurogenesis, we will define the period of PCD in SCG neurons and build an understanding of how intrinsic and extrinsic mechanisms sculpt sympathetic neural circuits.

Disclosures: C.L. Kaminski: None. **L.B. Schmidt:** None. **B.A. Pierchala:** None.

Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.08/B28

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

Support: NIH Grant R37-HD081168
NIH Grant F32-NS101858

Title: Functional divergence of sensory responses in developing sensory and motor cortex

Authors: *L. J. GOMEZ[1], J. C. DOOLEY[2], G. SOKOLOFF[2], M. S. BLUMBERG[2]
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Abstract: In adult rats, primary motor cortex (M1) and primary somatosensory cortex (S1) are functionally distinct cortical areas. However, M1's motor functions emerge late in development and both M1 and S1 function initially as sensory structures. Therefore, before adulthood, M1 and S1 must functionally diverge, but when and how this divergence occurs is unclear. Previous work from our lab has demonstrated that, through the first postnatal week, both M1 and S1 neurons preferentially respond to sensory feedback from myoclonic twitches generated during active (REM) sleep; in contrast, sensory feedback from wake movements is largely absent. By postnatal day (P) 12, M1 neurons preferentially respond to wake movements and fewer neurons respond to twitches. Less is known about the responses of S1 neurons to self-generated movements at P12. Given the similarity of sensory responses in M1 and S1 at P8, we hypothesized that M1 and S1 neurons will become preferentially wake responsive by P12; we further hypothesized that this transition marks the onset of functional divergence between these structures. To test these hypotheses, we conducted dual extracellular recordings at P8 and P12. We recorded multiunit activity from the forelimb representations of M1 and S1 and compared activity within and between these areas across ages. At P8, M1 and S1 neurons display similar activity profiles and respond preferentially to sensory feedback from myoclonic twitches. By P12, M1 and S1 now respond preferentially to wake movements, although a higher percentage of S1 neurons are responsive than M1 neurons. Thus, M1 and S1 begin to functionally diverge when the sensorimotor cortex transitions from being twitch responsive to wake responsive. Although the early sensory feedback from twitches plays a similar function in M1 and S1 development, differences in wake-movement responses reflect differences in the function of sensory feedback from wake movements in these two cortical areas.

Disclosures: L.J. Gomez: None. **J.C. Dooley:** None. **G. Sokoloff:** None. **M.S. Blumberg:** None.

Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.09/B29

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

Support: NIH Grant R01 NS078181

Title: Optical interrogation of V2a neurons reveals role in regulating cortical activity and sleep-wake behavior

Authors: *M. M. ISAAMULLAH[1], A. KUZHANDAIVEL[2], L. HOFFMAN[1], K. SHARMA[1]
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Abstract: In the developing mammalian neural tube, the V2a class of neurons is generated throughout the brainstem and spinal cord. Many studies have revealed that the primary function of these neurons is in patterning of motor behaviors such as breathing (Crone et al., 2012), reaching (Azim et al., 2014) and locomotion (Crone et al., 2009). In this report we show that optical stimulation of V2a neurons at the mid-hindbrain junction produces quantifiable changes in cortical oscillations. We find that brief (1min) stimulation of these neurons produces 3-7Hz oscillations in the prefrontal cortex (PFC). Similar slow oscillations in the medial PFC are known to correlate with freezing behavior (Karalis et al., 2016). Long term (8h) stimulation of the same V2a neurons promotes wakefulness that is sustained for days after stimulation. These experiments were performed in double transgenic mice (*chx10*$^{+/cre}$ *Rosa*$^{ChR2\text{-}GFP/+}$; p62-p106) expressing channelrhodopsin (ChR2) in V2a neurons with a sample size of 8 animals for each experiment. Littermate controls undergoing identical procedures and stimulation protocols but lacking ChR2 showed no cortical or behavioral response with optical stimulation at mid-hindbrain junction. This study is unique in its examination of cortical oscillations with optical stimulation of V2a at the mid-hindbrain junction. These findings suggest that V2a neurons at the mid-hindbrain junction can potentially mediate motor behaviors and wakefulness by modulating slow oscillations in the PFC.

Disclosures: M.M. Isaamullah: None. **A. Kuzhandaivel:** None. **L. Hoffman:** None. **K. Sharma:** None.

Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.10/B30

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

Support: UCR Complimentary Funds

Title: The racgap b-chimaerin is essential for cerebellar granule cell migration

Authors: *J. A. ESTEP[1], W. WONG[2], Y.-C. WONG[2], A. TAFT[2], M. RICCOMAGNO[2]
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Abstract: During mammalian cerebellar development, postnatal granule cell progenitors proliferate in the outer part of the External Granule Layer (EGL). Postmitotic granule progenitors

migrate tangentially in the inner EGL before switching to migrate radially inward, past the Purkinje Cell Layer, to achieve their final position in the mature Granule Cell Layer (GCL). Here, we show that the RacGAP b-chimaerin is expressed by a small population of late arriving, pre-migratory granule cells. b-chimaerin deficiency causes these cells to become arrested in the EGL, where they differentiate and form ectopic clusters of neurons. These clusters are mainly composed of granule cells and recruit aberrantly projecting mossy fibers. Collectively, these data suggest a role for b-chimaerin as an intracellular mediator of Cerebellar Granule Cell radial migration.

Disclosures: J.A. Estep: None. **W. Wong:** None. **Y. Wong:** None. **A. Taft:** None. **M. Riccomagno:** None.

Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.11/B31

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

Support: NIH Grant NS060123

Title: Characterization of cell type specific ATG14 deletion in mice reveals distinct functions of PI3KC3 activity in the nervous system via autophagy dependent and independent pathways

Authors: *K. PURTELL[1], M. PRUVOST[2], N. M. WADE[3], Z. YUE[1]
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Abstract: The class III phosphatidylinositol 3-kinase (PI3KC3) is required for macroautophagy, an essential lysosome-dependent degradation process that recycles large protein complexes and organelles to maintain cellular homeostasis. The catalytic subunit, VPS34, along with the scaffolding protein, VPS15 and the regulatory subunit, Beclin1 form the core complex which associates with either autophagy-related gene 14 (ATG14) or UVRAG in a mutually exclusive manner. ATG14-containing complexes are involved in autophagosome biogenesis whereas UVRAG-containing complexes are involved in vesicular trafficking. To investigate autophagy-specific functions of PI3KC3 in the brain, we knocked out ATG14 in neurons by crossing $ATG14^{flox/flox}$ mice with mice expressing Cre recombinase under the synapsin I promoter. This ATG14 conditional knock-out (CKO) resulted in a mixed neurodevelopmental and neurodegenerative phenotype characterized by developmental delay and motor dysfunction within 1 month, followed by progressive loss of motor function, hindlimb paralysis, seizures and early morbidity by 3 months of age. Neuron-specific ATG14 CKO animals have enlarged brains

and exhibit defective myelination of the corpus callosum. This is recapitulated in oligodendrocyte-specific ATG14 CKO mice, which points to a role for ATG14 in neuron-oligodendrocyte communication. In contrast to autophagy-deficient ATG7 CKO mice, ATG14 CKOs demonstrate a unique phenotype, which indicates a role for ATG14 outside the canonical autophagy pathway.

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Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.12/B32

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

Title: Infant leg movement activity intensity prior and post sleep throughout a week

Authors: *I. A. TRUJILLO PRIEGO[1], I. F. WERNER[4], W. DENG[2], B. A. SMITH[3]
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Abstract: ***Purpose/Hypothesis***
Movement activity in infancy is important to characterize as it allows infants to explore their movement repertoire, gain strength and improve their motor abilities. Young infants tend to produce frequent short bursts of high intensity leg movement activity when they are awake, interspersed with periods of napping. We hypothesized that infant leg movement activity intensity might be lower when infants are tired just before they fall asleep, followed by higher intensity post-sleep. Our purpose here was to characterize intensity of leg movement activity of infants with typical development prior and post sleep, across days.
Materials / Methods
Wearable sensor (Opals, APDM) data were collected in home from 10 infants with typical development (1 - 4 months of age) for 8-13 hours per day for 7 continuous days. Leg movements were identified as described in Smith et al. 2015. A custom made algorithm detected sleep events from the norm of tri-axial accelerometer and angular velocity time series. Events of sleep were defined as periods of time greater than 5 min with less than 3 leg movements. Once intervals of sleep were detected, periods of 20 min prior and post sleep were identified. Next, the resultant of acceleration of each 20 min period were calculated and low-pass filtered at a cutoff frequency of 9Hz. The absolute value of the filtered signal was used to calculate the area under the curve (AUC) for each 20 min period. Hence, AUC characterized leg movement activity intensity. All periods were visually checked for artefacts and manually corrected, leading to 234 total prior events out of 250 and 224 post events out of 237 taken into consideration for analysis. The median of the AUC of each day for each infant was calculated separately for prior and post sleep

events. AUC values were tested for normality. Repeated measures ANOVA (day, post to prior) was conducted to check for AUC differences with significance set at alpha =0.05.

Results

Repeated measures ANOVA revealed a trend towards higher intensity activity prior to sleep, $F(1,7) = 3.91$, $p = 0.089$, $\eta_p^2 = 0.358$. Eight of ten infants showed this phenomenon in the majority of days. Days showed no effect and no interaction, thus this trend was consistent throughout the 7 days of recording.

Conclusions

Preliminary results did not show a significant difference in intensity of leg movement activity before and after infant sleep periods across days. The observed trend in our results showed more vigorous activity prior to sleep, which was contrary to what we hypothesized. We will continue to analyze our data, and are also interested in expanding to other measures of fluctuation in leg movement activity across days.

Disclosures: I.A. Trujillo Priego: None. **I.F. Werner:** None. **W. Deng:** None. **B.A. Smith:** None.

Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.13/C1

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

Support: University of Louisiana at Lafayette GSO

Title: Inactivation of Fgfr1 and Fgfr2 in cerebellar glia

Authors: *L. RUBIN[1], A. PRUITT[2], K. M. SMITH[2]
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Abstract: Fibroblast growth factors (Fgfs) are a family of 22 cytokines that bind to 4 receptors, many of which play a critical role in cortical development. Fgf ligands, including Fgf2, and the Fgfr1 and Fgfr2 receptors are expressed by astrocytes and astrocytic stem cell lineages of the developing and adult CNS. Previous studies have shown that fgfrs can have compensatory effects on proliferation and development. We have inactivated Fgfr1 and Fgfr2 in postnatal astrocytes by tamoxifen inducible Cre mediated recombination using the hGFAP-CreERT2 (GCE) transgene. We targeted postnatal astrocytes by administering injections of tamoxifen from P14-17, 60 mg/kg i.p. We tested locomotor behavior of the mice for 30 minutes in an open field. Double KO mice showed hypoactivity compared to control littermates. This was not expected given previous findings with Fgfr1 single mutants. No differences in memory were observed in the 1-day morris water maze but observed mobility impairments. It was previously shown that

Fgfr1 and Fgfr2 double KO starting at E13.5 lead to multiple cerebellar abnormalities. We compared control and Fgfr1/Fgfr2 double KO mice on a hindlimb clasping test as well as a gait analysis. We found double KO mice had significantly higher scores on these test (p=.001) and a decreased number of PV+ purkinje neurons (p=.0245), indicating an impairment in motor coordination and altered cellular features. Future work will examine cerebellar morphology. We will compare the effects of Fgfr1 single and Fgfr1/Fgfr2 double mutants upon PV neuron maturation, and postnatal hippocampal proliferation.

Disclosures: L. Rubin: None. **A. Pruitt:** None. **K.M. Smith:** None.

Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.14/C2

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

RO1 EY025205
GM103650
GM103554
GM103440

Title: Oculomotor nerve requires an early interaction with muscle precursors for proper growth and branching pattern

Authors: *B. M. BJORKE[1], G. ROBINSON[2], K. WELLER[2], T. GOULD[3], P. J. GAGE[5], G. S. MASTICK[4]
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Abstract: Muscle function is dependent upon accurate motor nerve innervation. Motor nerves are composed of motor axons that innervate distinct muscle targets, yet travel in peripheral tissue as one compact nerve. A key transition point occurs during nerve development: following navigation through peripheral tissue, the fasciculated nerve halts further growth and initiates branching to innervate distinct muscle targets. The question of what guides this transition is particularly perplexing in nerves that do not interact with an apparent guidepost that directs the location of nerve targeting prior to branching. For the oculomotor nerve, targeting the eye muscles in embryonic mice, we discovered that a mass of muscle precursors acts to coordinate the nerve transitioning between nerve growth and accurate nerve branching. We find that the oculomotor nerve grows to the eye three days prior to the appearance of any eye muscles during which time it forms a plexus with muscle precursors. This plexus persists during primary

extraocular myogenesis.
To test the functional significance of the nerve-precursor plexus, we genetically ablated muscle precursors early in nerve development, prior to nerve contact. Muscle precursor ablation resulted in oculomotor nerve fibers failing to stop to form the plexus, but instead growing past the eye. In contrast, ablating the precursor pool at later stages, after the nerve has contacted the precursor cells, results in ectopic branching around the eye. These results demonstrate that muscle precursors are required for the oculomotor nerve to transition between nerve growth and distinct stages of terminal axon branching.

Disclosures: B.M. Bjorke: None. **G. Robinson:** None. **K. Weller:** None. **T. Gould:** None. **P.J. Gage:** None. **G.S. Mastick:** None.

Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.15/C3

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

Support: NIH-K07AT008027 ATR
UTRGV Institutional Research Support Program ATR and JLV

Title: Description and characterization of the developing and adult brain of the gray short-tailed opossum (Monodelphis domestica)

Authors: O. MALDONADO[1], *M. GIL[2,1], A. TORRES-REVERON[4], J. L. VANDEBERG[3], M. SCHWANZEL-FUKUDA[5], P. B. SAMOLLOW[6], B. FADEM[7], G. A. DE ERAUSQUIN[8,1]
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Abstract: *Monodelphis domestica* is a laboratory marsupial with unique advantages for neurodevelopmental studies over traditional models. At birth, *M. domestica* are developmentally similar to a 12.5-day old mouse embryo or 6-week old human embryo. The immaturity of the neonates makes this species an exceptional animal model for investigating high-risk events during embryonic development that may increase susceptibility to neurodevelopmental disorders like schizophrenia and autism spectrum disorder. However, there is little available

documentation of early brain development for this species. To address this gap in knowledge, we obtained sequential *M. domestica* brain preparations for anatomical studies during pre- and post-natal development. Here we present high-resolution images from Nissl-stained tissue sections of *M. domestica* brains throughout the lifespan: embryonic day 13.5, postnatal day (PND) 1, PND10, PND58 (weaned), PND149 (separated from siblings), and adult. Using image analysis software, we describe the general macroscopic and cytoarchitectural characteristics of different areas of the *M. domestica* brain across different developmental time periods. These descriptive findings open the door to use *M. domestica* as a novel model for studying environmental risk factors, such as influenza virus infections, that are linked to the subsequent development of schizophrenia.

Disclosures: O. Maldonado: None. **M. Gil:** None. **A. Torres-Reveron:** None. **J.L. VandeBerg:** None. **M. Schwanzel-Fukuda:** None. **P.B. Samollow:** None. **B. Fadem:** None. **G.A. De Erausquin:** None.

Poster

458. Development of Motor, Sensory, and Limbic Systems: Motor Systems

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 458.16/C4

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

Support: NIH Grant AT008027
UTRGV Institutional Research Support Rpogram

Title: Sensorimotor and memory assessment in zika virus inoculated monodelphis domestica (laboratory opossum)

Authors: *A. TORRES-REVERON[1], Y. VARGAS-GONZALEZ[2], L. RIVERA-LOPEZ[6], J. VANDEBERG[3], J. THOMAS[4], M. GIL[5], G. A. DE ERAUSQUIN[7]
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Abstract: The traditional animal models used for neurodevelopmental studies employ rodents. In contrast to rodents, opossums are born at a developmental stage equivalent to a human embryo at 6 weeks of gestation and continue developing extra-uterine, allowing for easy manipulations of the brain. In our previous studies, we characterized the behavior of normally developing pups to establish memory and motor coordination, as these are significantly affected by various

developmental pathologies. The goal of the current study is to assess the characteristic sensorimotor and memory modalities during early development in Zika-inoculated pups and to compare them with PBS-inoculated pups. We hypothesized that Zika-inoculated pups would display major deficiencies in cognitive and motor behaviors. Male and female opossums were inoculated intra-cranially with a Brazilian isolate of the Zika virus or PBS at 0 to 8post-natal days. The initial behavioral assessment was conducted at 4 weeks of age. Animals have been or will be tested using the following behavioral tests: Open Field (4-6 weeks), Object Recognition (8 weeks and 6 months), Rotarod (6 months), Barnes Maze (6 months) and Beam Balance (8 months), and behaviors are recorded and quantified using Any-maze software (Stoelting). Zika-inoculated pups did not show any gross anatomical abnormalities in head development. We have completed the Open Field test at 4 and 6 weeks of development. Exploratory behavior and locomotor activity have been measured by distance traveled, number of lines crossed, and overall time in the center of the arena. Results indicate that Zika-inoculated females have increased locomotor activity compared to Zika-inoculated males and to both sexes of PBS-inoculated pups. At 6 weeks, Zika-inoculated males and females spend, on average, half the amount of time in the center of the open field compared to PBS-inoculated males and females, suggesting increased anxiety-like behaviors. These data suggest that the virus affects different brain areas in males compared to females. The data obtained from this study will serve to examine the effects that prenatal infection with Zika virus can have on the central nervous system of infected subjects. We propose that the *M. domestica* can become a critical and unique model for assessing developmental abnormalities resulting from brain insults, such as Zika virus infection in the early stages of brain development.

Disclosures: Y. Vargas-Gonzalez: None. **L. Rivera-Lopez:** None. **J. VandeBerg:** None. **J. Thomas:** None. **M. Gil:** None. **G.A. De Erausquin:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 459.01/C5

Topic: B.03. G-Protein Coupled Receptors

Support: NCBS core funding
TIFR core funding

Title: Monoaminergic inputs to Mushroom Body (MB) output neurons extend flight bout durations in *Drosophila melanogaster*

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Abstract: Insect flight is a complex behaviour that requires the integration of multiple sensory inputs with the motor output. Flight defects can arise from either the inability to sense stimuli, from incorrect information processing in the interneurons or due to malfunctions in the motor output. Here we have studied a catecholaminergic circuit in the central brain, which helps maintain longer flight durations in *Drosophila melanogaster*. Longer flight durations are essential for reaching fresh sources of food, finding a mate and identifying suitable places for depositing eggs in the fly's natural environment. Independent studies previously have shown that *Drosophila* flight can be modulated by monoamines like octopamine, dopamine and serotonin as well as several neuropeptides. Both dopamine and octopamine (analogous to vertebrate norepinephrine) act as a neuromodulator as well as a neurotransmitter in invertebrates. Earlier we had shown that maintenance of flight for long durations requires the Protocerebral Anterior Medial (PAM) cluster of central dopaminergic neurons which project to MB[1]. Based on the contextual cues, dopaminergic inputs can modify MB output[2]. In this study, we try to understand the major octopaminergic and dopaminergic neurons that finally feed in to the MB and alter MB output to maintain long durations of flight. Using genetic tools to perturb neuronal activity, we identified subsets of central brain monoaminergic neurons required for flight. Acute perturbation of activity in MB output neurons, which receive inputs from specific dopaminergic neurons also resulted in decreased flight bout durations. Our data support a model where this octopaminergic-dopaminergic circuit feeding into the MB, help generate a contextually relevant flight motor output. In vertebrates, basal ganglia (BG) act as an action selection centre based on the inputs received from different regions of the brain, mainly the cortex[3]. Our studies suggest that MB can also act as a context dependent action selection centre like BG in addition to its role in learning and memory, which results in a contextually relevant motor output like longer flight durations.
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2. Cohn R, Morantte I, Ruta V. Coordinated and Compartmentalized Neuromodulation Shapes Sensory Processing in Drosophila. *Cell*. 2015;163(7):1742-1755. doi:10.1016/j.cell.2015.11.019
3. Stephenson-Jones M, Yu K, Ahrens S, et al. A basal ganglia circuit for evaluating action outcomes. *Nature*. 2016;539(7628):289-293. doi:10.1038/nature19845

Disclosures: S. B manjila: None. **M. Kuruvilla:** None. **J. Ferveur:** None. **S. Sane:** None. **G. Hasan:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 459.02/C6

Topic: B.03. G-Protein Coupled Receptors

Support: NHMRC Project Grant 1107088; “The Pharmacology and toxicity of synthetic cannabinoids”. CIA Professor Michael Kassiou, CIB Professor Iain McGregor, CIC Mark Connor ($744,807 Total, 2016-2018)

Title: *In vitro* determination of the CB1 efficacy of illicit synthetic cannabinoids

Authors: S. SACHDEV[1], K. VEMURI[2], S. BANISTER[3], M. KASSIOU[4], A. MAKRIYANNIS[2], *M. CONNOR[1]
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Abstract: BACKGROUND AND PURPOSE:
The rapid emergence of synthetic cannabinoids (SCs) as drugs of abuse poses a significant challenge to health care systems and policymakers worldwide. The morbidity and mortality associated with SC use highlights the need for a deeper understanding of the mechanisms underlying their toxicity. We have used a novel approach to determine the efficacy of SCs at CB1 receptors by using receptor depletion with the irreversible CB1 antagonist AM6544 and the Black and Leff operational model to calculate values of relative efficacy.
EXPERIMENTAL APPROACH:
Studies were carried out in mouse AtT20 neuroblastoma cells stably expressing human CB1. Receptor depletion was achieved following pre-treatment of cells with AM6544 (10 μM, 60 mins). We used membrane potential dye to measure CB1-mediated hyperpolarisation produced by activation of native G protein-gated K channels in the AtT20 cells. From the operational model, the efficacy (tau, or inverse of receptor occupancy needed to produce 50% of the maximal effect) and affinity (K_A) parameters were obtained for each drug.
RESULTS:
Pretreatment with AM6544 had no effect on the potency or maximal effect of native somatostatin receptor-induced hyperpolarization as compared to untreated cells (Control, pEC_{50} 9.13 ± 0.05, E_{max} 38 ± 1%; AM6544 treated pEC_{50} 9.18 ± 0.04, E_{max} 39 ± 0.7%). Pretreatment with AM6544 reduced the maximal response of the reference CB1 agonist CP 55,940 (6.43), which represents a loss of 94% of the receptors. In undepleted cells, CP55940 has a tau of 91, in comparison, the tau for THC was 1.33. The highest efficacy SC tested, 5F-MDMB-PICA, had a tau of 314. Interestingly, most of the SCs tested (JWH018, AM2201, WIN55,212, PB-22, 5F-PB-22, UR144, XLR11, AB-CHMINACA, AB-PINACA and 4 cyano-CUMYL-BUTINACA) had approximately 50 % of the efficacy of CP 55,940. However, there was no correlation between the affinity of SCs and their efficacy ($r^2 = 0.06$, $P > 0.05$), the SCs with highest affinity, 4 cyano-CUMYL-BUTINACA (pK_A 7.61) and AB-CHMINACA (pK_A 7.60) had tau of 45 and 42 respectively.
CONCLUSION AND IMPLICATIONS:
This study is the first to calculate the efficacy of wide range of SCs using Black and Leff operational model. We found that AM6544 did not interfere with SRIF receptors or their shared signalling pathways with CB1 reinforcing the idea that AM6544 is a specific, irreversible antagonist of CB1 receptor. There was no correlation between efficacy and affinity, or efficacy

and the emergence of SCs on the market. There was no obvious relationship between efficacy and reported toxicity of SCs, so toxicity could arise from yet unappreciated biased signalling or non-CB1 mediated effects.

Disclosures: S. Sachdev: None. **K. Vemuri:** None. **S. Banister:** None. **M. Kassiou:** None. **A. Makriyannis:** None. **M. Connor:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 459.03/C7

Topic: B.03. G-Protein Coupled Receptors

Support: AA26117
AA26551
AA17531
AA7565
AA022449

Title: Impairments in behavior and hippocampal synaptic function in the trace amine-associated receptor 2 knockout mouse

Authors: *A. G. ALMONTE[1], A. L. DEAL[2], J. K. KONSTANTOPOULOS[2], J. L. WEINER[1], E. A. BUDYGIN[2]
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Abstract: Trace amine-associated receptor 2 (TAAR2) is a member of a family of G-protein coupled receptors that are activated by a class of biogenic amines called trace amines, which are present at nanomolar concentrations in the brain and periphery. While previous work suggests that TAAR2 is expressed in olfactory sensory neurons and may function as a chemosensory receptor, little is known about TAAR2 expression and function in other brain areas. Here, we characterize a TAAR2 knockout mouse line in which the TAAR2 gene is deleted and replaced with a lacZ reporter. We show reporter expression in various brain regions, in particular the hippocampus. We also assessed a battery of behaviors and performed a screen of hippocampal neurophysiological function. We show that TAAR2 KO mice have increased locomotor activity in the open field arena, impaired performance in the novel object recognition task, and increased immobility time in the tail suspension task. Extracellular field potential recordings at hippocampal Schaffer collateral-CA1 synapses reveal differential effects of TAAR2 deletion along the dorsoventral axis. In the dorsal hippocampus, TAAR2 KO mice show normal baseline synaptic transmission, but impaired induction of long-term potentiation (LTP). In the ventral

hippocampus, however, TAAR2 KO mice show decreased baseline synaptic transmission and normal LTP induction. Notably, our observations of deficits in the novel object recognition task and in LTP induction in the dorsal hippocampus are consistent with the known roles of this region in encoding this type of declarative memory. Together, these behavioral and neurophysiological phenotypes suggest novel roles for TAAR2 function in modulating behavioral output, synaptic function, and the induction of synaptic plasticity.

Disclosures: A.G. Almonte: None. **A.L. Deal:** None. **J.K. Konstantopoulos:** None. **J.L. Weiner:** None. **E.A. Budygin:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 459.04/C8

Topic: B.03. G-Protein Coupled Receptors

Support: F30-DA40996
T32-GM007250
R01-DA35821
R01-NS95809
F32-DA44696
ZIADA000424-19
R01-DA036596

Title: Regional heterogeneity of D2-receptor signaling in the dorsal striatum and nucleus accumbens

Authors: *P. F. MARCOTT[1], S. GONG[2,1], P. DONTHAMSETTI[3,4], A. H. NEWMAN[5], L. BIRNBAUMER[6], K. A. MARTEMYANOV[7], J. A. JAVITCH[3], C. P. FORD[2]
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Abstract: Dopamine input to the dorsal and ventral striatum originates from separate populations of midbrain neurons. Despite differences in afferent inputs and behavioral output, little is known about how dopamine release is encoded by dopamine receptors on medium spiny neurons (MSNs) across striatal subregions. Here we examined the activation of D2 receptors following the synaptic release of dopamine in the dorsal striatum (DStr) and nucleus accumbens (NAc) shell using viral overexpression of a G-protein coupled inward rectifier potassium (GIRK)

channel. We found that D2 receptor-mediated synaptic currents were slower in the NAc and this difference occurred at the level of D2-receptor signaling. D2 receptors on MSNs demonstrated higher sensitivity for dopamine in the NAc. Deletion of two regulators of G-protein signaling (RGS7/9) slowed D2-receptor mediated signaling to a similar extent in both regions, but had no effect on dopamine sensitivity. We found that the regional difference in sensitivity of D2 receptors for dopamine was due to preferential coupling to Gαo in the NAc. These results identify differences in the sensitivity and timing of D2-receptor signaling across the striatum that influence how nigrostriatal and mesolimbic signals are encoded across these circuits.

Disclosures: P.F. Marcott: None. **S. Gong:** None. **P. Donthamsetti:** None. **A.H. Newman:** None. **L. Birnbaumer:** None. **K.A. Martemyanov:** None. **J.A. Javitch:** None. **C.P. Ford:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 459.05/C9

Topic: B.03. G-Protein Coupled Receptors

Support: NRF-2016R1D1A1B03930951
NRF-2017M3C7A1029611
NRF-2018R1A2B6004759
Brain Korea 21 PLUS program

Title: Beta-arrestins regulate mglu7 function by Nedd4-mediated ubiquitination

Authors: S. LEE, S. PARK, H. LEE, *Y. SUH
Dept. of Biomed. Sci., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Metabotropic glutamate receptors (mGlu receptors) are G protein-coupled receptors (GPCRs) that regulate synaptic transmission and neuronal excitability via downstream signaling cascades. Because abnormal regulation of mGlu receptor function is implicated in a number of neurological and psychiatric disorders, mGlu receptors are emerging as therapeutic targets in neuroscience field. Previously, we reported that SUMOylation at Lys889 on mGlu7, a member of Group III mGlu receptors regulates mGlu7 trafficking in neurons. In this study, we have further investigated the regulatory mechanism by ubiquitin-mediated modification on mGlu7, as there are several potential residues that can be modified by ubiquitination at the intracellular loops and the C-terminus of mGlu7. We found that mGlu7 is ubiquitinated via beta-arrestin 1-mediated Nedd4 recruitment in an activity-dependent manner. Ubiquitination regulates mGlu7 function not only by facilitating receptor endocytosis and degradation, but also by regulating mGlu7-mediated MAP kinase signaling. Given the importance of in-depth knowledge of the

precise mechanisms of receptor function for more elaborate therapeutic approaches, our findings will contribute to the improvement of therapeutic targets of mGlu7.

Disclosures: S. Lee: None. **S. Park:** None. **H. Lee:** None. **Y. Suh:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 459.06/C10

Topic: B.03. G-Protein Coupled Receptors

Support: NRF-2016R1D1A1B03930951
NRF-2017M3C7A1029611
NRF-2018R1A2B6004759
Brain Korea 21 PLUS program

Title: Characterization of N-linked glycosylation of metabotropic glutamate receptor 7

Authors: *D.-H. PARK, Y. SUH
Dept. of Biomed. Sci., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Metabotropic glutamate receptor 7 (mGlu7) has been shown to mediate excitatory synaptic neurotransmitter signaling and plasticity in the mammalian brain and is implicated in multiple neuropsychiatric disorders. Therefore, it is important to understand trafficking mechanism of mGlu7 from the ER to presynaptic terminal. A series of studies have reported that extracellular N-linked glycosylation modulates receptor surface expression and receptor-protein interactions in the central nervous system. Using biochemistry and confocal imaging technology, we have investigated the pattern and effects of N-glycosylation of mGlu7 in HEK 293T cells and rat cultured neurons. We identified that mGlu7 has four N-linked glycosylation residues in its extracellular domain, all of which tend to be glycosylated at similar levels. We found that mutations in the N-glycosylation sites of mGlu7 lead to a marked reduction of receptor surface expression, retention of receptors in the ER, and degradation of mGlu7 via the lysosomal degradation pathway. We also explore the possibility that N-linked glycosylation may regulate the proper localization of mGlu7 in the presynaptic active zones. Taken together, these data support that N-linked glycosylation of mGlu7 contributes to receptor trafficking, stability, and synaptic localization of mGlu7 in neurons.

Disclosures: D. Park: None. **Y. Suh:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

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Program #/Poster #: 459.07/C11

Topic: B.03. G-Protein Coupled Receptors

Support: National Research Foundation of Korea (NRF), funded through the Ministry of Science, ICT South Korea (2017R1D1A3B03030324)

Title: Inhibitory elements in the promoter region of mouse lysophosphatidic acid receptor gene Lpar1

Authors: H. PARK, N.-H. KIM, *A. SADRA, S.-O. HUH
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Abstract: Lysophosphatidic acid (LPA) is a prominent endogenous lysophospholipid with signaling properties outside the cell. It signals through specific G protein-coupled receptors, known as LPA1-6. For one of its receptors LPA1 (gene name Lpar1), details on the cis-acting elements for transcriptional control have not been defined. Using 5'RACE analysis, we report the identification of an alternative transcription start site of mouse Lpar1. We also characterized approximately 3,500bp of non-coding flanking sequence 5' of mouse Lpar1 gene. In mouse neocortical neuroblasts with constructs from the 5' regions of mouse Lpar1, it is revealed that the region between -248 to +225 serves as the basal promoter for Lpar1. We also found that the 5' proximal promoter region lacked a TATA box. The region between -761 to -248 contains a negative regulatory element affecting the basal expression of Lpar1. This region possesses three E-box sequences. Mutagenesis of these E-boxes and transient expression demonstrated that two of the E-boxes are negative modulators of Lpar1. One of these binds the HeLa E-box binding protein (HEB), and modulation of HEB levels in transfected cells regulates the transcription of the reporter gene. Based on our data, we propose that HEB may be required for a proper regulation of Lpar1 expression in the model cells as to affect its functions in both normal brain development and disease settings.
Significance statement
Regulation of the expression of Lpar1, the major receptor for the bioactive lipid LPA, is characterized in this research by defining the cis-acting negative regulatory elements. LPA/Lpar1 axis is required for normal brain development and the role of HEB E-box protein is explored here.
Funding
This work was supported by the grant from the National Research Foundation of Korea (NRF), funded through the Ministry of Science, ICT South Korea (2017R1D1A3B03030324).

Disclosures: H. Park: None. **N. Kim:** None. **A. Sadra:** None. **S. Huh:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

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Program #/Poster #: 459.08/C12

Topic: B.03. G-Protein Coupled Receptors

Support: Hungarian Academy of Sciences Momentum Program LP-54/2013
US NIH NS089575
US NIH NS099457

Title: NECAB1 and NECAB2 are the two major calcium-binding proteins of the CB_1 cannabinoid receptor-positive GABAergic interneuron population in the neocortex, hippocampus and the basolateral amygdala

Authors: *J. R. GLAVINICS[1,2], V. MICZÁN[1,2], K. KELEMEN[1,3], Z. LÁSZLÓ[1,4], I. KATONA[1]
[1]Inst. of Exptl. Medicine, HAS, Budapest, Hungary; [2]Fac. of Information Technol. and Bionics, Pazmany Peter Catholic Univ., Budapest, Hungary; [3]Univ. of Med. and Pharm. of Tirgu Mures, Tirgu Mures, Romania; [4]Sch. of PhD Studies, Semmelweis Univ., Budapest, Hungary

Abstract: Most GABAergic interneuron types can be distinguished based on their calcium-binding protein expression profiles. However, surprisingly, to date no specific EF-hand calcium-binding proteins have been described in CB_1 cannabinoid receptor-positive interneurons, which represent a major population of GABAergic cells throughout the forebrain. Since calcium buffering has a fundamental role in shaping various neuronal functions, we investigated whether this interneuron family expresses yet undetected calcium-binding proteins. *In silico* analysis of a publicly available single-cell RNA-sequencing database (Zeisel et al., 2015, Science, 347:1138-42), in situ hybridization, immunofluorescence staining and confocal microscopy were used to identify the EF-hand calcium-binding proteins expressed by the CB_1-positive interneurons. *In silico* analysis uncovered high mRNA expression levels of the N-terminal EF-hand calcium binding proteins 1 and 2 (NECAB1 and NECAB2) in the CB_1-positive hippocampal interneuron population. We confirmed that the majority of CB_1-positive cells indeed expressed NECAB1 and NECAB2 mRNA at high levels by using RNAScope multiplex fluorescent in-situ hybridization assay in hippocampal mouse brain slices. To verify these findings at the protein level, we performed CB_1 and NECAB1 or NECAB2 double fluorescent immunostainings, which revealed high abundance of these calcium binding proteins in CB_1-positive interneurons throughout the neocortex, hippocampus and the basolateral amygdala. Finally, after biocytin-labeling and morphological characterization of perisomatic and dendritic CB_1-positive interneurons in the CA1 subfield of the hippocampus, we found that NECAB1 tends to be present primarily in the somatodendritic compartment, whereas NECAB2 has a higher density in the axon terminals.

Taken together, the present observations demonstrate that NECAB1 and NECAB2, two previously uncharacterized calcium-binding proteins are highly expressed by CB_1-positive interneurons in the hippocampus, neocortex and basolateral amygdala. Moreover, the results also support the possibility that the different calcium-binding protein profiles of the major interneuron types play specific roles in controlling the distinct physiological properties of these GABAergic interneurons.

Disclosures: J.R. Glavinics: None. **V. Miczán:** None. **K. Kelemen:** None. **Z. László:** None. **I. Katona:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 459.09/C13

Topic: B.03. G-Protein Coupled Receptors

Support: NIH 5R21MH099457
Hussman Foundation
NIH Neurobiobank
Autism BrainNet
Autism Tissue Program

Title: Receptor density and distribution of 5-HT_2 receptors in the cingulate cortex and fusiform gyrus in autism: A multiple concentration saturation binding study in children and adults

Authors: *C. BRANDENBURG[1], G. J. BLATT[1], D. SIDIBE[2]
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Abstract: Background: Although SSRIs are among the most commonly prescribed medications in autism, several studies show variable efficacy during SSRI use. Some of this variability may be a result of differential expression of serotonin (5-HT) receptors across individuals. A previous single concentration autoradiographic study from our laboratory showed decreased 5-HT_2 receptor binding in postmortem sections in the superficial layers of the posterior cingulate cortex (PCC) and the fusiform gyrus (FG) in autism and control cases. 5-HT_2 receptors are G-protein coupled receptors that are located mostly postsynaptically in limbic regions such as the anterior cingulate cortex (ACC) and PCC as well as in some neocortical areas including the FG. In autism cases, all three cortical areas were also shown to have decreased GABA-ARs and GABA-BRs in previous studies. Objective: Determine differences in 5-HT_2 receptor density and affinity between autism and neurotypical individuals through a saturation binding assay. Methods: Utilizing a large cohort of postmortem brain tissue, a saturation binding assay was conducted on 20µm sections from the ACC, PCC and FG (n=16-19 autism, n=18-19 controls) by incubation

with ^{3}H ketanserin (Perkin Elmer) at concentrations of 120, 90, 30, 9, 3, 1.5 and 0.5 nM then loaded into X-ray cassettes with tritium standards and tritium-sensitive hyperfilm. Non-specific binding was determined with a competitive displacer (Ritanserin 100µM). After exposure, films were developed and digitized to quantify ligand binding in femtomoles per milligram of tissue in superficial and deep layers of each region. A Welch's t-test was utilized for statistical analysis. Results: $5HT_2$ receptor density and affinity in the ACC, PCC and FG did not have statistically significant binding density differences between total autism and control cases. However, when the cases were grouped into children (≤16) (n=8-9) and adults (>16) (n=9) the superficial and deep layers of the adult ACC showed a significantly lower B_{max} in the autism cases (p=0.040 and p=0.050). No differences were seen in the PCC or FG. Conclusion: A Cochrane review concluded that SSRI use has variable efficacy in autism, with adverse effects infrequent in adults but significant in children. Our cohort of data is consistent with this finding, in that children in the autism group did not show differences in receptor number or affinity, but adults with autism had lower mean levels of binding suggesting that SSRIs may be useful in such cases. Comparison of $5HT_2$ expression to other potentially altered 5HT receptors in these cases will provide useful insight into how the 5HT system may be differentially impacted.

Disclosures: C. Brandenburg: None. **G.J. Blatt:** None. **D. Sidibe:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 459.10/C14

Topic: B.03. G-Protein Coupled Receptors

Title: Pallido-pallidal terminals expreses cannabinoid receptors types 1 and 2

Authors: *I. O. CONDE ROJAS, III[1], R. CABALLERO-FLORÁN[2], J. ACEVES[3], D. ERLIJ[4], G. B. FLORAN[5]
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Abstract: It´s generally accepted that pallidal neurons does not express CB1 receptors, whereas recent evidence indicates CB2 receptors in Globus pallidus (GPe) in primates. Here we explore the existence of mRNA of CB1 and CB2 receptors in pallidal neurons of the mouse, their expression and function in pallido-pallidal terminals. We made RT-PCR experiments in slices and primary neural cultures of globus pallidus from 12-14 days old mouse. Typical bands corresponding to CB1 and CB2 receptors were found. Immunochemical studies shown an intense mark corresponding to CB1 and CB2 receptors in the same neurons. To evaluate the presence in terminals we decided to perform functional tests through electrophysiological recordings in C57

mouse GPe slices using patch-clamp whole-cell recordings with pharmacology. Recording evoked inhibitory postsynaptic currents (eIPSC) using a stimulus train protocol (5 pulses at 20 Hz) for test intranuclear axon collaterals (GPe-GPe), we evaluate the function of these receptors in the modulation of GABA release. GPe-GPe synapses were characterized by activity-dependent depression. Once the synaptic terminal was characterized, we recorded the basal current for 5 minutes, then, for 15 minutes, we administered agonists of CB1 (ACEA 100 nM) and CB2 receptors (GW833972A 100 nM) observing a decrease in the amplitude of the eIPSCs by almost 40% for CB1 (n = 26 neurons) and 20% for CB2 (n = 16 neurons) associated with a presynaptic effect since the ratio (pulse rate x/pulse1) changed significantly. Selective CB1 and CB2 AM 251 and AM 630 blocked respectively the effects indicating a receptor mediated effect. These data indicate the presence and functionality of CB1 and CB2 receptor on pallido-pallidal terminals.

Disclosures: I.O. Conde Rojas: None. **R. Caballero-Florán:** None. **J. Aceves:** None. **D. Erlij:** None. **G.B. Floran:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

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Program #/Poster #: 459.11/C15

Topic: B.03. G-Protein Coupled Receptors

Support: FONDECYT grant N° 1150244

Title: Interaction between type-2 corticotropin releasing factor and D1 dopaminergic receptors in the amygdala-prefrontal cortex transmission

Authors: *H. E. YARUR, I. M. VEGA-QUIROGA, K. GYSLING
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Abstract: The prefrontal cortex (PFC) is a brain area involved in working memory, attention and goal directed behavior. Stressful events could modify the animal behavior, affecting the performance of working and/or emotional memories. Neuronal activity in PFC is reduced when stressful events occur (García et al, 1999). One of the brain areas which projects heavily to the ventral region of the PFC and that has been implicated in sending crucial information about emotional stimuli to the PFC, is the basolateral amygdala (BLA) (LeDoux 2000). Maroun and Richter-Levin (2003), showed that acute stressful stimuli can block the induction of plasticity between the BLA and the PFC. Corticotrophin releasing factor (CRF) is a central regulator of endocrine and behavioral responses to stressors. We have observed that type-2 CRF receptor (CRF2) modulates the transmission of BLA to PFC. There is also evidence showing that D1 and D2 dopamine receptors (D1R and D2R) modulate neuronal transmission in BLA-PFC synapsis

(Floresco and Tse 2007). Furthermore, it has been shown that CRF and dopamine act synergistically to regulate the BLA to PFC synapsis (Orozco-Cabal et al, 2008). Thus, we decided to further study whether CRF2 and D1R regulate synaptic transmission between BLA and PFC. To this end, we performed *in vivo* microdialysis experiments in anesthetized rats in which the BLA was stimulated by a depolarizing solution and PFC extracellular levels of glutamate and dopamine were analyzed, in the presence or absence of pharmacological antagonists for CRF2 and dopamine receptors. The results show that CRF2 antagonist increased the extracellular levels of glutamate and decreased the dopamine levels in PFC induced by BLA stimulation. The CRF1 antagonist did not modify glutamate levels but increased significantly dopamine levels in the PFC after BLA stimulation. The combination of D1R and CRF2 antagonists blunted the increase of PFC glutamate levels induced by BLA stimulation. The results suggest that CRF2 exerts control of the BLA transmission over PFC and that modulates the dopaminergic component in the BLA-PFC transmission.

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

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 459.12/C16

Topic: B.03. G-Protein Coupled Receptors

Title: D3/D3nf isoform expression determines the functional response to D3 receptor activation on cAMP formation and [^{3}H] GABA release in the striatum

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Abstract: The functional response to the activation of dopamine D3Rs can be mediated by two different signaling pathways: In one, designated as "typical", the receptors couple with Gi proteins and inhibit the activity of adenylyl cyclase and the formation of cAMP. In the other, the "atypical", the receptors stimulate Gs mediated responses when D1Rs are co-activated, further increasing adenylyl cyclase activity. It has been suggested that the abundance of the non-functional isoform of the D3R called D3nf, determines the density of D3Rs in the plasma membrane. In the substance nigra pars reticulata, the signaling of the D3R normally is "atypical" but becomes "typical" during experimental Parkinson. In this study we determined whether the two modalities of signaling are correlated with the relative expression of the D3R and D3nf

isoforms during experimental Parkinson.
We induced hemiparkinsonism in adult Wistar male rats by the unilateral administration of 6-OHDA in the middle forebrain bundle. Using Real-Time qRT-PCR, we found a decrease in D3nf isoform mRNA expression in the lesioned striatum. Western Blot determinations showed that D3nf protein levels were also decreased in the lesioned side. This decrease in the relative expression of the D3nf isoform was accompanied by a change in the functional response to D3R activation. In the control hemisphere, activation of D3Rs potentiated the formation of cAMP and [^{3}H] GABA release induced by activation of D1Rs depolarized with high K^+, i.e., it induced an "atypical" response. In contrast, in the denervated hemisphere the activation of D3Rs inhibited the formation of cAMP and [^{3}H] GABA release stimulated by D1R activation. These data indicate that the relative expression of D3Rs and D3nf isoform correlates with the functional response produced by activating D3Rs. This response is probably mediated by changes in the number of receptors located in the membrane.

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Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 459.13/C17

Topic: B.03. G-Protein Coupled Receptors

Support: NIH RO1 NS083410
NIH T32 NS041218
Cosmos Club Foundation of Washington, D.C.

Title: The role of PAR-1 activation in sharp wave ripple event frequency

Authors: *P. BOZZELLI[1], P. LI[3], S. VILLAPOL[2], J.-Y. WU[1], K. CONANT[1]
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Abstract: Protease-activated receptor 1 (PAR-1) is unique amongst G-protein-coupled receptors in that it is activated through proteolytic cleavage of its N-terminus by various extracellular enzymes. Previous work has shown that PAR-1 is critical for NMDA-receptor-mediated long term potentiation (LTP) and hippocampal-dependent memory. Through in situ hybridization, we observe that PAR-1 is prominently expressed in the CA2 region of the hippocampus. PAR-1's involvement in hippocampal-dependent memory tasks has been well established; however, given that CA2 and its associated circuitry are involved in sociability and anxiety, we seek to evaluate these behaviors in WT and PAR-1 knock-out mice. Both CA1 and CA2 are involved in

triggering sharp-wave ripples (SWRs), which are highly synchronous neuronal population events; therefore, we have sought to determine whether PAR-1 activation, through distinct activating enzymes, is involved in SWR event frequency. PAR-1 is canonically activated by the serine protease thrombin; however, a subset of the matrix metalloproteinase (MMP) class of enzymes, MMPs -1, -3, and -13, are also able to activate the receptor through cleavage of the N-terminus at non-canonical sites. Through local field potential recordings, we are able to evaluate whether PAR-1 activation, by canonical and non-canonical peptide agonists, results in a disruption to SWR event frequency. Preliminary data reveals that both MMP- and thrombin-generated peptide agonists alter SWR event frequency. This work has clinical implications in that the PAR-1-activating proteases are upregulated in diseases/injuries such as neuroHIV infection and stroke, and that aberrant activation of PAR-1 may underlie certain brain dysfunctions.

Disclosures: P. Bozzelli: None. **P. Li:** None. **S. Villapol:** None. **J. Wu:** None. **K. Conant:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 459.14/C18

Topic: B.03. G-Protein Coupled Receptors

Support: DFG-IRTG 2150

Title: Role of serotonin in the neuromodulation of layer 5 neurons in rat prefrontal cortex

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Abstract: Serotonin (5HT) is a key neurotransmitter that can modulate both excitatory and inhibitory synaptic neurotransmission through differential activation of its receptor subtypes. Neuronal activity within prefrontal cortex (PFC) is modulated by the activation of specific 5HT receptors, 1A and 2A ($5HT_{1A}R$, $5HT_{2A}R$), which are coupled to $G_{i/o}$ and G_q proteins, respectively. Activation of 1A reduces the excitability by inducing hyperpolarisation (HP) whereas, activation of 2A enhances excitability by inducing depolarisation (DP). A correct balance between excitation (E) and inhibition (I) is important for brain function. Disruption in the E/I balance is thought to be involved in several neuropsychiatric disorders including autism and schizophrenia. Results: Here, we have investigated role of 5HT in layer 5 (L5) of PFC using whole-cell patch-clamp recordings with simultaneous biocytin fillings. Based on the neuronal morphology and action potential firing pattern, we identified two major types of pyramidal cells (PCs): 1) broad tufted PCs with apical dendrites with many terminal branches and 2) slender

tufted PCs with only few tuft dendrites. As individual PCs express both $5HT_{1A}R$ and $5HT_{2A}R$, we hypothesized that 5HT has the ability to modulate E/I balance in PFC. A majority (80%) of PCs showed DP (4.0 ± 1.9, n=22) while a minority (20%) showed HP (1.6 ± 0.2, n=5) with 5HT application. Notably, the extent of DP significantly different between broad (3.0 ± 1.2, n=9) and slender (6.2 ± 2.3, n=12) tufted PCs. $5HT_{1A}R$ agonists in presence of a $5HT_{2A}R$ antagonist induced a HP in DP neurons. Similarly, $5HT_{2A}R$ agonists in presence of $5HT_{1A}R$ antagonists induced a DP in HP neurons. Discussion: 5HT facilitates DP in one set and HP in another set of PCs. The overall 5HT response results from an interaction between inhibition and excitation mediated by $5HT_{1A}R$ and $5HT_{2A}R$ respectively. The net DP response in one set is due to a dominant $5HT_{2A}R$ activity while the net HP in the other set of PCs is a result of predominant $5HT_{1A}R$ activity. Its already known that $5HT_{1A}R$ and $5HT_{2A}R$ largely (80%) co-localise in rat and mice PFC and our data further confirm these findings at a single cell level. Further, slender tufted PCs showed a greater DP 5 HT response than broad-tufted PCs. This differential response may be related to their distinct projections to cortical and subcortical structures. However, additional studies will be required to characterize the neuronal connectivity between PCs and these brain structures.

Disclosures: R. Rama: None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 459.15/C19

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant AG005214

Title: Additive effects of allosteric ligands acting at distinct sites on muscarinic acetylcholine receptors: Signal shaping

Authors: *J. ELLIS, G. ELMSLIE
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Abstract: It is known that muscarinic acetylcholine receptors possess multiple distinct allosteric sites (Lazareno et al, 2000, Mol Pharmacol 58:194). We have recently reported that amiodarone and dronedarone interact with their own novel allosteric site on these receptors (Stahl et al, 2011, Mol Pharmacol 80:378; Jayasuriya et al, 2017, Pharmacol 99:128). Interestingly, the major effect of amiodarone is to enhance the maximal degree of response elicited by acetylcholine and other agonists, without significantly altering the potency of the agonist. Most muscarinic positive allosteric modulators (PAMs) act by enhancing the potency of agonists without affecting the maximal effect evoked. Dronedarone displays mixed effects on muscarinic responses. The

orthogonality of the effects elicited (i.e., changes in maximal response on the y-axis vs changes in potency on the x-axis) allows a clear demonstration of the simultaneous binding of different allosteric modulators to their distinct sites. For example, the negative modulator tacrine shifts the dose-response curve for acetylcholine to the right; pairing appropriate concentrations of tacrine and amiodarone leads to the enhancement of response at high concentrations of acetylcholine at the same time that responses to low concentrations are inhibited. Pairing of different ligands produces the opposite effect. Because of this ability to differentially modify the low and high ends of the concentration-response curve, we have named this modulation "*signal shaping*". It is likely that neurotransmitter levels differ at different locations in the synapse. For example, it is known that transmitter spillover exerts effects at relatively distant sites, but the concentration at those sites will necessarily be significantly lower than at the post-synaptic receptors within the original synapse. Similarly, presynaptic autoreceptors and postsynaptic receptors may be exposed to different concentrations of transmitter. The effect of signal shaping, as described above, occurs in the sense that responses above a certain magnitude are enhanced, while responses below that magnitude are reduced, or vice versa. We speculate that signal shaping may provide a novel means to regulate the ratio of extra-synaptic (spillover) to intra-synaptic signaling, or of presynaptic to post-synaptic signaling.

Disclosures: J. Ellis: None. **G. Elmslie:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 459.16/C20

Topic: B.03. G-Protein Coupled Receptors

Support: MH107648
MH093672

Title: D2 receptor upregulation in accumbens cholinergic interneurons: Effects on pause duration and associative conditioning

Authors: *E. F. GALLO[1], E. TEBOUL[2], B. AKDOGAN[3], N. ZARRELLI[3], B. COTTEN[5], P. D. BALSAM[6], J. A. JAVITCH[4], C. KELLENDONK[3]
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Abstract: Alterations in striatal dopamine D2 receptor (D2R) availability are associated with several neuropsychiatric disorders that feature motivational dysfunction. Cholinergic interneurons (CINs), which express D2Rs, account for 2-3% of the striatal cell population, but

exert widespread control over striatal circuit function. *In vivo*, CINs exhibit a dopamine-dependent pause in firing activity in response to reward-related stimuli that is deemed critical for cue-reward associations. *In vitro* studies have implicated the D2R in mediating the dopamine-dependent pause recorded in CINs. However, conventional pharmacological tools are limited in their ability to disentangle the specific contribution of CIN D2Rs to the pause and to associative learning given that other cell types that operate within striatum to process reward also express D2Rs. Because reward-related cues are known to evoke increases in phasic dopamine release in the NAc, we sought to determine whether increased D2R expression in CINs alters their response to dopamine release. To this end, we expressed D2Rs or EGFP in CINs of the NAc while expressing ChR2 in midbrain dopamine neurons using a ChAT-Cre x DAT-Cre mouse line. Using acute slices, we measured the duration of the pause in CIN firing evoked by 20 Hz optogenetic stimulation of dopamine afferents. CINs overexpressing D2Rs showed a significant pause elongation compared to EGFP-expressing CINs (D2R: 2.18 ± 0.28 s, n = 22; EGFP: 0.77 ± 0.11 s; $p < 0.005$, n = 20), without altering the average interspike interval. Blocking D2Rs with sulpiride abolished the pause in both conditions, indicating that D2Rs are necessary for the light-evoked pause in CINs. We then tested whether D2R upregulation in CINs leads to alterations in associative learning using a Pavlovian conditioning task in which animals are presented a brief 8-s conditioned stimulus (CS) that predicts reward. We found that both EGFP and D2-expressing mice increased their rates of responding to the CS (head entries/s) similarly over 16 days, suggesting that associative learning is unaltered. However, analysis of the response patterns during the 8-s CS, revealed that, unlike controls which increased responding in the later phases of the 8-s cue (i.e. closer to reward delivery), D2R overexpressing mice showed sustained responding across the duration of the cue, reflecting an alteration in temporal control over conditioned responding. These results indicate that D2Rs expressed in CINs of the NAc are important regulators of pause duration, and raise the possibility that the D2R-dependent pause elongation leads to alterations in appropriate responding to reward-related cues.

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Poster

459. G-Protein Coupled Receptors

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Program #/Poster #: 459.17/C21

Topic: B.03. G-Protein Coupled Receptors

Support: NSERC Discovery Grant
Canada Foundation for Innovation

Title: Muscarinic receptor isoforms differentially regulate pyramidal neuron excitability within layer VI of the mouse medial prefrontal cortex

Authors: A. V. PATEL, *C. D. BAILEY
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Abstract: Pyramidal neurons located within layer VI of the rodent medial prefrontal cortex (mPFC) play an important modulatory role in prefrontal cognitive networks. This role is facilitated by acetylcholine activation of nicotinic receptors (nAChRs) and muscarinic receptors (mAChRs), which both act to regulate the excitability of mPFC layer VI neurons. Although the function of nAChRs has been extensively characterized, the function of mAChRs on mPFC layer VI neurons is not fully understood. Activation of mAChRs induces a complex response in neighboring mPFC layer V neurons, where the Gq-coupled M1 isoform mediates a transient inhibition followed by a prolonged excitation. The objective of this current study was to determine the role of mAChR isoforms toward the overall muscarinic response in layer VI neurons. Of particular interest was the relatively-rare Gq-coupled M3 isoform that is selectively expressed in layer VI. Whole-cell current-clamp electrophysiological recordings were made in active mPFC layer VI neurons sampled from male and female mice during young postnatal life (postnatal day (P) 15-20) and in adulthood (P60-100). Responses to bath-applied ACh (1 mM for 30 s) were measured in the continuous presence of nAChR antagonists. The majority of sampled neurons exhibited an early, transient inhibition followed by a prolonged excitation. The proportion of neurons exhibiting the inhibition response, and the duration of this response, were significantly greater in young mice than in adult mice. In contrast, the magnitude of the excitatory response did not change with age. Neither measure was affected by sex. Pharmacological experiments using isoform-selective antagonists demonstrated that both the M1 and M3 isoforms were required for the inhibition response in all groups tested, whereas the M2 isoform contributed to this response in male mice only. The M1 isoform contributed to the excitatory response in all groups tested, whereas the M2 and M3 isoforms contributed to this response in adult mice only. Ongoing experiments aim to confirm the expression of mAChR M1, M2, and M3 isoforms within recorded neurons, and to determine whether the function of these mAChR isoforms relates with the morphology of recorded neurons. Collectively, our findings suggest that mAChR regulation of mPFC layer VI neuron excitability is mediated via distinct contributions of M1, M2, and M3 receptor isoforms, and that these contributions vary across sex and age.

Disclosures: A.V. Patel: None. **C.D. Bailey:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

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Program #/Poster #: 459.18/C22

Topic: B.03. G-Protein Coupled Receptors

Support: CNPq
Capes
FAPESP 2015/ 07019-4

Title: Extracellular cyclic AMP-adenosine pathway: A potential target for treating skeletal muscle atrophy

Authors: *F. RODRIGUES ELOI, T. CHIAVEGATTI, A. ANDRADE-LOPES, R. OLIVEIRA GODINHO
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Abstract: Introduction: The GsPCR/ adenylyl cyclase / intracellular cAMP pathway is an interesting therapeutic target for treating skeletal muscle atrophy since it is involved in attenuation of muscle proteolysis. Assuming that the intracellular cAMP suffers efflux, is degraded into adenosine extracellularly, and that the skeletal muscle cells express all 4 adenosine receptor subtypes, herein we evaluate the possible modulatory effects of the "extracellular cAMP-adenosine pathway" on skeletal muscle proteolysis. Material and Methods: L6 rat cell line ($3x10^5$ cells/ mL) were grown in DMEM plus 10% fetal calf serum on 35 mm dishes. Myogenic differentiation was induced with DMEM plus 5% horse serum. Activation of GPCR was evaluated using the functional [^{35}S]GTPγS binding assay. Briefly, membrane fractions from L6 myotubes (n=4-5) were incubated with 0.1 nM [^{35}S]GTPγS and 50 μM GDP, in the absence or presence of cAMP or adenosine. Nonspecific binding was determined in the presence of 50 μM unlabeled GTPγS. The effect of cAMP, adenosine, CGS-15943 (non-selective adenosine receptor antagonist) and DMPX (selective A_2 receptor antagonist) on L6 myotubes proteolysis was evaluated by measuring the rate of tyrosine release into the incubation medium using a fluorometric method (at 485/590 nm). Results and Conclusion: cAMP increased by up to 150% the basal binding of [^{35}S]GTPγS to L6 myotube membranes. This effect was mimicked by adenosine or its analog NECA. Treatment of cultures for 4 h with cAMP reduced by up to 18% the basal rate of tyrosine release. The anticatabolic effect of cAMP was sustained for up 5 h and mimicked by incubation of cells with adenosine, which reduced by up to 28% the basal rate of tyrosine released. Interestingly, pre-treatment of cells with CGS-15943 or DMPX completely abolished the antiproteolytic effects of either cAMP or adenosine. This data shows that extracellular cAMP can modulate the skeletal muscle proteolysis through activation of adenosine receptor coupled to stimulatory G protein, becoming a target for developing pharmacological strategies for treating skeletal muscle atrophy. Ethical Committee: CEUA Nº 5523140415

Disclosures: T. Chiavegatti: None. **A. Andrade-Lopes:** None. **R. Oliveira Godinho:** None.

Poster

459. G-Protein Coupled Receptors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 459.19/C23

Topic: B.03. G-Protein Coupled Receptors

Title: An effort to build an *in vitro* high-throughput screening for seizure liability based on calcium oscillation of human ipsc-derived neurons

Authors: *Y. WANG[1], S. DU[1], S. HISADA[2]
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Abstract: Drug-induced seizure liabilities are typically tested in expensive and low throughput ex vivo rat hippocampal brain slices. An in vitro model based on micro-electrode arrays using human iPSC derived neurons has been suggested (https://doi.org/10.1093/toxsci/kfy029). There is a surge of interest in higher throughput methods, one of them being fluorescence measurement of calcium oscillations in neuronal cultures. However, progress has been limited by the long imaging acquisition time for an entire 96- or 384-well plate, and also by the heterogeneity of neurons derived from human iPSCs. With the advent of new camera technologies as well as availability of highly enriched, functionally mature human neurons derived from iPSCs, these limitations can now be overcome. Here we attempt to build a model to compare human iPSC derived neurons, with and without astrocyte, with rat primary cells upon treatment of reference and control compounds.

Disclosures: Y. Wang: None. **S. Du:** None. **S. Hisada:** None.

Poster

459. G-Protein Coupled Receptors

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Topic: B.03. G-Protein Coupled Receptors

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R01 MH062646
R01 MH073676

R01 MH082867
CIHR DFS146189

Title: Biased M1 PAMs reveal critical role of phospholipase D in M1 PAM enhancement of cortical function

Authors: *S. P. MORAN[1,2], C. A. DOYLE[6], H. P. CHO[3], Z. XIANG[7], J. T. MAKSYMETZ[8], S. FALTIN[2], C. M. NISWENDER[4], J. M. ROOK[9], C. LINDSLEY[10], P. CONN[5]
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Abstract: Highly selective positive allosteric modulators (PAMs) of the M1 subtype of muscarinic acetylcholine receptor have emerged as an exciting new approach for the potential improvement of cognitive function in patients suffering from Alzheimer's disease and schizophrenia. To date, M1 PAM discovery programs have produced a structurally diverse range of M1 PAMs with distinct pharmacological properties, including different levels of agonist activity and differences in signal bias. Previously, we have shown that intrinsic agonist activity is detrimental to M1 PAM efficacy in our preclinical animal models. However, little is known about the impact of signal bias on M1 PAM efficacy *ex vivo* and *in vivo*. Canonical M1 signaling induces activation of phospholipase C (PLC) and it was assumed that activation of PLC is a key mechanism by which M1 activation induces multiple CNS effects. However, our lab has shown that M1 activation can also lead to activation of phospholipase D (PLD), independent of PLC activation. Therefore, to characterize the role of PLD downstream of M1 in the CNS, we set out to characterize the role of PLD in three different M1-dependent electrophysiological assays in *ex vivo* brain slices. Using selective PLD inhibitors, we report that PLD does not play a role in cholinergic agonist-induced increases in medium spiny neuron excitability in the striatum nor agonist-induced increases in spontaneous excitatory post synaptic currents in layer V medial prefrontal cortex (mPFC) pyramidal neurons, both of which are M1-dependent. Interestingly, we find that inhibition of PLD, specifically the PLD1, blocks cholinergic agonist-induced long-term depression (LTD) of layer V field excitatory post synaptic potentials electrically stimulated in layer II/III of the mPFC. Importantly, loss of LTD at this mPFC synapse is known to correlate with behavioral deficits in *in vivo* rodent cognition assays. Recently, we have published that some M1 PAMs display a signal bias in which they potentiate signaling through PLC but not through PLD. Therefore, using the same brain slice electrophysiology paradigms, we set out to compare the nonbiased M1 PAM, VU0453595, with two biased M1 PAMs, VU0405652 and VU0405645, that potentiate signaling through PLC but not PLD. Interestingly, we find that biased M1 PAMs fail to potentiate M1 LTD in the mPFC and that a biased M1 PAM can actually block a robust LTD induced by a high concentration of cholinergic agonist, suggesting true signal bias. These finding suggest that PLD plays a critical role in the ability of M1 PAMs to

modulate some CNS functions and that screening for signal bias is essential to fully understand and evaluate M1 PAM clinical candidates.

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Poster

459. G-Protein Coupled Receptors

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Topic: B.03. G-Protein Coupled Receptors

Support: MJFF Target Advancement Program Grant
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Title: Selective antagonists of the M_4 muscarinic acetylcholine receptor relieve parkinsonian motor deficit

Authors: *M. S. MOEHLE[1], J. M. ROOK[2], D. J. FOSTER[2], S. E. YOHN[2], C. M. NISWENDER[2], C. LINDSLEY[2], C. K. JONES[2], P. CONN[2]
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Abstract: Anti-muscarinic therapy that broadly targeted each of the 5 muscarinic acetylcholine receptors was the first approved therapy for Parkinson's Disease (PD), and has efficacy in reducing the primary motor symptoms of other movement disorders as well. However, the clinical utility of these compounds is greatly limited by severe central and peripheral side effects. Recently, our lab has made major breakthroughs in the development of selective antagonists and allosteric modulators of individual muscarinic subtypes. Using these compounds we have identified the M_4 subtype as a major regulator of dopaminergic signaling, release, and related motor behaviors. These data have highly implicated that selective antagonists of the M_4 receptor may yield robust anti-parkinsonian efficacy without the severe central and peripheral side effects observed with non-selective muscarinic antagonists, yet there has been little evidence or tools available to directly test this hypothesis. Here, we report the development and characterization of the first selective M_4 antagonist that possess at least 100 fold selectivity over other muscarinic subtypes. Using this novel antagonist, we performed a series of electrophysiological and behavioral experiments to directly test the hypothesis that selective antagonists of M_4 will have robust anti-parkinsonian motor efficacy. We found that selective inhibition of M_4 was able to relieve motor deficits in several animal models that have predictive validity of anti-parkinsonian

efficacy such as haloperidol induced catalepsy and forelimb asymmetry. Additionally, we found that this antagonist can reverse M_4 activation induced suppression of dopamine release in the striatum and M_4 activation induced suppression of D_1 dopamine receptor signaling in the substantia nigra pars reticulata. These initial studies provide compelling evidence that M_4 selective antagonists will have broad efficacy in removing parkinsonian motor disability, and provide critical pre-clinical rationale for larger drug discovery efforts.

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Poster

459. G-Protein Coupled Receptors

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CIHR DFS146189
VISP
PhRMA
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Title: M_1 muscarinic receptors modulate discrete glutamatergic inputs to the prefrontal cortex: Implications for novel treatments of posttraumatic stress disorder

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Abstract: The medial prefrontal cortex (mPFC) integrates a diverse array of cortical and subcortical inputs to mediate higher order cognition and the neuromodulator acetylcholine is highly implicated in these functions. We previously reported a form of muscarinic long-term

depression (mLTD) of synaptic transmission in the mouse mPFC, however, it is unknown if this mLTD occurs at distinct subcortical inputs. Using an optogenetic approach in *ex vivo* layer V mPFC brain slices, we found that muscarinic activation with the non-selective agonist oxotremorine-M induces mLTD at inputs from the ventral hippocampus (vHipp) and basolateral amygdala (BLA) but not the mediodorsal nucleus of the thalamus. Similar to mLTD observed with electrical stimulation, the mLTD at the vHipp and BLA inputs is blocked by an M_1 antagonist, and M_1 activation with a selective atypical M_1 agonist is sufficient to induce mLTD at these inputs. We also found that vHipp-mPFC mLTD is lost in pyramidal neurons in which M_1 has been selectively deleted using viral-mediated expression of Cre recombinase. Taken together, these data indicate that M_1 is poised to regulate synaptic transmission at two long-range limbic inputs to the mPFC, whose activity is necessary for the extinction of learned fear. Based on this, we tested the hypothesis that M_1 activity can bidirectionally modulate fear extinction. First, we found that systemic administration of the M_1 antagonist VU0255035 impaired contextual fear extinction. We then proceeded to test whether enhancing M_1 receptor activity could rescue deficits in a model in which contextual fear extinction is impaired. To this end, we used the extensively validated stress-enhanced fear learning (SEFL) model of posttraumatic stress disorder (PTSD). We found that mice subjected to SEFL exhibited enhanced contextual fear compared to control animals and exhibited impaired extinction to the conditioning context. Excitingly, treatment with the M_1 positive allosteric modulator (PAM) VU0453595 before extinction enhanced contextual fear extinction in SEFL conditioned mice. Altogether, these data suggest that the M_1 muscarinic receptor dynamically modulates the strength of fear-related inputs into the mPFC. Through these actions, M_1 PAMs may provide a novel treatment strategy to facilitate exposure therapy in the clinic for the treatment of PTSD.

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Poster

460. Epilepsy: Ion Channels

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 460.01/C27

Topic: B.10. Epilepsy

Support: R01 NS083402

Title: Reduced axonal surface expression and PIP_2 sensitivity in K_v7 channels disrupts their function to inhibit neuronal excitability in Kcnq2 epileptic encephalopathy

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Abstract: Neuronal Kv7/KCNQ channels are voltage-gated potassium channels composed of Kv7.2/KCNQ2 and Kv7.3/KCNQ3 subunits. Enriched at the axonal membrane, they potently suppress neuronal excitability. *De novo* and inherited dominant mutations in Kv7.2 cause early onset epileptic encephalopathy characterized by drug resistant seizures and profound psychomotor retardation. However, their precise pathogenic mechanisms remain elusive. Here, we investigated select epileptic encephalopathy mutations in calmodulin (CaM)-binding helices A and B of Kv7.2. We discovered that R333W, K526N, and R532W mutations located peripheral to CaM contact sites decreased axonal surface expression of heteromeric channels although only R333W mutation reduced CaM binding to Kv7.2. These mutations also altered gating modulation by phosphatidylinositol 4,5- bisphosphate (PIP2), revealing novel PIP2 binding residues. While these mutations disrupted Kv7 function to suppress excitability, hyperexcitability was observed in neurons expressing Kv7.2-R532W that displayed severe impairment in voltage-dependent activation. The M518V mutation at the CaM contact site in helix B caused most defects in Kv7 channels by severely reducing their CaM binding, K+ currents, and axonal surface expression. Interestingly, the M518V mutation induced ubiquitination and accelerated proteasome-dependent degradation of Kv7.2, whereas the presence of Kv7.3 blocked this degradation. Furthermore, expression of Kv7.2-M518V increased neuronal death. Together, our results demonstrate that epileptic encephalopathy mutations in helices A and B of Kv7.2 cause abnormal Kv7 expression and function by disrupting Kv7.2 binding to CaM and/or modulation by PIP2. We propose that such multiple Kv7 channel defects could exert more severe impacts on neuronal excitability and health, and thus serve as pathogenic mechanisms underlying Kcnq2 epileptic ncephalopathy

Disclosures: E. Kim: A. Employment/Salary (full or part-time):; UIUC. **J. Zhang:** A. Employment/Salary (full or part-time):; UIUC.

Poster

460. Epilepsy: Ion Channels

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Topic: B.10. Epilepsy

Support: NIH Grant MH48432
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Title: Nonuniform changes in h channel expression along the dorsoventral axis of the hippocampus in a rat model of temporal lobe epilepsy

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Abstract: The CDC estimates one percent of adults in the United States have epilepsy. Temporal Lobe Epilepsy (TLE), which affects the hippocampus and surrounding cortices, is the most common form of focal epilepsy. In animal models of TLE, CA1 neurons have been shown to be susceptible to selective changes in ion channel expression, called acquired channelopathies, which increase the excitability of a neuron. In addition, several recent studies in normal rodents find differences in ion channel expression along the dorsoventral axis of CA1. We hypothesized that the presence of these acquired channelopathies in an animal model of epilepsy might depend on the dorsoventral region of CA1. To test this, we modeled TLE in the rat by inducing status epilepticus (SE) with kainic acid. We found spontaneous seizures occurred in the first month post-SE. For all experiments, slices of the dorsal and ventral hippocampus were prepared from rats 1-2 months post-SE. In acute slices, we used current clamp recordings to compare the intrinsic membrane properties post-SE to control. We expected that neurons along the dorsoventral axis might show a uniform increase in excitability superimposed on the gradient described in normal rats. Our data, however, suggests otherwise – the firing of dorsal and ventral neurons does not appear to be uniformly regulated. Neurons in the dorsal, but not the ventral, CA1 are more excitable post-SE firing more action potentials and possessing an elevated input resistance. We then hypothesized the increase in firing of dorsal CA1 neurons was due, in part, to a reduction in the presence or activity of ion channels open at subthreshold voltages. Targeting the subunits of two ion channel classes, HCN and GIRK, we used immunohistochemistry to assess the localization of these proteins. While the expression of GIRK channels did not appear to have changed in dorsal or ventral hippocampus post-SE, we found a reduction in HCN1 immunostaining in the dorsal dendrites, which corresponded to our physiological findings. Next, we tested the physiological contribution of h channels to membrane properties via whole cell recordings at the apical dendrites of dorsal CA1 neurons. We found a dramatic reduction in electrophysiological markers associated with h channels post-SE including peak resonance frequency and sensitivity to the channel blocker, ZD7288. In this study, we have provided evidence that post-SE neurons in the dorsal CA1 modify their intrinsic properties by reducing h channel expression, and this acquired channelopathy does not occur in ventral CA1 neurons.

Disclosures: E.C. Arnold: None. **R.A. Gray:** None. **D. Johnston:** None.

Poster

460. Epilepsy: Ion Channels

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Topic: B.10. Epilepsy

Support: MIND Institute IDDRC grant U54 HD079125

Title: Using zebrafish as a tool to model patient mutations of KCNB1 and its role in epilepsy

Authors: *A. COLON-RODRIGUEZ[1,2], K. F. BURBACH[2], E. FERINO[2], M. BADER[2], P. J. LEIN[3], L.-E. JAO[4], M. Y. DENNIS[2]
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Abstract: Genetic factors responsible for complex neurological disorders, including epilepsy, are poorly understood. De novo mutations in KCNB1 encoding $K_v2.1$ voltage-gated potassium channel have been identified in patients with sporadic infantile epilepsy. Nearly all variants identified are missense making their pathogenicity uncertain. Knock out (KO) *Kcnb1* mice exhibit neuronal hyperexcitability, sensitivity to convulsant-induced seizures, defects in spatial learning and motor activity, and anxiety-like behavior. A recent study examining *kcnb1* KO in zebrafish resulted in a reduced ventricular system and gain of function caused hydrocephalus; however, additional phenotypic and neuronal alterations were not examined. The focus of this study is to recapitulate neurological phenotypes in zebrafish observed in patients and mouse models and characterize them molecularly and phenotypically. Using zebrafish as a model allows us the potential to conduct more robust, higher throughput experiments. This mainly due to the ability of zebrafish to reproduce robustly and their rapid development. To create our mutants, we used CRISPR gene editing to generate novel KO alleles for *kcnb1* in zebrafish. Zebrafish were then characterized by Illumina sequencing identifying a 23-bp deletion allele. To quantify molecular impacts on the resulting mutant *kcnb1* transcripts and protein, we performed quantitative real-time PCR and western blot, respectively, of 10 days post fertilization (dpf) larvae. Subsequent morphological and behavioral analyses were performed on 5 dpf zebrafish. Our results show no significant differences between mutant zebrafish carrying one (heterozygote) or two (homozygous) copies of KO alleles compared to wildtype fish in body size or head size. However, there was a significant increase in activity (distance moved) between heterozygous and homozygous fish in the presence of PTZ, a $GABA_A$ antagonist, recapitulating phenotypes observed previously in *Kcnb1* KO mice. Ongoing studies include characterizations of synaptic alterations in *kcnb1* mutants via electroencephalograms, immunohistochemistry, and RNA-seq. Additionally, efforts are ongoing to introduce evolutionarily conserved missense patient mutations in zebrafish using gene editing. The results of this study will lay the groundwork to (1) identify neurodevelopmental alterations of *kcnb1* mutations in zebrafish, and (2) develop tools that we will continue to use as we move forward to characterize unknown disease-related mutations in a higher-throughput manner.

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Poster

460. Epilepsy: Ion Channels

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Program #/Poster #: 460.04/C30

Topic: B.10. Epilepsy

Support: NIH R01 NS094461

Title: Epileptogenic seizures and increased excitability promote upregulation of KCNQ M-type K+ channels in the hippocampus

Authors: *S. D. HASTINGS, C. CARVER, M. S. SHAPIRO
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Abstract: M-type (KCNQ2/3) K+ channels play a key role in the excitability of neurons, however, their role in acquired epileptogenesis is not well understood. Previous studies by our group found that KCNQ2 and KCNQ3 mRNA was upregulated in the hippocampus in response to chemoconvuslant seizure activity. Using transgenic mice with a GFP reporter to detect expression of KCQN2 mRNA (GENSAT KCNQ2-EGFP/FW221Gsat/Mmucd, 015412-UCD), we are able to visualize seizure-dependent effects on KCNQ2 expression in the subregions of the hippocampus.
KCNQ2-GFP reporter mice were administered either the muscarinic agonist pilocarpine or the GABAA receptor antagonist pentylenetetrazol to induce clonic seizures in adult, 2-month old mice. Alternatively, a subset of animals were given 280 mg/kg pilocarpine to induce status epilepticus (SE). Brains were removed either 48 hours or 7 days after seizure induction and fixed in 4% PFA for immunohistochemistry. Dorsal hippocampus sections were immunostained with anti-GFP and anti-MAP2 antibodies and secondary fluorescent labels. GFP/MAP2 fluorescence was quantified for dentate gyrus (DG), CA1, and CA3 pyramidal regions.
Chemoconvulsant seizures induced increase of KCNQ2 mRNA in CA1 and CA3 subregions at the 48 hr timepoint, but no signficant increase was observed in the DG. CA1 and CA3 levels of KCNQ2 mRNA increased in response to both pilocarpine or pentylentetrazol, signifying that KCNQ2 upregulation occurs independent of the mechanism of convulsant activity. Total KCNQ2 protein levels were also increased in the whole hippocampus. In hippocampi examined 7 days after seizure, levels of KCNQ2 mRNA were reduced in all regions below that of control. In a subset of mice experiencing SE, there was a significant increase in KCNQ2-expressing DG granule cells, but excitoxicity induced widespread neuronal death in CA1 and CA3 pyramidal neurons.
Brain-slice electrophysiology recordings of M-current were taken from CA1 and DG neurons in comparison of naive and pilocarpine seizure animals. CA1 demonstrated increased M-current after seizure challenge, however there were no significant changes in M-current between control

and seizure DG granule cells.
We demonstrate that a single seizure promotes KCNQ2 upregulation in the hippocampus in a region-specific manner and in a limited window after seizure. Such novel ion channel plasticity may serve as a compensatory mechanism after a hyperexcitable event. The upregulation we describe could be potentially leveraged in anticonvulsant enhancement of KCNQ2 channels as therapeutic target for preventing epileptogenic seizures.

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Poster

460. Epilepsy: Ion Channels

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Topic: B.10. Epilepsy

Support: Seattle Children's Research Institute
NIH

Title: Human KCNQ5 (Kv7.5) gain-of-function and loss-of-function de novo mutations underlie epilepsy and intellectual disability validated by Cas9-targeted mKCNQ5 KO mice

Authors: *A. D. WEI[1], F. K. KALUME[1,2], T. A. ZWINGMAN[1], P. WAKENIGHT[1], A. BARD[1], N. SAHAI[1], M. H. WILLEMSEN[4,5], H. J. SCHELHAAS[6], J. S. VERHOEVEN[6], D. N. SHINDE[7], K. HELBIG[7], A. BASINGER[8], D. F. RODRIGUEZ-BURITICA[9], J. J. MILLICHAP[10,11], K. J. MILLEN[1,3], W. DOBYNS[1,3], J.-M. RAMIREZ[1,2]
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Abstract: The mammalian KCNQ (Kv7) gene family encodes M-currents, carried by subthreshold voltage-gated K^+ channels strongly modulated by diverse Gq-coupled GPCRs such as muscarinic receptors. The importance of this subclass of K^+ channels is highlighted by human mutations in all 5 members of this gene family (KCNQ1-5) associated with genetic channelopathies affecting cardiac, brain and auditory function, with mutations in KCNQ5 being most recently reported. We report here functional characterization of 6 new human KCNQ5 *de novo* mutations comprising 4 missense and 2 nonsense mutations identified by whole exome

sequencing in patients with epilepsy and intellectual disability, non-overlapping with mutations previously reported. Surprisingly, all missense mutations resulted in gain-of-function channels shifted in voltage-dependence of activation towards hyperpolarized potentials, demonstrated by heterologous expression and patch-clamp recordings in HEK293 cells. By contrast, both nonsense mutations conceptually truncate the channel protein prematurely, likely resulting in loss-of-function. Loss-of-function was confirmed for one nonsense allele that preserved all membrane-spanning domains S1-S6. This allele failed to express functional currents, nor traffic properly to the plasma membrane. To validate linkage of these *de novo* mutations to *in vivo* channelopathies, we generated 2 independent mKCNQ5 KO mouse lines, using Cas9/sgRNA to target exon 5 which encodes the turret domain immediately preceding the K^+ selectivity filter. Selective mKCNQ5 loss-of-function in both KO lines was confirmed by genomic sequencing, qRT-PCR and western blot analysis, without compensatory misregulation of mKCNQ1-4. Homozygous mKCNQ5 KO mice from both lines exhibited spontaneous tonic clonic convulsions and absence-type seizures during routine cage handling, with late adult onsets (>P150) and moderate penetrance (~25% of observed animals). Cortical EEG recordings from both KO lines during resting/sleep revealed abnormally higher activity in alpha (8-12 Hz) and beta bands (12-30 Hz) compared to WT, and a higher propensity for interictal spikes, poly-spikes and generalized synchronous oscillations. Similar to SCN1A mouse models of Dravet Syndrome, KCNQ5 KO mice exhibited abnormal thermal-induced seizures, with a temperature threshold of 40.5 ºC at which 50% of animals seized. Taken together, these results identify both gain-of-function and loss-of-function molecular phenotypes due to human KCNQ5 mutations linked to epilepsy and intellectual disability, and provide *in vivo* validation for the epileptogenic potential of KCNQ5 loss-of function.

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Poster

460. Epilepsy: Ion Channels

Location: SDCC Halls B-H

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Program #/Poster #: 460.06/C32

Topic: B.10. Epilepsy

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National Natural Science Foundation of China Grant 81371432
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Title: ERG3 potassium channel-mediated suppression of neuronal intrinsic excitability and prevention of seizure generation in mice

Authors: *Z. HUANG[1], X. KUO[2], S. Z. MING[2], F. M. HUA[2]
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Abstract: The input-output relationship of neuronal networks depends heavily on the intrinsic properties of their neuronal elements. Profound changes in intrinsic properties have been observed in various physiological and pathological processes, such as learning, memory and epilepsy. However, the cellular and molecular mechanisms underlying acquired changes in intrinsic excitability are still not fully understood. Here, we demonstrate that ERG3 channels are critically involved in the regulation of intrinsic excitability in hippocampal CA1 pyramidal neurons and DG granule cells. Knock-down of ERG3 channels significantly increases neuronal intrinsic excitability, which is mainly caused by decreased fast afterhyperpolarization (AHP), delayed time to the generation of an action potential (AP) and enhanced summation of somatic excitatory post-synaptic potentials (EPSPs). Interestingly, the expression level of ERG3 protein is significantly reduced in human and mouse brain tissues with temporal lobe epilepsy. Moreover, ERG3 channel knock-down in hippocampus significantly enhanced seizure susceptibility, while mice treated with ERG3 channel activator NS1643 were less prone to epileptogenesis. Taken together, our results suggest ERG3 channels play an important role in determining the excitability of hippocampal neurons and dysregulation of these channels may be involved in the generation of epilepsy. ERG3 channels may thus be a novel therapeutic target for the prevention of epilepsy.

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Poster

460. Epilepsy: Ion Channels

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Support: NIH Grant R01NS092705
Postdoctoral Research Fellowship American Epilepsy Society
Trustee Award Cincinnati Chidren's Research Foundation

Title: MicroRNA-mediated regulation of hippocampal A-type currents is associated with reduced seizure frequency in a mouse model of epilepsy

Authors: D. TIWARI[1], D. H. BRAGER[2], N. EL-SAYED[1], J. KRZESKI[1], J. RYMER[1], L. SCHROEDER[1], S. DANZER[1], *C. GROSS[1]
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Abstract: Epilepsy is characterized by changes in neuronal excitability and is often associated with altered expression or function of ion channels. One example of such a channelopathy observed in genetic and acquired epilepsy is the reduction of hyperpolarizing A-type potassium currents in the hippocampal CA1 region. These A-type currents are mainly mediated by the voltage-gated potassium channel Kv4.2, and here we confirm that Kv4.2 protein and mRNA are reduced in the pilocarpine mouse model of epilepsy. Emerging evidence suggests that microRNAs (miRNAs), small non-coding RNAs that regulate post-transcriptional expression of protein-coding mRNAs, are crucial regulators of genes involved in epilepsy. In line with this hypothesis, we have shown previously that expression of Kv4.2 is regulated by microRNA-induced silencing. Here, we show that antisense-mediated inhibition of the Kv4.2-targeting microRNA miR-324-5p in mice selectively increases A-type potassium currents in pyramidal neurons of the CA1, while leaving membrane potential, channel properties and other potassium currents unaltered. Using a pilocarpine mouse model of acquired epilepsy we found that inhibition of microRNA-induced silencing of Kv4.2 by intracerebroventricular injection of an antagomir (miRNA inhibitor) specific to miR-324-5p caused a reduction in seizure frequency. Our results suggest that miR-324-5p selectively regulates A-type potassium currents and that its manipulation can reduce seizures in epilepsy. Ongoing studies are assessing if reduced RNA-induced silencing of Kv4.2 underlies the observed reduction in seizure frequency.

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Poster

460. Epilepsy: Ion Channels

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Support: Sigmund Kiener Promotionstipendium für Studierende der Humanmedizin am Hertie Institut für klinische Hirnforschung

Title: A functional characterisation of missense mutations in CACNA1E, a novel epilepsy gene

Authors: *R. LAUERER[1,2], K. HELBIG[3], J. BAHR[1,2], B. UYSAL[1,2], N. SCHWARZ[1,2], U. B. S. HEDRICH[1,2], H. C. MEFFORD[4], H. LERCHE[1,2]
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Abstract: Developmental and epileptic encephalopathies (DEEs) are a heterogeneous group of severe early onset diseases of childhood characterized by developmental delay, intellectual disability, pharmacoresistant epileptic seizures and often other neuropsychiatric deficits. DEEs are commonly caused by *de novo* mutations which often affect voltage-gated ion channels. With mutations in Na^+ and K^+ channels at the focus of research on DEEs and other infantile epilepsy syndromes, knowledge about disease causing mutations in Ca^{2+} channels is emerging more slowly. Here, we present a functional characterization of missense mutations in *CACNA1E*, which we recently identified in patients with a form of West syndrome. This widely expressed gene encodes the voltage gated $Ca_V2.3$ (R-type) presynaptic Ca^{2+} channel. Mutations in this gene have so far not been identified as a causative factor in human epilepsy. To characterize the gating defects of mutant channels, we performed whole cell patch clamp recordings of tsA201 cells that were transiently transfected with the pore forming wild type (wt) or mutant α_{1E}-subunit and the β_{2d}-subunit. Functional effects of three mutations identified in patients with DEE, all located in the S6 segment of the second domain of $Ca_V2.3$, revealed clear gain of function effects with a significant hyperpolarizing shift of the voltage dependence of activation and a slowing of the inactivation time course. Our findings establish *CACNA1E* as a new 'epilepsy gene' and provide novel insights in the mechanisms causing the various forms of DEE.

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Poster

460. Epilepsy: Ion Channels

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Program #/Poster #: 460.09/C35

Topic: B.10. Epilepsy

Title: Efficacy of sodium channel inhibitors as anticonvulsants in the mouse maximal electroshock seizure assay is predictive of the therapeutic plasma concentration in humans

Authors: *P. KARIMI TARI[1], K. NELKENBRECHER[1], M. WALDBROOK[1], G. DE BOER[2], R. KWAN[2], C. M. DUBE[1], T. FOCKEN[3], C. DEHNHARDT[3], N. SHUART[4], S. GOODCHILD[4], L. SOJO[2], J. EMPFIELD[5], C. J. COHEN[5], J. JOHNSON[5]
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Abstract: The Maximal Electroshock Seizure (MES) assay has been widely used to characterize the efficacy of antiepileptic drugs. This assay involves induction of epileptic-like event in rodents and measures the ability of test compounds to inhibit seizures. Efficacy in this assay has often been considered a requirement for development of new therapeutic agents. In particular, clinically effective inhibitors of voltage-gated sodium channels (Na_V's) are all active in the MES assay. Although the dose-dependence of activity has been well defined, the relationship between plasma and brain concentration and efficacy is not often assessed. Here, we report the plasma and brain EC_{50}'s in the mouse MES assay and compare them with plasma concentrations observed to be effective at reducing epilepsy symptoms in patients. For the Na_V channel inhibitors phenytoin, carbamazepine and lacosamide, the plasma concentration needed for clinical efficacy is 1-5 times the plasma EC_{50} in the mouse MES assay. In other words, for efficacy in humans one needs to achieve plasma levels that are equivalent to or greater than the EC_{50} for protection in the mouse MES assay. We find that plasma levels associated with adverse effects in mice are similar to those associated with adverse events in the clinic. Thus the ratio between the mouse MES EC_{50} and toxicity in mice may serve as a predictor of clinical therapeutic safety index.

We find that a very high therapeutic index in mice can be achieved with Na_V inhibitors that selectively block $Na_V1.6$, with >100 fold selectivity against all other Na_V isoforms. We present an exemplar compound that safely achieves >90% suppression in the MES assay. We anticipate that this new class of selective Na_V inhibitors will achieve greater seizure suppression in humans with a significantly improved tolerability than is currently possible with available, non-selective Na_V inhibitors. The first exemplar of this class, XEN901, is currently in Phase I clinical trials.

Disclosures: P. Karimi Tari: A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **K. Nelkenbrecher:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **M. Waldbrook:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **G. de Boer:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **R. Kwan:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **C.M. Dube:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **T. Focken:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **C. Dehnhardt:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **N. Shuart:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **S. Goodchild:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **L. Sojo:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **J. Empfield:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **C.J. Cohen:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals. **J. Johnson:** A. Employment/Salary (full or part-time):; Xenon Pharmaceuticals.

Poster

460. Epilepsy: Ion Channels

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Program #/Poster #: 460.10/C36

Topic: B.04. Ion Channels

Support: NS053422

Title: Distinct functional alterations in SCN8A epilepsy mutant channels

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Abstract: More than 60 epilepsy-related mutations have been identified in *SCN8A*, the gene that encodes voltage-gated sodium channel isoform 1.6. However, effective treatments to temper the highly active network in such patients are often lacking, in part due to the functional heterogeneity of *SCN8A* mutations. Here we characterized a novel epilepsy mutation, R850Q, in the human Nav1.6 and compared its aberrant functional alterations with three other SCN8A epilepsy mutants previously characterized in rodent Nav1.6 constructs. We discovered that R850Q conducted higher level of persistent current, with no increase in resurgent current amplitude. R850Q also had slightly hyperpolarized voltage-dependence of activation, which increased its window current. We observed that the human Nav1.6 channel bearing the T767I mutation also displayed increased persistent current and hyperpolarized voltage-dependence of activation. In contrast, R1617Q showed a slower rate of inactivation, faster recovery from inactivation, increased persistent current, and an increased resurgent current amplitude. R1872Q had an increased current density, a slower rate of inactivation, a hyperpolarizing shift in voltage-dependence of activation, and a depolarizing shift in voltage-dependence of inactivation. Interestingly, all the mutant channels exhibited distinctive resurgent current kinetics compared to the wild-type channel. We propose that these changes, including the kinetic changes in resurgent currents, are likely to contribute to aberrant neuronal excitability.

Disclosures: Y. Pan: None. **T.R. Cummins:** None.

Poster

460. Epilepsy: Ion Channels

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 460.11/C37

Topic: B.10. Epilepsy

Support: NIH grant NS032387

Title: Dyshomeostatic mechanisms of KCNQ2-related epileptic encephalopathy in patient-specific iPSC-derived excitatory neurons

Authors: *D. SIMKIN[1,2], T. J. SEARL[1], J. J. MILLICHAP[3], B. N. PIYEVSKY[2], G. L. ROBERTSON[2], M. FORREST[4], P. PENZES[4], A. L. GEORGE, Jr.[1], E. KISKINIS[2]
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Abstract: Mutations in *KCNQ2*, which encodes a pore-forming K^+ channel subunit responsible for neuronal M-current, have been associated with neonatal epileptic encephalopathy (NEE), a complex disorder that manifests as severe early-onset seizures and impaired neurodevelopment due to an imbalance in neuronal circuit activity in the brain. While the effects of *KCNQ2* mutations have been studied extensively in heterologous expression systems, their effects on the inherent properties of human neurons have not. Specifically, what remains unclear is how the likely defects in M-current affect the electrophysiological properties of human neurons during a critical period of neuronal maturation. Here we use KCNQ2-NEE patient-specific and isogenic control iPSC-derived excitatory neurons to elucidate the dynamic functional effects of a *KCNQ2* mutation.
Our data indicate that neurons from a NEE patient carrying a KCNQ2 loss-of-function mutation (T274M) develop hyperexcitability progressively over time in culture but are no different from isogenic control neurons in terms of network or intrinsic excitability at early time points of maturation (using multi-electrode arrays and current-clamp electrophysiology, respectively). However, M-current amplitude is ~60% smaller in KCNQ2-NEE neurons as compared to isogenic and healthy control neurons at early and later time points in maturation. This suggests a dissociation between loss of M-current and hyperexcitability. We demonstrated that suppression of M-current in isogenic control neurons by acute inhibition of KCNQ2/3 channels with XE991 evokes hyperexcitability by slowing action potential (AP) repolarization and reducing the post-burst afterhyperpolarization (AHP). However, KCNQ2-NEE neurons exhibit faster repolarization and enhanced AHPs indicating an ability to generate more APs per burst. Moreover, we found that we were able to recapitulate the defects of KCNQ2-NEE neurons, only when we treated isogenic control neurons chronically but not acutely with XE991. Thus, mere

loss of M-current does not account fully for hyperexcitability exhibited by KCNQ2-NEE neurons. We conclude that neuronal hyperexcitability in KCNQ2-NEE neurons is a result of dyshomeostatic changes initiated by dysfunctional KCNQ2 channels.

Disclosures: D. Simkin: None. **T.J. Searl:** None. **J.J. Millichap:** None. **B.N. Piyevsky:** None. **G.L. Robertson:** None. **M. Forrest:** None. **P. Penzes:** None. **A.L. George:** None. **E. Kiskinis:** None.

Poster

460. Epilepsy: Ion Channels

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 460.12/C38

Topic: B.04. Ion Channels

Support: NIH NINDS K08 NS097633
Burroughs Wellcome Fund Career Award for Medical Scientists

Title: Effects on neuronal excitability of SCN3A mutations causing early infantile epileptic encephalopathy

Authors: *E. M. GOLDBERG[1,2,3], N. P. SOTUYO[2], T. ZAMAN[1]
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Abstract: Epilepsy is a severe neurological disease defined by recurrent seizures and associated with comorbid developmental delay and intellectual disability. The most severe type of epilepsy, the early infantile epileptic encephalopathies, are largely due to mutation in genes important for brain development and function. Voltage gated Na+ channels underlie action potential generation and propagation in excitable cells, and mutation in genes encoding voltage-gated sodium (Na+) channel α subunits are well-known causes of disease including childhood epilepsy. We recently showed that heterozygous *de novo* variants in *SCN3A* encoding the Na+ channel subunit Nav1.3 is a cause of very early onset epileptic encephalopathy; such mutations produce increased slowly-inactivating/persistent current and a left-shift in the voltage dependence of activation to more hyperpolarized potentials, suggesting a gain of channel function as the underlying pathogenic mechanism. However, the effect of such mutations on native neuronal function is not known. Here, to assess the impact of epilepsy-associated Nav1.3 variants on neuronal excitability, we express wild-type and mutant human Nav1.3 (Nav1.3-WT, Nav1.3-Ile875Thr, and Nav1.3-Val1769Ala) in cultured rat hippocampal pyramidal neurons via transient transfection, and in layer 2/3 pyramidal neurons in mouse neocortex using *in utero* electroporation. Current clamp recordings revealed spontaneous bursting from resting membrane potential with transition to depolarization block in cells expressing mutant hNav1.3, but not in

cells overexpressing hNav1.3-WT or in untransfected cultured neurons or in neighboring non-electroporated cells in brain slices. Such results further support the pathogenic nature of the identified epilepsy-associated Nav1.3 variants yet indicate that the effects of such variants on neuronal excitability may be complex.

Disclosures: E.M. Goldberg: None. **N.P. Sotuyo:** None. **T. Zaman:** None.

Poster

461. Calcium Channels

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 461.01/D1

Topic: B.04. Ion Channels

Support: NIH Grant R01GM102525

Title: Alterations in oscillatory activity of CeM neurons in mice lacking $Ca_V3.1$ isoform of T-channels during isoflurane-induced unconsciousness

Authors: *T. TIMIC STAMENIC, S. FESEHA, S. TODOROVIC
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Abstract: Previous studies established that $Ca_V3.1$ T-channels in the thalamus are inhibited by prototypical volatile anesthetic isoflurane (ISO) at clinically relevant concentrations. However, the specific mechanisms underlying the role of $Ca_V3.1$ channels in thalamocortical oscillations *in vivo* during general anesthesia with volatile anesthetics are largely unknown.
We recorded *in vivo* local field potentials (LFPs) from adult wild type (WT) and $Ca_V3.1$ knockout ($Ca_V3.1$ KO) mice under ISO anesthesia. Additionally we recorded changes in LFPs 30 minutes after injection of pan-selective T-channel blocker TTA-P2 (3,5-dichloro-N-[1-(2,2-dimethyl-tetrahydro-pyran-4-ylmethyl)-4-fluoro-piperidin-4-ylmethyl]-benzamide, 60 mg/kg i.p.) in WT and $Ca_V3.1$ KO mice. The LFPs are recorded from Barrel cortex and central medial nucleus of thalamus (CeM), part of intralaminar complex that is heavily implicated in control of arousal.
Baseline relative power revealed decreased delta (two-way RM ANOVA, $p<0.001$) and increased alpha oscillations ($p<0.01$) in $Ca_V3.1$ KO vs. WT mice in CeM, but not in the cortical leads.
Under 1% ISO anesthesia, relative power of delta oscillations in $Ca_V3.1$ KO mice was diminished (24.2%, 10 animals), when compared to WT mice (40.9%, 6 animals) in CeM (two-way RM ANOVA, $p<0.001$). Moreover, the change of relative delta power from awake state during 1% ISO revealed different level of delta rise: 12.0% in WT and 5.7% in $Ca_V3.1$ KO (t-test, $p<0.01$) in CeM. These changes were not detected in cortex. During 2% ISO anesthesia the same trend was observed. Importantly, suppression-to-burst ratio was higher during 1.4% ISO

administration in $Ca_V3.1$ KO (0.38) than in WT (0.10) mice ($p<0.05$), indicating greater suppression of thalamocortical information transfer in $Ca_V3.1$ KO mice.
In WT animals we observed that TTA-P2 increased relative power of delta oscillations to 50.7% (7 animals), while in $Ca_V3.1$ KO mice its effect was much smaller (29.9%, 10 animals, $p<0.001$) in CeM. On the other hand, relative power for alpha and beta oscillations were two-fold higher in $Ca_V3.1$ KO mice when compared to WT mice ($p<0.001$ and $p<0.01$, respectively). The same was detected in cortex. Consistent with this notion, the change of relative delta power from awake state after TTA-P2 administration revealed different level of delta increase: 26.5% in WT and 13.6% in $Ca_V3.1$ KO mice (t-test, $p<0.001$) in CeM, and 32.6% in WT and 15.3% in $Ca_V3.1$ KO mice (t-test, $p<0.001$) in cortex.
Our results demonstrate for the first time the importance of thalamic $Ca_V3.1$ T-channels in thalamocortical oscillations that underlie clinically important effects of volatile anesthetics.

Disclosures: T. Timic Stamenic: None. **S. Feseha:** None. **S. Todorovic:** None.

Poster

461. Calcium Channels

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 461.02/D2

Topic: B.04. Ion Channels

Support: SFB Grant 1089

Title: Effect of conditional ryanodine receptor 2 knockout on neuronal activity in the hippocampus and learning

Authors: *M. MITTAG[1], L. WISCHHOF[2], F. BERTAN[3], L. SOSULINA[4], D. DALÜGGE[4], S. REMY[4], D. BANO[2], P. NICOTERA[3], M. FUHRMANN[1]
[1]Neuroimmunology and Imaging, [2]Aging and Neurodegeneration, [3]Synaptic Connectivity and Neurodegeneration, [4]Neuronal Networks, DZNE German Ctr. for Neurodegenerative Dis., Bonn, Germany

Abstract: Ca^{2+} signaling, mediated by entry of Ca^{2+} through the plasma membrane or release from the endoplasmic reticulum (ER), plays an important role in neuronal function. Elevation of intracellular Ca^{2+} triggers release of neurotransmitters at the synapse, contributes to dendritic spikes, induces activity-dependent changes in gene expression and regulates synaptic plasticity. Although much of the entry of Ca^{2+} into neurons occurs through plasma membrane channels, the ER is the major dynamic pool for intracellular Ca^{2+}. We hypothesize that ryanodine receptor 2 (RyR2), a receptor that is situated at the ER mediating the release of Ca^{2+} from the ER into the cell, is involved in spatial information processing in the hippocampus. To address this hypothesis, we locally restricted the conditional knockout of RyR2 to CA1 neurons and recorded

Ca^{2+}-transients of CA1 neurons in anaesthetized and awake head-fixed mice during spatial navigation. Furthermore, we tested whether conditional RyR2 knockout affected spatial learning. We observed that the conditional RyR2 knockout resulted in a changed Ca^{2+}-event frequency in the awake, resting animal. Furthermore we observed a decreased fraction of place cells as well as a decreased firing probability of place cells within their respective place field. In addition RyR2 knockout mice exhibited impaired learning in the radial arm maze after conditional knockout. These findings indicate a major role of RyR2 in spatial learning in the hippocampus.

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Poster

461. Calcium Channels

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 461.03/D3

Topic: B.04. Ion Channels

Title: Development of a high-throughput screening assay for l-type calcium channels in neurons

Authors: Y.-L. ZHANG[1], E. NACU[1,2], M. E. FITZPATRICK[1], W. CROTTY[1,2], E. M. SCOLNICK[1], K. EGGAN[1,2], *J. R. COTTRELL[1]
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Abstract: Genetic analysis of psychiatric disease has implicated *CACNA1C* and *CACNA1D* as important schizophrenia and bipolar susceptibility genes. These risk genes encode the α1 subunits of the two major L-type calcium channels (LTCC), $Ca_V1.2$ and $Ca_V1.3$, expressed in the brain. However, LTCC modulators have potential for significant on-target cardiac liability, and no brain selective LTCC antagonists are currently available. As individual LTCC genes are expressed as multiple isoforms due to alternative splicing or proteolytic processing, some of these isoforms show markedly higher expression in human brain than in human heart. In addition, there may be brain-specific mechanisms for modulating LTCC function that can only be identified through their analysis in a neuronal context. Here, we report a high throughput calcium influx assay for identifying positive and negative modulators of LTCCs directly in primary rat hippocampal neurons and iPSC-derived human neurons. We validated this assay using LTCC pharmacological tools and performed a pilot screen of 4,551 compounds from the Broad Institute's repurposing library. From the screen, we were able to identify known LTCC blockers and activators in both type of neurons. More importantly, we discovered novel LTCC modulators in both rat hippocampal and Ngn2-induced human neurons, pointing to potential novel approaches for modulating LTCC function directly or indirectly. In summary, our assay

could prove a powerful approach for identifying neuron-specific modulators of LTCCs that avoid cardiac liabilities for the potential treatment of multiple psychiatric disorders.

Disclosures: Y. Zhang: None. **E. Nacu:** None. **M.E. Fitzpatrick:** None. **W. Crotty:** None. **E.M. Scolnick:** None. **K. Eggan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Q-State Biosciences. **J.R. Cottrell:** None.

Poster

461. Calcium Channels

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 461.04/D4

Topic: B.04. Ion Channels

Support: Collaboration grant from the Boettcher Foundation

Title: A mutation in CaV2.1 linked to ataxia, hypotonia and developmental delay profoundly impairs channel voltage-sensitivity

Authors: *S. TYAGI[1], T. R. BENDRICK[1], D. FILIPOVA[2], S. PAPADOPOULOS[2], R. A. BANNISTER, 80045[1]
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Abstract: Ca^{2+} flux into axon terminals via P/Q-type $Ca_V2.1$ channels is the trigger for neurotransmitter vesicle release at neuromuscular junctions and many central synapses. Recently, an arginine to proline substitution (R1673P) in the S4 voltage-sensing helix of the fourth membrane-bound Repeat of $Ca_V2.1$ was linked to a severe neurological disorder characterized by hypotonia, ataxia, cerebellar atrophy and global developmental delay. Since the R1673P substitution occurs at a position that is likely to be critical for sensing membrane potential, we investigated its effect on channel gating. To do so, we fused Venus fluorescent protein to the amino-termini of wild-type rat $Ca_V2.1$ and rat $Ca_V2.1$ carrying the equivalent of the human R1673P mutation (R1624P). These constructs were then expressed in tsA-201 cells for use in whole-cell patch-clamp experiments. With 2 mM Ca^{2+} serving as the charge carrier, we observed a profound depolarizing shift in activation of V-$Ca_V2.1$ R1624P relative to V-$Ca_V2.1$ ($V_{1/2act}$ = 16.8 ± 1.8 mV, n = 17 *vs*. -3.4 ± 1.7 mV, n = 16, respectively; $p < 0.001$). A similar shift was observed when 2 mM Ba^{2+} was used as the charge carrier ($V_{1/2act}$ = 11.5 ± 4.8 mV, n = 4 *vs*. -4.6 ± 3.6 mV, n = 6, respectively; $p < 0.05$). Application of roscovitine (12.5 μM), a compound previously shown to stabilize the open state of wild-type $Ca_V2.1$ channels, increased Ca^{2+} flux via R1624P at test potentials corresponding to peak activation of wild-type $Ca_V2.1$ (~3-fold at +10 mV, n = 9; $p < 0.005$) and slowed deactivation following repolarization from +10 mV to -40

mV (τ_{deact} = 0.62 ± 0.05 *vs*. 1.07 ± 0.14 ms before and during roscovitine application, respectively; $p < 0.01$). Taken together, our results indicate that the $Ca_V2.1$ R1673P mutation almost certainly causes a profound impairment of channel voltage-sensitivity *in vivo*, thereby increasing the probability of synaptic failure at both neuromuscular junctions and central synapses. In addition, our data raise the possibility that therapeutic agents that increase $Ca_V2.1$ open probability or prolong action potential duration may be effective in combatting this and other related disorders.

Disclosures: S. Tyagi: None. **T.R. Bendrick:** None. **D. Filipova:** None. **S. Papadopoulos:** None. **R.A. Bannister:** None.

Poster

461. Calcium Channels

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Topic: B.04. Ion Channels

Support: NIH grant GM102525
NIH grant R0144517
NIH grant R0144517-S
NIH grant GM118197
NIH grant HD080281

Title: Cognitive and affective behavioral phenotype of $Ca_V3.1$ knock-out mice: The importance of subicular circuitry

Authors: *S. M. JOKSIMOVIC[1], N. BUSQUET[2], R. VALDEZ[3], S. M. TODOROVIC[1]
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Abstract: Low-voltage activated T-type calcium channels (T-channels) are important regulators of neuronal excitability and oscillatory activity. Thus far, only mice lacking the $Ca_V3.2$ isoform of T-channels have been studied in experimental protocols assessing hippocampal activity, with limited data on the role of the $Ca_V3.1$ isoform, which has been mainly associated with aberrant sleep patterns. We have recently shown that $Ca_V3.1$ T-channels regulate burst firing and synaptic plasticity in the subiculum, the main output structure of the hippocampal formation. However, the role of T-channels, particularly the $Ca_V3.1$ isoform, in cognitive processing, as well as affective behavior, remain largely unexplored.
First, we recorded local field potentials (LFPs) from the dorsal subiculum (dSub) and cortical EEG activity of freely-moving adult male WT and $Ca_V3.1$ knock-out (KO) mice using bilateral depth electrodes (in mm from bregma; AP: -2.8, ML: ±1.0, DV: 1.9) and cortical screws (AP: -

1.0, ML: ±3.0), respectively. Then, we performed behavioral characterization of KO mice using an extensive behavioral battery aimed to assess learning and memory [Y-maze, radial arm water maze (RAWM), novel object recognition test (NORT), and contextual fear conditioning (CFC)] or anxiety-related behavior (open field and elevated zero maze).
In vivo LFP recordings revealed a profound decrease in high-frequency oscillations in dSub of KO mice, without significantly affecting lower frequency bands, as compared to WT mice. For example, both absolute and relative gamma power (30-50 Hz) were decreased for about 50% in left dSub of KO animals ($p=0.010$ and $p=0.043$, respectively). Interestingly, we did not detect significant changes in the cortical oscillatory activity. In behavioral testing, mice lacking $Ca_V3.1$ isoform showed impaired spatial navigation in RAWM, as well as diminished recognition memory in NORT, as compared to the WT group. These cognitive deficits in KO animals were accompanied by alterations in emotional processing, as assessed by the behavior in the open field test and elevated zero maze, as well as by the magnitude of the freezing response to fear conditioning.
Our findings provide the first evidence that high-frequency oscillations in the dorsal subiculum heavily rely on $Ca_V3.1$ T-channel activity. We recently showed a vital role of these channels in synaptic plasticity of the subiculum, but not CA1 region. Based on these two important observations, we propose that specific changes in subicular activity observed in mice lacking $Ca_V3.1$ T-channels may be accountable for a variety of behavioral deficits associated with cognitive and affective processing.

Disclosures: N. Busquet: None. **R. Valdez:** None. **S.M. Todorovic:** None.

Poster

461. Calcium Channels

Location: SDCC Halls B-H

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Program #/Poster #: 461.06/D6

Topic: B.04. Ion Channels

Support: NIMH Grant T32MH020065
NIH Grant R01NS094665-03

Title: Neuronal voltage gated calcium channel genes produce secondary nuclear proteins that are subcellularly regulated in an activity-dependent manner

Authors: *E. RAO[1], D. P. HEJAZI[2], X. DU[3], J. GODFREY[3], C. M. GOMEZ[4]
[1]Neurobio., [3]Neurol., [4]Dept Neurol., [2]Univ. of Chicago, Chicago, IL

Abstract: Voltage-gated calcium channels (VGCCs) play crucial roles in the central nervous system, including regulating fast and slow neurotransmitter release, altering gene expression through a myriad of signaling pathways, and inducing post-synaptic responses such as long-term

potentiation and long-term depression. Our lab has shown previously that the P/Q-type VGCC gene *CACNA1A* is bicistronic, meaning that it encodes two structurally unrelated proteins with distinct functions from the same mRNA. The *CACNA1A* gene encodes the CaV2.1 VGCC subunit through canonical, cap-dependent translation, and additionally encodes a transcription factor, α1ACT, through a cryptic Internal Ribosomal Entry Site (IRES) within the open reading frame. We propose that this bicistronic expression mechanism is conserved throughout the larger VGCC superfamily, and to this end we have shown that the L-type VGCC gene *CACNA1C* and the T-type VGCC gene *CACNA1H* also produce secondary proteins that localize to the nucleus in cultured cells and endogenous neuronal tissue. These secondary proteins produced by *CACNA1C* and *CACNA1H*, termed CCAT and α1HCT respectively, translocate to the nucleus under control of cellular ionic milieu where they act as nuclear regulatory units, affecting expression of a wide array of genes. We hypothesize that these secondary proteins function as activity coupled transcription factors that regulate an ensemble of genes coincident with calcium channel activity. Furthermore we propose that dysfunction or dysregulation of these novel secondary proteins could contribute to the complex phenotypes observed in neuropsychiatric diseases related to mutations in *CACNA1C* and *CACNA1H*, and could therefore potentially be attractive therapeutic targets. The findings of this project may have vast implications for a wide variety of neurological disorders affecting *CACNA1C* and *CACNA1H*, and could provide novel therapeutic targets for the treatment of such disorders.

Disclosures: E. Rao: None. **D.P. Hejazi:** None. **X. Du:** None. **J. Godfrey:** None. **C.M. Gomez:** None.

Poster

461. Calcium Channels

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Program #/Poster #: 461.07/D7

Topic: B.04. Ion Channels

Support: NHMRC PG1105944

Title: Non-linear Ca^{2+} events along apical obliques of layer 5 cortical pyramidal neurons

Authors: M. L. CASTANARES, H. MA, *V. DARIA
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Abstract: Apical obliques are thin branches that are densely expressed in CA1 pyramidal neurons and sparsely in Layer5 (L5) pyramidal neurons. While the number of apical obliques is less (~ 4-10 branches along the trunk) in L5 neurons, they bifurcate from the apical trunk at Layer 4 making them synaptic targets of projections from the thalamus. In addition, forward-propagating impulses from the tuft dendrites to the soma (e.g. synaptic inputs or dendritic Ca^{2+}

spikes) and back-propagating action potentials (bAPs) traverse a section along the apical trunk where these obliques start to bifurcate. What is the role of these obliques in the propagation of these impulses? Objective: We aim to understand whether these oblique dendrites act as passive leaky segments that attenuate the signals or if they are capable of generating regenerative dendritic events that can potentially boost forward- or backward- propagating signals. Method: Using a multi-compartmental model of a L5 pyramidal neuron [Shai, *et al*, 2015], we describe a condition where there is a non-linear rise in the membrane potential following a train of two bAPs. Within 4 to 40 Hz of the bAP train, a critical frequency of about 20 to 30 Hz, sets a non-linear Ca^{2+} influx. The non-linear rise in the Ca^{2+} response is observed after the second bAP and are concentrated at apical obliques situated about 100microns from the soma. On the other hand, these non-linear responses are not found at proximal (~50 microns) and distal (>150microns from the soma) obliques where they exhibited a linear increase in Ca^{2+} transients. Unlike the Ca^{2+} spikes generated at the nexus (an event which requires a train of 4-6 bAPs at 80-100Hz), the Ca^{2+} spikes at the obliques occurs at a more physiologically lower frequency of 20-30Hz. This suggests that oblique dendrites can potentially function as active sub-integration sites at a slower somatic activity way before Ca^{2+} spikes at the nexus are generated.

Disclosures: M.L. Castanares: None. **H. Ma:** None. **V. Daria:** None.

Poster

461. Calcium Channels

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Program #/Poster #: 461.08/D8

Topic: B.04. Ion Channels

Support: Intramural funding from Rajiv Gandhi Centre for Biotechnology
Research grant from Kerala State Council for Science, Technology and Environment, India
Postdoctoral fellowship to MJ from Department of Biotechnology, Govt. of India
Senior research fellowship to MK from Kerala State Council for Science, Technology and Environment, India

Title: Regulation of NMDA receptor phosphorylation *in vivo* by administration of voltage gated calcium channel agonist, BayK8644

Authors: *R. V. OMKUMAR, M. JOHN, M. KUMAR, M. MADHAVAN
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Abstract: Calcium influx through N-methyl-D-aspartate receptors (NMDAR) and voltage gated calcium channels (VGCC) plays major roles in postsynaptic signaling mechanisms. Eventhough multiple calcium signaling pathways converge at the level of free calcium release in the cytosol,

they maintain specificity towards their respective targets that are further downstream. NMDAR subunit GluN2B is phosphorylated at Ser^{1303} (*J Biol Chem. 1996, 271, 31670-8*). Phosphoryation at this site is a prominent event in cell culture systems as well as *in vivo* (*Int. J. Neuropsychopharmacol., 2010, 13, 1255-1260*). and influences the conductance of NMDAR channel (*Cell 2010, 140, 222-234*). Level of phosphorylation of GluN2B-Ser^{1303} is likely to be sensitive to calcium signaling since the calcium sensitive kinases, CaMKII (*J Biol Chem. 1996, 271, 31670-8*) and PKC (*Mol. Pharmacol., 2001, 59, 960*) are known to phosphorylate this site. Protein phosphatase 1 dephosphorylates this site (*Neurochem. Int. 2012, 61, 961-5; PLoS One, 2012, 7, e34047*). Despite the available data, the functional significance of phosphorylation at this site is not completely understood. In this study, we explored the effect of calcium signaling through VGCC on phosphorylation status of GluN2B-Ser^{1303} in the rat *in vivo* model. VGCC was activated by intraperitoneal (IP) injection of the VGCC activator, BayK8644. Subsequently, the levels of phospho-GluN2B-Ser^{1303} in the cortex and in the hippocampus were monitored by western blotting. We find that phosphorylation at this site increases in response to activation of VGCC by BayK8644 treatment. However the level of GluN2B remains largely unchanged indicating that the effect is brought about by kinases or phosphatases. The effect could be prevented by prior intracerebroventricular (ICV) administration of the specific blocker of VGCC, nifidipine. The effect was also blocked by pretreatment of the animals with ICV administration of KN-93 indicating that it is mediated through CaM kinase. The levels of various other proteins involved in cell survival and cell death are also being studied. We conclude that under *in vivo* conditions, calcium influx through VGCC activates CaM kinase. This in turn phosphorylates GluN2B-Ser^{1303}.

Disclosures: **R.V. Omkumar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Designated as inventor in patents, but not involving the data reported in this abstract. **M. John:** None. **M. Kumar:** None. **M. Madhavan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Designated as inventor in patents, but not involving the data reported in this abstract.

Poster

461. Calcium Channels

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 461.09/D9

Topic: B.04. Ion Channels

Support: AG052934-03

Title: The development and characterization of a new, conditional mouse model over-expressing $Ca_v1.2$

Authors: *R. PARENT[1], L. J. OUILLETTE[2], H. BURNS[2], A. SMARSH[2], V. A. CAZARES[3], G. G. MURPHY[4]
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Abstract: L-type voltage gated Ca^{2+} channels (LVGCC) are integral membrane proteins that modulate the influx of Ca^{2+} into excitable cells in response to membrane depolarization. In the brain, $Ca_v1.2$ is the most abundant LVGCC and accounts for ~89% of LVGCCs. $Ca_v1.2$ has been shown to couple Ca^{2+} currents to transcriptional regulation, playing an important role in dendritic development, synaptic plasticity, neuronal survival and learning and memory. The $Ca_v1.2$ protein complex is an assemblage of three different subunits, with the main pore forming subunit, α1C, being encoded for by *CACNA1C*. Functional mutations within exon 8 cause Timothy Syndrome, which is characterized by heart defects and autism spectrum symptoms, likely resulting from a gain of function mutation. Additionally, GWAS studies have linked several SNPs within *CACNA1C*, most of which are found in intron 3, to bipolar disorder, schizophrenia and major depression disorder. It is not clear how polymorphisms in *CACNA1C* function to modulate psychiatric disease, but it is likely the result of alterations in transcriptional regulation, with evidence suggesting that genetic variation at SNP rs1006737 results in an increase in expression levels of *CACNA1C*.
Changes in expression of $Ca_v1.2$ have also been linked to Alzheimer's disease (AD). It is a well-supported hypothesis that calcium dysregulation contributes to the pathology of AD, with amyloid proteins being able to induce Ca^{2+} influx into neurons. It has also been shown that APP interacts directly with $Ca_v1.2$, and complete loss of APP results in a substantial increase in $Ca_v1.2$ in GABAergic neurons, and a comparable increase in Ca^{2+} currents.
It is clear that changes in the *CACNA1C* sequence and $Ca_v1.2$ expression are associated with several different disease states. There has been a significant amount of work demonstrating the loss of $Ca_v1.2$ in mice produces a number of behavioral and affective phenotypes, but surprisingly little effort has been made to understand the impact of increased expression. Therefore, we have created a novel line of transgenic mice that over express $Ca_v1.2$, which contains an HA tag allowing us to detect the exogenous protein expression. Expression of the full length transgene is driven by the CAG promoter, and contains a Lox-Stop-Lox cassette upstream of the cDNA sequence, allowing us to control its expression using cre-recombinase. We have achieved germline transmission of the transgene in six different founder lines, with expression of the HA tag in at least two of them when crossed with synapsinI cre driver mice. Additional characterization is ongoing.

Disclosures: R. Parent: None. **L.J. Ouillette:** None. **H. Burns:** None. **A. Smarsh:** None. **V.A. Cazares:** None. **G.G. Murphy:** None.

Poster

461. Calcium Channels

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 461.10/D10

Topic: B.04. Ion Channels

Support: NIH Grant NS087068
NIH Grant NS096246

Title: Determining the molecular identity of the mitochondrial Na^+/Ca^{2+} exchanger in neurons

Authors: *G. C. WALTERS[1], J. E. RYSTED[1], Z. LIN[2], A. GNANASEKARAN[2], R. A. MERRILL[2], S. STRACK[2], Y. M. USACHEV[2]
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Abstract: In neurons, mitochondria efficiently buffer Ca^{2+} influx during excitation, and then release Ca^{2+} back into the cytosol, which helps shape $[Ca^{2+}]_i$ transients and regulates many Ca^{2+}-dependent neuronal functions. The putative identity of the uniporter required for mitochondrial Ca^{2+} efflux was previously reported as the $Na^+/Ca^{2+}/Li^+$ exchanger known as NCLX (*SLC8B1*). However, our findings showed that NCLX did not localize to mitochondria in neurons. Therefore, we further explored the role of NCLX in neurons by simultaneously monitoring Ca^{2+} concentration in the cytosol ($[Ca^{2+}]_{cyt}$) and mitochondria ($[Ca^{2+}]_{mt}$) of cultured DRG neurons obtained from wild type (WT) and NCLX knockout (KO; Jackson Lab, C57BL/6J background) mice. In these experiments, $[Ca^{2+}]_{cyt}$ and $[Ca^{2+}]_{mt}$ elevations were elicited by trains of action potentials (5-8 Hz, 4-8 s) using extracellular field stimulation. Surprisingly, NCLX deletion did not significantly affect either $[Ca^{2+}]_{mt}$ elevation or the rate of Ca^{2+} extrusion from mitochondria. Similarly, NCLX deletion had no significant effect on the rate of Ca^{2+} extrusion from mitochondria in hippocampal neurons. As prior studies examined the role of NCLX in HeLa cells rather than neurons, we next used simultaneous measurements of $[Ca^{2+}]_{cyt}$ and $[Ca^{2+}]_{mt}$ in HeLa cells. In these experiments, we found that there was no effect of shRNA knockdown of NCLX in either $[Ca^{2+}]_{cyt}$ or $[Ca^{2+}]_{mt}$ amplitude or response duration to histamine, arguing against the role of NCLX in this process. To identify other genes involved in mitochondrial Ca^{2+} regulation we compared gene arrays from mice deficient in mitochondrial Ca^{2+} influx (MCU KO) to WT and identified the $Na^+/Ca^{2+}/K^+$ exchanger 2 (NCKX2/*SLC24a2*) as a putative target. In neurons, we found that NCKX2 was primarily localized to the mitochondria, suggesting a possible role of NCKX2 in mitochondrial Ca^{2+} extrusion. In Hela cells, we found that NCLX localized primarily to the ER whereas NCKX2 was localized to the mitochondria or Golgi. Overall, these data suggest that NCLX is not the main regulator of mitochondrial Ca^{2+} extrusion in neurons and possibly non-neuronal cells.

Disclosures: G.C. Walters: None. **J.E. Rysted:** None. **Z. Lin:** None. **A. Gnanasekaran:** None. **R.A. Merrill:** None. **S. Strack:** None. **Y.M. Usachev:** None.

Poster

461. Calcium Channels

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 461.11/D11

Topic: B.04. Ion Channels

Support: Austrian Science Fund SFB F4415
Austrian Science Fund DOC 30-B30
Deutsche Forschungsgemeinschaft SFB1348-TPA03

Title: Axonal wiring and postsynaptic $GABA_A$-receptor abundance are regulated by the presynaptic calcium channel $\alpha_2\delta$-2 subunit via a trans-synaptic mechanism

Authors: S. GEISLER[1], C. L. SCHÖPF[1], R. I. STANIKA[1], M. KALB[1], M. CAMPIGLIO[1], D. REPETTO[2], L. TRAXLER[1], M. MISSLER[2], *G. J. OBERMAIR[1]
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Abstract: Auxiliary $\alpha_2\delta$ subunits modulate current properties and membrane trafficking of voltage-gated calcium channels and have been implicated in synapse formation. Indeed, we could recently demonstrate that excitatory synapse formation failed in a cellular $\alpha_2\delta$ triple knockout model (Schöpf et al., *submitted*). Thus $\alpha_2\delta$ subunits are redundant key regulators of glutamatergic synaptogenesis, however, their role in inhibitory synapses is still elusive. Here we show that the specific expression of a single isoform, $\alpha_2\delta$-2, in presynaptic glutamatergic terminals induces a mismatched localization of postsynaptic $GABA_A$-receptors ($GABA_A$Rs). In theory this puzzling observation can be explained by (1) a compensatory upregulation of postsynaptic $GABA_A$Rs in response to $\alpha_2\delta$-mediated enhanced excitatory activity, (2) an active participation of presynaptic $\alpha_2\delta$-2 in the trans-synaptic anchoring of postsynaptic $GABA_A$Rs, and (3) aberrant axonal wiring induced by presynaptic expression of $\alpha_2\delta$-2. In order to distinguish between these hypotheses we analyzed the consequences of presynaptic $\alpha_2\delta$-2 expression on glutamatergic and GABAergic synapse composition and synaptic transmission. Using high-resolution immunofluorescence analysis we show that presynaptic $\alpha_2\delta$-2 increases postsynaptic $GABA_A$Rs both in glutamatergic and GABAergic synapses. The synaptic cell adhesion molecules α-neurexins have previously been shown to regulate presynaptic calcium channels by acting together with $\alpha_2\delta$ subunits. Here we show that $\alpha_2\delta$-2-induced clustering of mismatched postsynaptic $GABA_A$Rs is further upregulated in hippocampal neurons lacking all three α-neurexins. Thus, α-neurexins can modulate the effect of presynaptic $\alpha_2\delta$-2; however, they are not required for recruiting $GABA_A$Rs by presynaptic $\alpha_2\delta$-2. Most importantly, by employing high-

and super-resolution (gSTED) microscopy we demonstrate that presynaptic expression of $\alpha_2\delta$-2 induces an aberrant wiring of glutamatergic axons to GABAergic postsynaptic positions. Electrophysiological recordings in cultures of paired neurons revealed that the aberrant wiring resulted in reduced synaptic transmission (EPSC) and increased paired-pulse facilitation. Finally, using structure homology modeling and immunofluorescence analyses we identify a single splice region in $\alpha_2\delta$-2 responsible for mediating the trans-synaptic effect on $GABA_ARs$. Taken together, our findings provide novel insights into trans-synaptic mechanisms and are particularly interesting considering neuropsychiatric diseases such as autism spectrum disorders, which are associated with axonal wiring defects.

Disclosures: S. Geisler: None. **C.L. Schöpf:** None. **R.I. Stanika:** None. **M. Kalb:** None. **M. Campiglio:** None. **D. Repetto:** None. **L. Traxler:** None. **M. Missler:** None. **G.J. Obermair:** None.

Poster

461. Calcium Channels

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 461.12/D12

Topic: B.04. Ion Channels

Support: CHIR F15-01311

Title: L-type calcium channels modulate the firing pattern of the basolateral amygdala principal neurons

Authors: *Y. ZHANG, E. GARCIA, L. YANG, R. GOPAUL, T. SNUTCH
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Abstract: Calcium influx via neuronal L-type calcium channels (LTCCs) has been implicated in regulating neurotransmitter release, neuronal excitability, synaptogenesis, and dendritic growth. However to date, the functional role of LTCCs in regulating neuronal excitability and homeostasis during early developmental stages of the brain has not yet been thoroughly explored. LTCCs are highly expressed in the basolateral amygdala (BLA), an integrative center of the brain for emotional behaviors, where they are known to play a role in fear extinction. Here, we utilized whole-cell patch clamp techniques on acute brain slices from Sprague Dawley rats to examine the contributions of LTCCs to the excitability of BLA principal neurons during critical developmental periods. Results show that acute application of the LTCC agonist (S)-Bay K8644 increased excitability of BLA principal neurons from both immature post-natal day 7 (P7) and juvenile post-natal day 21 (P21) stages. The suprathreshold steady-state firing frequency (sSSFF) increased from 9.02±0.44 Hz to 13.89±3.68 Hz at P7 and from 6.58±0.57 Hz to 14.46±3.98 Hz at P21. In the presence of neurotransmission blockers, increased intrinsic

excitability was evident at P7 (sSSFF: 6.47±0.85 Hz to 11.38±1.64 Hz) but not in P21 neurons. The acute local injection of (S)-Bay K8644 (50 µg/kg) into the BLA of P10 animals produced subsequent changes in the firing pattern at P21: ~83% of P21 neurons displayed burst-firing compared to ~56% in control animals; further, firing adaptation during stimulation was fully abolished in slices from (S)-Bay K8644-treated but not control animals. We hypothesize that these effects may be related to LTCC-mediated modification to the calcium-activated potassium channel-related afterhyperpolarization. Dysfunction of the BLA has been implicated in the etiology of psychiatric disorders including anxiety, depression, and autism spectrum disorders. Our findings suggest that functional increases in LTCC activity during neurodevelopment could potentially underlie alterations of neuronal circuitry and contribute to neurodevelopmental disorders.

Disclosures: Y. Zhang: None. **E. Garcia:** None. **L. Yang:** None. **R. Gopaul:** None. **T. Snutch:** None.

Poster

461. Calcium Channels

Location: SDCC Halls B-H

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Program #/Poster #: 461.13/D13

Topic: B.04. Ion Channels

Support: R21NS077330
R01NS087033

Title: CRAC channels contribute to TRPV1-mediated calcium entry in dorsal root ganglion neurons

Authors: *Y. MEI, D. WEI, H. HU
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Abstract: TRPV1 (transient receptor potential vanilloid 1) is a member of the transient receptor potential (TRP) superfamily of cation channels. TRPV1 acts as a transducer and molecular integrator of noxious stimuli in the periphery. It is well-known that TRPV1 is expressed not only on the plasma membrane, but also on the ER membrane. However, the functional significance of $TRPV1_{ER}$ remains exclusive. Previous reports have shown that activation of TRPV1 by agonist capsaicin causes Ca^{2+} release from the intracellular Ca^{2+} stores in rodent dorsal root ganglia (DRG) neurons. We have demonstrated that store-operated calcium channels (SOCs) are mainly expressed in nociceptors including TRPV1 positive neurons. These findings prompted us to ask whether capsaicin-induced Ca^{2+} release can trigger store-operated calcium entry (SOCE). To answer this question, we performed immunofluorescence staining using specific antibodies. We observed that TRPV1 was co-expressed with STIM1, a major component of the SOC family, in

DRG neurons. Live-cell imaging results showed that activation of TRPV1 with capsaicin triggered a translocation of STIM1 from the ER towards to the plasma membrane. TRPV1-mediated Ca^{2+} entry was also attenuated by CRAC inhibitors, YM-58483 and Synta66. Knockout of Orai1 or knockdown of Orai2 or Orai3 significantly decreases capsaicin-induced Ca^{2+} entry, indicating that CRAC channels contribute to TRPV1-mediated Ca^{2+} entry. We then attempted to identify the ER Ca^{2+} stores that are involved in TRPV1-mediated Ca^{2+} release. Ryrodine receptors (RyRs) are known to be expressed in nociceptors. We found that depletion of ryanodine sensitive Ca^{2+} pools by caffeine caused SOCE. Interestingly, caffeine attenuated/abolished TRPV1-mediated Ca^{2+} release in the majority of TRPV1 positive neurons, suggesting that TRPV1-mediated Ca^{2+} release may be from caffeine-sensitive stores, at least partially. In addition, our *in vivo* studies indicated that Orai1 or STIM1 deficient mice showed a decrease in TRPV1-mediated nociception. Collectively, our findings reveal that$TRPV1_{ER}$ activation triggers CRAC channel activation and SOCE. This study provides a novel mechanism underlying TRPV1-mediated nociception.

Disclosures: Y. Mei: None. **D. Wei:** None. **H. Hu:** None.

Poster

461. Calcium Channels

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 461.14/D14

Topic: B.04. Ion Channels

Support: Fondazione Telethon Italia - GGP16029

Title: The role of the Mitochondrial Ca^{2+} Uniporter (MCU) in the pathogenesis of Alzheimer's disease

Authors: *B. D'ORSI[1], L. GALLO[1], E. GREOTTI[1], D. DE STEFANI[1], T. POZZAN[1], R. RIZZUTO[2]
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Abstract: Ca^{2+} homeostasis impairment and mitochondrial dysfunction are crucial events associated with several neurological conditions, including Alzheimer's disease (AD), ultimately leading to neurodegeneration. In recent years, the role of the Mitochondrial Calcium Uniporter (MCU), a 40 kDa protein of the inner mitochondrial membrane, has been extensively studied. MCU is responsible for Ca^{2+} uptake into the matrix and is modulated by several regulatory subunits. However, the authentic connection between mitochondrial Ca^{2+} overload, through the MCU, and AD has never been directly addressed. The composition of the MCU complex in neurons is unique, indicating a specific and specialized role of mitochondrial Ca^{2+} uptake in the

CNS. In particular, MICU3, whose expression is mainly restricted to neurons, is a highly potent MCU stimulator. Using genetic approaches in combination with improved variants of organelle-targeted Ca^{2+} indicators, biochemical and imaging techniques, we determined that silencing of designated MCU regulators drastically increased (MICU2) or decreased (MICU3) cytosolic and mitochondrial Ca^{2+} uptake in response to 4-Aminopyridine/Bicuculline in wild-type (WT) cortical neurons. As the homozygous deletion of *MCU* mostly results in embryonic lethality, while $MCU^{+/-}$ mice are viable and fertile, with no evident phenotype, we also examined mitochondrial Ca^{2+} uptake in post-natal cortical neurons derived from $MCU^{+/-}$ mice. Notably, deletion of *MCU* diminished mitochondrial Ca^{2+} transients in response to NMDA-induced excitotoxicity. Moreover, WT and transgenic mice carrying the FAD-linked PS2-N141I mutation in the presence of the APP Swedish mutation APPswe were employed to investigate whether and how MCU complex components (MCU, MCUb, EMRE, MICU1, MICU1.1, MICU2 and MICU3) are altered during AD disease progression *in vivo*. In summary, we are not only providing direct evidence of the contribution of each MCU in promoting mitochondrial Ca^{2+} uptake following AD-related toxic stimuli *in vitro*, but also elucidate the physiological and pathophysiological role of MCU *in vivo*. Our results may provide the necessary mechanistic detail to be exploited in the drug discovery process towards the treatment of AD.

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Poster

461. Calcium Channels

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Program #/Poster #: 461.15/D15

Topic: B.04. Ion Channels

Support: National Research Foundation of Korea (NRF) grant 2016R1A2B2006474
National Research Foundation of Korea (NRF) grant 2017R1A5A2015395

Title: TRPM2 deficiency modulates neural plasticity in the mouse hippocampus

Authors: *S. KO[1], S. WANG[1], S. LEE[1], M. PARK[1], S. JUNG[1,2], H. SON[1,3]
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Abstract: Transient receptor potential melastatin type 2 (TRPM2) is an oxidative stress-sensing calcium-permeable channel that is abundantly expressed in the CNS. Recent studies have reported that TRPM2 contributes to the calcium dysregulation associated with neurodegenerative diseases. However, it remains unclear whether TRPM2 affects neurogenesis and synaptic

plasticity which can lead to a variety of neurological disorders. Here we show that the genetic ablation of TRPM2 resulted in increased neurogenesis in adult mouse hippocampus. In addition, TRPM2 ablation induced expression of synaptic molecules, such as Synapsin 1 (Syn1), NMDA receptor subunit 1 (NR1), and AMPA receptor subunit 2 (GluR2). As both impaired neurogenesis and synaptic plasticity in hippocampus have been implicated in major depressive disorder (MDD), our findings suggest that TRPM2 might play a central role in MDD.

Disclosures: S. Ko: None. **S. Wang:** None. **S. Lee:** None. **M. Park:** None. **S. Jung:** None. **H. Son:** None.

Poster

461. Calcium Channels

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Program #/Poster #: 461.16/D16

Topic: B.04. Ion Channels

Support: DBT BT/PR6371/COE/34/19/2013
ICMR LS/133/92183
NCBS Core Funds

Title: Investigating the role of STIM1 and store-operated calcium entry in mouse purkinje neurons

Authors: *S. K. DHANYA, SR[1,2], G. HASAN[1]
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Abstract: Calcium plays a significant role in different aspects of neuronal signaling and function. Apart from various modes of calcium entry through ligand and voltage-gated calcium channels in neurons, it is known that Store-operated channels (SOCs) which consists of the pore-forming Orai proteins and the Endoplasmic Reticulum (ER) calcium sensor Stromal Interaction Molecule (STIM) also exist in neurons. Store-Operated Calcium Entry (SOCE) is based on the interaction of STIM proteins with Orai which opens in response to depletion of ER calcium. Previous studies have proposed that SOCE is required for the maintenance of neuronal calcium homeostasis that in turn can influence synaptic transmission and plasticity in the mature brain. However, the importance of SOCE and its relevance to mammalian neuron function is not very well studied. Studies have proposed that deranged calcium signaling in cerebellar Purkinje neurons might leads to neuronal degeneration and Spinocerebellar Ataxia (SCA). It has been found that mGluR1-dependent synaptic potentials and IP3R-dependent calcium signals are strongly attenuated in the absence of STIM1 in Purkinje neurons, but the molecular mechanisms explaining the deficits is not well understood. We have used Mouse Purkinje neurons as a

mammalian model system to understand how STIM1 modulates neuronal function and how altered function of STIM1 leads to neurodegeneration. We generated STIM1 knock out mice that lack STIM1 selectively in Purkinje neurons using the Cre-lox system. Immunostaining of cerebellar sections revealed that STIM1 protein was abolished in Purkinje neurons from 12 week old mice whereas levels of the Calbindin protein remained unaltered. STIM1 knock out mice exhibit impaired motor learning from 17 weeks onwards when subjected to the accelerating rotarod assay. To understand if knockout of STIM1 followed by loss of SOCE affects the global gene expression profile of Purkinje neurons we carried out an RNAseq experiment comparing micro-dissected 1year old STIM1 KO Purkinje neurons with control Purkinje neurons. Preliminary analysis suggests that pathways down regulated through STIM1 knockout were related to nervous system development and cation transmembrane transport. These data suggest that RNAseq experiments could help in identifying potential therapeutic targets for SCA and other neurodegenerative disorders.

Disclosures: S.K. Dhanya: None. **G. Hasan:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.01/DP02/D17

Topic: B.06. Synaptic Transmission

Support: ERC-2013-CoG NeuroMolAnatomy
SFB1286 Quantitative Synaptology

Title: The Dendrite Nanomap - A quantitative 3D nanoscale model of dendritic spines

Authors: *M. HELM[1,3], T. DANKOVICH[2], S. MANDAD[4], T. A. SCHIKORSKI[5], S. RIZZOLI[4]
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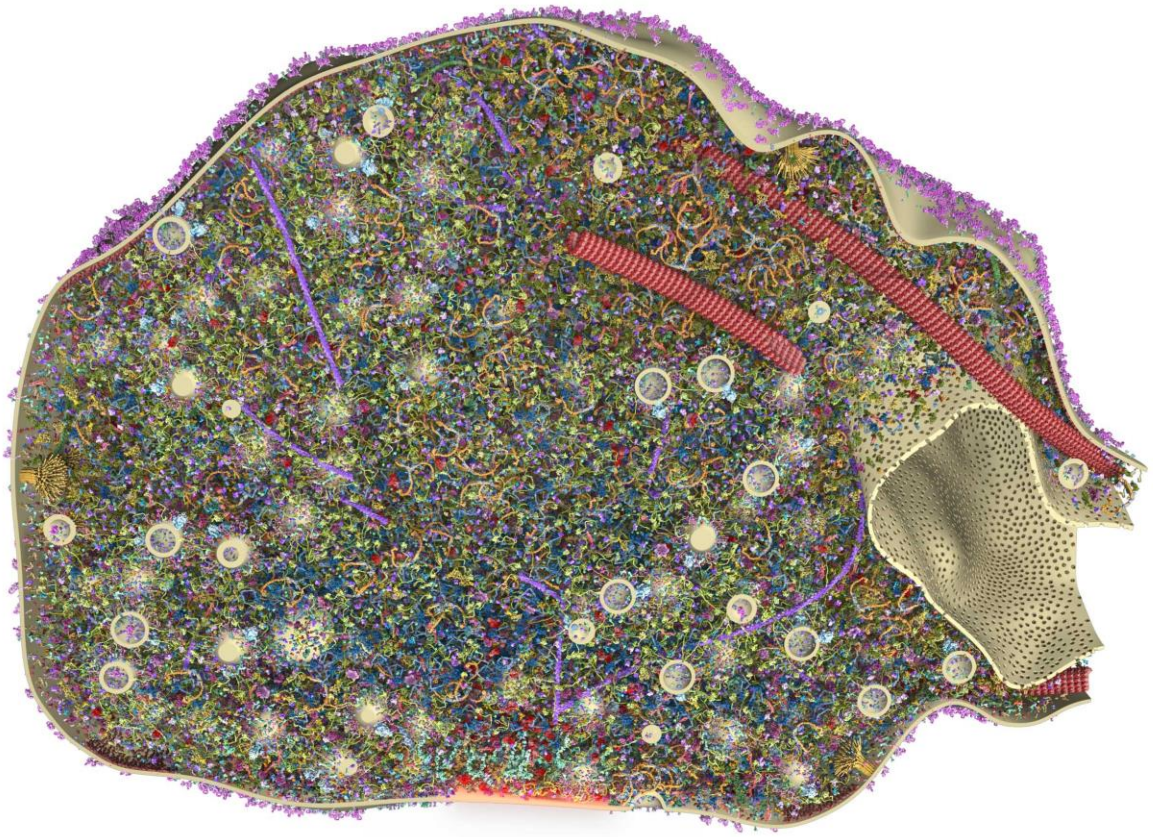
Abstract: ‘Form follows function’ is one of the underlying principles in the organization of biological structures. Conversely, if we know the form and organization of a given structure, we can draw conclusions on its function. Following this credo, we are investigating postsynaptic function by elucidating its nanoscale architecture. To do so, we employ a wide range of techniques, ranging from super-resolution microscopy, over electron microscopy to quantitative biochemistry with the goal to generate a 3D model of a dendritic spine, the main postsynaptic compartment of glutamatergic synapses.
Using STED microscopy, we resolved the precise localization of over 100 proteins in dendritic

spines, including, for example, all SNARE proteins. Finally, we also followed the relocalization of several proteins during homeostatic plasticity, analyzing, for example, the redistribution of SNAP47 during different activity states.
We determined the absolute copy numbers of ~5000 proteins in a neuron, using quantitative mass spectrometry. We were able to break down these numbers to dendritic copy numbers with imaging techniques. This yields the first comprehensive description of a dendritic spine in absolute quantitative terms, and will also enable us to infer protein complex stoichiometry, further augmenting our model and our understanding of structures such as the scaffold organization in the post-synaptic density.
Finally, we are using serial-sectioning electron microscopy to determine the morphology of the spines in culture, which will serve as the backbone for the 3D model.
In total, this data will not only reveal the intricate architecture of dendritic spines and enable us to simulate physiological processes such as depolarization in dendritic spines, but it will also serve as a tool for other researchers in the neuronal cell biology field.
The final model will comprise a large databank on the proteome of the neuron in general, and even more detailed analysis in the postsynaptic compartment, which colleagues can use to develop and test novel hypothesis.



Disclosures: M. Helm: None. **T. Dankovich:** None. **S. Mandad:** None. **T.A. Schikorski:** None. **S. Rizzoli:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.02/D18

Topic: B.06. Synaptic Transmission

Title: Synapse size predicts EPSP amplitude in mouse barrel cortex

Authors: *G. F. SCHUHKNECHT, S. HOLLER-RICKAUER, G. KÖSTINGER, K. A. C. MARTIN
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Abstract: The field of connectomics is currently subject to great attention and immense research efforts. One of its central promises holds that acquiring the complete wiring diagram of all the neurons and their synaptic connections in a block of the brain using an electron microscope (EM) will ultimately lead to a deep understanding of the embedded neuronal circuits. A serious difficulty is that we do not yet understand how the anatomical features of even a single cortical synapse seen in the EM correlate with its physiological strength. To bridge this gap, we studied the physiology and ultrastructure of the same synapses. First, we recorded pairs of synaptically connected layer 2/3 pyramidal neurons in mouse barrel cortex (at postnatal days 21 to 30) *in vitro* and measured the mean amplitude and variance of the excitatory postsynaptic potentials (EPSPs). The synapses in this study (n = 8 connected pairs) had mean EPSP amplitudes varying between 0.4mV and 2.3mV and further analyses indicated that multiple release sites were present. The pre- and postsynaptic neurons were filled with biocytin, which allowed us to identify all putative synaptic contacts between the axon of the presynaptic neuron and the dendrites of the postsynaptic neuron in the light microscope (LM; average of 4.1 contacts per pair). Finally, we performed correlated LM-EM on all contacts seen in LM to test whether these contacts formed synapses. Surprisingly, of the 8 pairs, 6 were connected by only a single anatomical synapse. Two pairs (both of which also had the largest EPSPs) were connected by 2 synapses, each. Significantly, in all cases, the number of physiological release sites exceeded the number of anatomical synapses found in EM. This implies that individual cortical synapses contain multiple transmitter release sites and that release of a single vesicle does not saturate all the postsynaptic receptors. Most previous correlative studies relied on LM and likely overestimated the number of synapses, and so concluded that each synapse contains only a single release site. Importantly for the interpretation of structural connectomes, we found that a synapse's postsynaptic density (PSD) size was strongly correlated with its average evoked EPSP (r = 0.9). This relation could be a key step in giving functional attributes to the structural connectomes of neocortex.

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Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.03/D19

Topic: B.06. Synaptic Transmission

Support: R01-MH63232
T32-DK07563

Title: Physiological effects of a direct interaction between postsynaptic proteins Shank3 and CaMKII

Authors: *T. L. PERFITT[1], C. R. MARKS[2], X. WANG[3], T. NAKAGAWA[2], D. A. JACOBSON[2], R. J. COLBRAN[4]
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Abstract: Shank3 is a postsynaptic scaffolding protein that is important for organizing neurotransmitter receptor signaling complexes at excitatory synapses. Mutations or deletions in the SHANK3 gene are associated with neuropsychiatric disorders, such as autism spectrum disorder (ASD) and schizophrenia. Shank3 contains several protein-protein interaction domains that link postsynaptic receptors and channels, such as $Ca_V1.3$ L-type calcium channels, to downstream signaling molecules and the actin cytoskeleton Calcium/calmodulin-dependent protein kinase II (CaMKII) is a signaling protein that is activated by calcium influx through these postsynaptic receptors. Recent proteomics data from our lab found that Shank3 is highly abundant in CaMKII complexes isolated from mouse brain synaptic fractions. Therefore, we hypothesized that CaMKII can directly bind to Shank3.
Here, we confirm that complexes containing Shank3 and CaMKII can be co-immunoprecipitated from mouse forebrain and co-transfected HEK293T cells. Using GST-pulldown and purified CaMKII, we have identified a minimal CaMKII-binding domain in Shank3. This *in vitro* direct interaction requires pre-activation of CaMKII by Thr286 autophosphorylation. We used site-directed mutagenesis to identify residues in Shank3 that are critical for the direct Shank3-CaMKII interaction *in vitro*, as well as for co-immunoprecipitation from transfected HEK293T cells, but not for Shank3 binding to other proteins, such as $Ca_V1.3$. These residues are also critical for co-localization of transfected CaMKII and Shank3 in HEK293 cells and immortalized striatal Q7 cells. Moreover, co-immunoprecipitation from transfected HEK293 cells is essentially abrogated by mutation of the Thr286 autophosphorylation site to phospho-null Alanine. Knockdown of Shank3 in primary hippocampal neurons significantly reduces CaMKII-

dependent LTCC-CREB signaling to the nucleus.
Ongoing studies are testing the physiological effects of disrupting the Shank3-CaMKII interaction on Shank3/CaMKII localization, neuronal morphology, and calcium signaling.

Disclosures: T.L. Perfitt: None. **C.R. Marks:** None. **X. Wang:** None. **T. Nakagawa:** None. **D.A. Jacobson:** None. **R.J. Colbran:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.04/D20

Topic: B.06. Synaptic Transmission

Support: AMED 17bk0104077h0001

Title: Drebrin depletion affects accumulation of NMDAR subunits and causes less immunoreactivity of MAP2

Authors: *N. KOGANEZAWA, H. YAMAZAKI, T. SHIRAO
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Abstract: Dynamic microtubules have an important role in the maintenance of dendritic spines. Inhibition of microtubule growth or depletion of EB3, one of the microtubule plus-end binding proteins, affects spine morphology. Drebrin, an actin binding protein, is known to regulate actin dynamics and has critical roles in neuronal development, neuronal migration and synaptic plasticity. Although the presence of microtubules in dendritic spines was disputed, it is now generally believed. However, the small number of spines containing microtubules suggests a dynamic and transient entering of microtubules into spines. Microtubules entry into spines is known to occur in response to $Ca2^{+}$ influx through synaptic NMDA receptors (NMDARs). Drebrin directly binds to EB3 and regulates this entry. These facts suggest that microtubule dynamics couple with actin dynamics that is regulated by drebrin. Here, to investigate if drebrin regulates microtubules dynamics in dendrites, we used primary hippocampal cultured neurons derived from drebrin knockout (DXKO) mice. Microtubule-associated protein 2 (MAP2) binds to microtubules and modulates microtubule stability. As MAP2 and EB3 binds directly, we first observed MAP2 immunoreactivity using wild-type (WT) neurons and DXKO neurons. We detected less MAP2 positive neurons in DXKO neurons than in WT neurons. Because the close relationship between glutamate activation and MAP2 alterations are well known, we then applied AP-5, an NMDAR antagonist, to both neurons. Interestingly, we found that WT neurons treated by AP-5 showed less immunoreactivity of MAP2 whereas there was no change in DXKO neurons. This result suggests low functionality of NMDARs in DXKO neurons. We therefore examined the accumulation of NMDAR subunits immunocytochemically and found that DXKO

neurons had different pattern of their accumulation compared to WT neurons. Taken together, drebrin depletion alters NMDAR function and affects MAP2 immunoreactivity which might affect stability of microtubules.

Disclosures: N. Koganezawa: None. **H. Yamazaki:** None. **T. Shirao:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

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Topic: B.06. Synaptic Transmission

Support: Research Grants Council of Hong Kong, General Research Fund (GRF) 16100814
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University of Hong Kong Seed Funding for Basic Research 201511159170
University of Hong Kong Seed Funding for Basic Research 201611159231

Title: The epilepsy gene tbc1d24 encodes a novel synaptic protein that is required for the maintenance of excitatory synapses in hippocampal neuron

Authors: *L. LIN, Q. LYU, X. SHEN, J. ZHAO, A. CHAI, K.-O. LAI
Sch. of Biomed. Sci., The Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Many inherited neurodevelopmental disorders are resulted from mutations that disrupt synapse development and function. Numerous mutations have been identified in the human *tbc1d24* gene associated with epilepsy and intellectual disability, but the physiological role of TBC1D24 in the brain is not well defined. Here we investigate the potential function of TBC1D24 at excitatory synapse of hippocampal neurons. Using super-resolution structured illumination microscopy (SR-SIM), we found that TBC1D24 co-localized with the postsynaptic scaffold protein PSD-95 in dissociated hippocampal neurons. Short-hairpin RNA (shRNA)-mediated depletion of TBC1D24 in mature hippocampal neurons *in vitro* led to reduction of dendritic spine density, number of excitatory synapses and the frequency of miniature excitatory postsynaptic current (mEPSC). Knockdown of TBC1D24 in adult mouse hippocampus further demonstrated the essential role of TBC1D24 in the maintenance of dendritic spines *in vivo*. Our findings therefore suggest that synaptic dysfunction might contribute to the pathophysiology of epilepsy and intellectual disability in individuals harboring the *tbc1d24* gene mutations.

Disclosures: L. Lin: None. **Q. Lyu:** None. **X. Shen:** None. **J. Zhao:** None. **A. Chai:** None. **K. Lai:** None.

Poster

462. Postsynaptic Organization and Structure

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Program #/Poster #: 462.06/D22

Topic: B.06. Synaptic Transmission

Support: OeAW DOC Fellowship
The European Union (HBP - Project Ref. 720270)

Title: Differential involvement of GluN2B and GluA1 in formation of left-right asymmetry in the hippocampus

Authors: *D. KLEINDIENST[1], R. KAWAKAMI[2], M. J. CASE[1], K. KOBAYASHI[3], N. KOMIYAMA[4], M. ABE[5], K. SAKIMURA[6], R. SHIGEMOTO[1]
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Abstract: Glutamate is the major excitatory neurotransmitter in the brain mediating fast neurotransmission. Among postsynaptic ionotropic glutamate receptors, NMDA receptors (NMDAR) play an important role in plastic changes in synaptic strength, often through changes in synaptic AMPA receptors (AMPAR) content and spine structure. We have previously discovered an input-side dependent left-right asymmetry of spine structure and synaptic glutamate receptor content at the CA3-CA1 connection in the hippocampus: Synapses in CA1 *stratum radiatum* made by inputs from the right hemisphere have, on average, 50% larger size of postsynaptic density (PSD) and twice higher ratio of perforated synapses, higher density of the AMPAR subunit GluA1 and lower density of the NMDAR subunit GluN2B than synapses with inputs from the left. Interestingly, left-input synapses have been reported to produce stronger long-term potentiation, which correlates with a specific role of left CA3 in forming associative spatial long-term memory. The ratio of GluN2A/GluN2B affects synaptic plasticity, and insertion of GluA1 induces enlargement of PSD. We also found that PSD size correlates positively with GluA1 density but negatively with GluN2B density. No such correlation exists for the densities of other AMPAR (GluA2, GluA3) or NMDAR (GluN1, GluN2A) subunits. These findings prompted us to assess the roles of GluA1 and GluN2B in formation of the input-side dependent asymmetry, by assessing PSD size asymmetry with electron microscopy in CA1-selective GluA1 and GluN2B knock-out mice, and GluN2B-2A swap mice, in which the carboxyl-terminal domain of GluN2B was changed to that of GluN2A. We found that CA1-selective GluA1 knock-out mice lack asymmetry of PSD size, with similar size and ratio of

perforated synapses as left-input synapses in wild-type mice. CA1-selective GluN2B knock-out mice also lack the asymmetry, but with similar structural properties to wild-type right-input synapses. Interestingly, PSD size correlates negatively with GluN2B density in GluA1 KO similarly to wild-type mice but not in GluN2B-2A swap mice, suggesting that the asymmetrical allocation of GluN2B occurs upstream of that of GluA1. Altogether our data indicate that both GluA1 and GluN2B are necessary for formation of the input-side dependent asymmetry, but in different manners. GluA1 is necessary for development of the right-input phenotype with larger PSD. GluN2B, on the other hand, is necessary for formation of the left-input phenotype, depending on its carboxyl-terminal domain. Our results are consistent with an idea that GluN2B allocation serves as the most upstream asymmetry, followed by that of GluA1 and PSD size.

Disclosures: D. Kleindienst: None. **R. Kawakami:** None. **M.J. Case:** None. **K. Kobayashi:** None. **N. Komiyama:** None. **M. Abe:** None. **K. Sakimura:** None. **R. Shigemoto:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.07/D23

Topic: B.06. Synaptic Transmission

Support: Ingeborg Ständer Foundation

Title: Distinct neurodevelopmental and neuropsychiatric-like phenotypes in Shank2 gene-targeted mice

Authors: *A. ELTOKHI[1,2,3], G. A. RAPPOLD[1], R. SPRENGEL[2,3]
[1]Inst. of Human Genet., Heidelberg, Germany; [2]Max Planck Inst. for Med. Res., Heidelberg, Germany; [3]Inst. of Anat. and Cell Biol., Heidelberg, Germany

Abstract: The *SHANK2* gene, also known as *ProSAP1*, is a member of the *SHANK* gene family encoding postsynaptic scaffold proteins. At excitatory synapses in the mammalian brain, the SHANK proteins link the ionotropic and metabotropic glutamate receptor via other receptor-associated proteins to the actin cytoskeleton and intracellular signaling pathways. Damaging variants in *SHANK* genes are frequently associated with diverse neuropsychiatric disorders including autism and schizophrenia. However, due to the limitations of *in vitro* systems and ethical limitations of studies involving humans, the causal relation between *SHANK* variants and the underlying molecular mechanisms for the neurodevelopmental and neuropsychiatric disorders need to be unraveled in animal models. In our review, we focused on the differences in the *Shank2* gene manipulations in mice and the different experimental designs and conclusions of the different studies. By comparing ten different conventional and conditional *Shank2* knockout mouse models, we were able to demonstrate that they all had very distinct molecular,

electrophysiological and behavioral phenotypes i.e. autistic-like and mania-like phenotypes. This indicates that different mutations within *Shank2* gene lead to different outcomes. To this end, we present our view as to why a spectrum of phenotypes can arise from different *SHANK2* variants and which neuronal circuits are affected by the different mutations in mouse models.

Disclosures: A. Eltokhi: None. **G.A. Rappold:** None. **R. Sprengel:** None.

Poster

462. Postsynaptic Organization and Structure

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Program #/Poster #: 462.08/D24

Topic: B.06. Synaptic Transmission

Support: NIH Grant MH080046

Title: Regulation of trans-synaptic nanoalignment by the actin cytoskeleton

Authors: *A. D. LEVY, A.-H. TANG, T. A. BLANPIED
Physiol., Univ. of Maryland, Baltimore, Baltimore, MD

Abstract: Each side of the synapse contains underlying architecture critical for neurotransmission. On the presynaptic side, the axonal bouton organizes neurotransmitter-containing vesicles and the associated vesicle release machinery in a region called the active zone (AZ). On the postsynaptic side, the dendritic spine organizes neurotransmitter receptors and associated signaling proteins in the postsynaptic density (PSD). The AZ and PSD are further organized at the nanoscale: AZ proteins are distributed heterogeneously within the AZ and form nanoscale clusters that preferentially guide where vesicle fusion occurs, and PSD proteins form clusters that concentrate neurotransmitter receptors and their scaffolds. The organization and function of both the AZ and PSD depends on the specialized underlying structure of the actin cytoskeleton. At the AZ, actin interacts with vesicular proteins, and actin depolymerization regulates vesicle release and recycling. At the PSD, actin is heavily enriched in spines, and its remodeling acutely destabilizes PSD internal structure.
We recently discovered that vesicles fuse in the AZ preferentially at RIM nanoclusters, and these clusters align trans-synaptically with postsynaptic nanoclusters of scaffolds and receptors. This trans-synaptic “nanocolumn” positions receptor densities at the highest concentration of neurotransmitter, and therefore enables fast, strong, and tunable responses. However, the molecular mechanism of the establishment and maintenance of the nanocolumn is still unknown. We hypothesize that the actin cytoskeleton controls synaptic nanoalignment.
We find that treatment of mature dissociated hippocampal cultures with the actin depolymerizing drug latrunculin A disrupts nanoalignment of RIM and PSD95 nanoclusters within minutes, without destroying nanoclusters themselves. This result suggests that normal actin dynamics are

required for proper alignment of the nanocolumn. To test whether actin dynamics on only one or on both sides of the synapse are required for nanoalignment, we have developed new methods for acute, optical, cell-specific regulation of actin polymerization. In concert with post-hoc super-resolution imaging, these tools allow us to address the cell- and synapse-specific roles of actin dynamics in controlling the structure of the nanocolumn.

Disclosures: A.D. Levy: None. **A. Tang:** None. **T.A. Blanpied:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.09/D25

Topic: B.06. Synaptic Transmission

Support: NIH MH080046

Title: Regulation of NMDA receptor activation following spontaneous glutamate release

Authors: *S. RANSOM METZBOWER[1], T. A. BLANPIED[2]
[1]Physiol., Univ. of Maryland Baltimore, Baltimore, MD; [2]Dept. of Physiol., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: NMDA receptor (NMDAR) activation due to spontaneous release of neurotransmitter plays a critical role in both maintenance and modification of synaptic strength. Because Ca^{2+} influx through NMDA receptors gates multiple signaling cascades at the postsynaptic density (PSD), the mechanisms that regulate receptor activation are important to delineate. However, the sources of variability between synapses in NMDAR activation by spontaneous release are not clear. Here, we asked what NMDAR subtype mediates the majority of response to spontaneous neurotransmitter release, and whether structural aspects of the synapse contribute to inter-synaptic variability.
To isolate NMDA receptor-mediated Ca^{2+} influx, we imaged GCaMP6f in cultured hippocampal neurons (21 to 35 DIV) in the presence of TTX, 0 Mg^{2+}, ryanodine, DNQX, and thapsigargin, allowing detection of miniature spontaneous Ca^{2+} transients (mSCaTs) in single spines. The GCaMP6f response reflected the total NMDAR-mediated Ca^{2+} influx, since mSCaT amplitude was modulated bidirectionally by altering extracellular [Mg^{2+}] or [Ca^{2+}]. Amplitude and frequency of mSCaTs were remarkably variable between and within synapses. A low concentration of the high-affinity antagonist CPP strongly decreased event frequency, but prompted a much smaller reduction in amplitude. Importantly, in essentially all synapses, responses were at least partially blocked by the GluN2B-specific antagonist ifenprodil, and in many, mSCaTs were eliminated. Thus, in these cells, very few NMDARs are activated by spontaneous release, and the majority of these contain GluN2B.

We next asked whether synapse size or subcellular position contribute to the magnitude of NMDAR activation. We measured spine area, and in order to obtain a highly resolved measurement of PSD area, we performed live or post hoc correlative super-resolution imaging of PSDs following Ca^{2+} imaging of the same synapses. Neither spine area nor PSD area correlated with NMDAR activation, revealing that NMDAR activation is independent of synapse size. Additionally, we found no evidence that NMDAR activation was affected by synapse distance or number of branch points from the soma.
These data suggest that following spontaneous glutamate release, the magnitude of spine Ca^{2+} elevation is highly variable despite the low number of NMDA receptors activated per release event. This variance may arise principally from the stochastic properties of channel opening rather than the many other factors that contribute to the number of activated receptors. Additionally, this reveals a novel role of GluN2B-NMDARs in responding to spontaneous release at individual hippocampal synapses.

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

Poster

462. Postsynaptic Organization and Structure

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.10/D26

Topic: B.06. Synaptic Transmission

Support: Hussman Foundation HIAS15003 grant

Title: Autism-associated variants of syntaxin binding protein 5 (STXBP5) disrupt dendritic morphology via the regulation of rho signaling

Authors: *W. SHEN, M. KILANDER, Y.-C. LIN
Hussman Inst. for Autism, Baltimore, MD

Abstract: Autism is a neurological condition characterized by marked qualitative differences in communication and social interaction. Genetic studies have implicated numerous genes, which encode proteins important for synaptic development and function, and may contribute to autism phenotypic diversity. Deletion and mutations of syntaxin binding protein 5 (STXBP5, also known as tomosyn) have been identified in a small number of individuals with autism. STXBP5/tomosyn is a syntaxin binding protein that negatively regulates neurotransmitter release. STXBP5/tomosyn contains an N-terminal WD40 domain and a C-terminal SNARE motif. STXBP5/tomosyn has also been shown to regulate neurite outgrowth in immature neurons via the interaction with ROCK, downstream effector of RhoA. Here we examined the mechanism regulated by STXBP5/tomosyn to control dendritic structures in mature neurons and also tested the hypothesis that the autism-associated variants in STXBP5/tomosyn disrupts

dendritic morphology by altering the Rho signaling pathway.
We first used shRNA knockdown approach to examine dendritic complexity in cultured hippocampal neurons. Tomosyn knockdown neurons exhibited compromised dendrite arborization and reduced dendritic spine density. These neurons also showed increased Rho activity measured by Rho biosensor. Inhibiting Rho activity with dominant negative RhoA or C3 transferase was sufficient to restore complete dendritic morphology. However, inhibition of ROCK rescued dendrite complexity but not dendritic spine density. The shRNA-resistant wildtype tomosyn, but not autism-associated variants, rescued the dendritic phenotype in tomosyn knockdown neurons. In addition to binding to syntaxin-1, tomosyn also bound to syntaxin-4, which plays a role in the trafficking of AMPA receptors. The tomosyn knockdown neurons exhibited fewer surface-expressed AMPA receptors, suggesting a role of tomosyn in regulating receptor trafficking. Interestingly, the autism-associated tomosyn variants displayed altered binding to syntaxin-4, suggesting a potential disruption of AMPA receptor trafficking. In conclusion, we showed that STXBP5/tomosyn controls dendritic morphology via regulation of Rho signaling. *STXBP5* variants found in individuals with autism may disrupt this process, resulting in altered dendritic structures and receptor trafficking, thereby impacting normal circuitry and function.

Disclosures: W. Shen: None. **M. Kilander:** None. **Y. Lin:** None.

Poster

462. Postsynaptic Organization and Structure

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Program #/Poster #: 462.11/D27

Topic: B.06. Synaptic Transmission

Support: NIH grant R01MH103374-03
NIH grant R01MH111684-02

Title: InSyn1 regulates GABAergic synaptic transmission and cognitive behaviors

Authors: *A. UEZU[1], T. W. BRADSHAW[2], P. DEVLIN[2], E. SPENCE[3], Y. GAO[4], I. KIM[5], R. RODRIGUIZ[6], S. H. SODERLING[1]
[2]Cell Biol. and Neurobio., [3]Cell Biol., [4]Dept. of Cell Biol., [5]Psychiatry and Behavioral Sci., [6]Mouse Behavioral and Neuroendocrine Analysis Core Facility, [1]Duke Univ., Durham, NC

Abstract: Previously we have developed an *in vivo* chemico-genetic approach for the discovery of local proteomes of neuronal substructures. Using this technique, termed *in vivo* BioID or iBioID, we uncovered the molecular framework of the inhibitory postsynaptic complex (iPSD), with over 140 novel trafficking, transmembrane, and signaling proteins enriched at this structure. We also found several previously uncharacterized proteins, one of which we named Inhibitory

Synaptic protein 1 (InSyn1) that was tightly associated with the iPSD. We report here InSyn1 is a novel regulator of the dystroglycan complex (DGC) in neurons. DGC is composed of several proteins and we found InSyn1 interacts with one of these to target it to inhibitory synapses. Furthermore, CRISPR-based depletion further confirmed dystroglycan is critical for InSyn1 iPSD localization. To better understand the physiological relevance of InSyn1 in the nervous system, we generated InSyn1 KO mice. Interestingly, InSyn1 null hippocampal neurons show defects in the spatial distribution of the DGC, which was further supported by electrophysiological recordings. Because genetic mutations in the DGC not only display severe muscular dystrophy but also exhibit cognitive dysfunctions, we performed a battery of hippocampal-dependent behavioral tests and found InSyn1 null mice exhibit complex cognitive abnormalities. These data indicate that InSyn1 is critical for the function of a distinct subset of inhibitory synapses and is important for cognitive behaviors.

Disclosures: A. Uezu: None. **T.W. Bradshaw:** None. **P. Devlin:** None. **E. Spence:** None. **Y. Gao:** None. **I. Kim:** None. **R. Rodriguiz:** None. **S.H. Soderling:** None.

Poster

462. Postsynaptic Organization and Structure

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Program #/Poster #: 462.12/D28

Topic: B.06. Synaptic Transmission

Support: OA1678

Title: Regional variations of excitatory vs. inhibitory input to cortical pyramidal neurons *in vivo*

Authors: *W. WENG, D. B. ARNOLD
Dept. of Biol. Sci., USC, Los Angeles, CA

Abstract: Although excitatory/inhibitory balance in cortical neurons has been studied in the context of whole cells using electrophysiology, less is known about the spatial distribution of excitatory and inhibitory inputs within the dendrites of individual neurons. To examine the distributions of synaptic inputs we expressed FingRs (Fibronectin intrabodies generated with mRNA display) that recognize PSD-95 and gephyrin in mouse cortical neurons in vivo using in utero electroporation. At 3 weeks of age we added cranial windows to these mice and subsequently imaged the distributions of endogenous PSD-95 and Gephyrin using two photon microscopy. Examination of FingR expression in pyramidal neurons revealed that PSD-95 puncta are distributed in a dense and uniform manner, whereas gephyrin puncta are sparse and unevenly distributed. The density of gephyrin puncta varies dramatically between dendritic branches of the same neuron and is increased towards the proximal end of dendritic branches. In addition, gephyrin puncta tend to occur in small clusters, despite their overall sparse distribution.

Given the overall uniform distribution of PSD-95 puncta, these results indicate that excitatory/inhibitory balance varies dramatically between different sub-compartments within dendrites of cortical pyramidal neurons.

Disclosures: W. Weng: None. **D.B. Arnold:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.13/D29

Topic: B.06. Synaptic Transmission

Title: Connectivity maps of layer 5-Cre lines and comparison with afferent inputs to layer 1

Authors: *J. LEDDEROSE[1], T. A. ZOLNIK[4], T. TRIMBUCH[2], C. ROSENMUND[2], B. J. EICKHOLT[3], M. E. LARKUM[4], R. N. S. SACHDEV[4]
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Abstract: A theory of cognitive function proposes that inputs to the distal dendrites of neocortical pyramidal neurons contribute to binding external and internal information into a global perceptual concept (Larkum, 2013). The cell-sparse, dendrite-rich neocortical layer (L) 1 of somatosensory cortex is a central locus of those dynamic interactions between feedback inputs that include M1 and S1 and feedforward inputs that drive action potentials in the cell body. L1 is the site of many disparate converging information streams, including afferent input from paralemniscal thalamus, and including a large number of local afferent inputs. These inputs to L1 are in position to target the apical tufts of both the intratelencephalic (IT) and pyramidal tract (PT) neurons.
Here, we used a rabies retrograde tracing approach in L5-Cre lines (PT, Sim-Cre; IT, TLX3-Cre) in conjunction with fast blue application in L1 to compare how inputs to these classes of pyramidal neurons differ, and whether the input to L1 arises from the same brain areas and layers as input to the L5 pyramidal neurons. We show that 1) within S1, IT and PT neurons connect extensively to L2/3 and L5, to some extent to L4, and to some bipolar neurons in L6b; 2) A subset of neurons that are presynaptic to IT and PT neurons and double-labeled with rabies virus also connect to L1; 3) More presynaptic connections are found in the ventro-basal thalamus in PT neurons than in IT neurons, some of which are also connected to L1; 4) Other regions are presynaptically connected to somatosensory IT and PT neurons, including somatosensory cortex S2, motor cortex M1 and M2, and midline and paralemniscal (POm) thalamic neurons; 5) While there is overlap between presynaptic neurons to L1 and the Cre-lines tested, there are clusters of neurons that only project to IT or PT neurons, or to L1.
Taken together, our results suggest that presynaptic inputs to the distinct classes of L5 neurons

are different locally within S1, and for long-range projections from a variety of other brain regions. There is a mix of convergent and divergent input to L1 and to each type of pyramidal neurons.

Disclosures: T.A. Zolnik: None. **T. Trimbuch:** None. **C. Rosenmund:** None. **B.J. Eickholt:** None. **M.E. Larkum:** None. **R.N.S. Sachdev:** None.

Poster

462. Postsynaptic Organization and Structure

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Program #/Poster #: 462.14/D30

Topic: B.06. Synaptic Transmission

Support: NHMRC Grant APP1083209
Australian Government Research Training Program Scholarship

Title: Tropomyosin isoforms Tpm3.1 and Tpm4.2 modulate synaptic function

Authors: *C. CHAICHIM, H. STEFEN, M. BRETTLE, P. W. GUNNING, E. C. HARDEMAN, T. FATH, J. M. POWER
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Abstract: The neuronal actin cytoskeleton is crucial for forming, maintaining, and modulating synapses. Actin filament dynamics are regulated by many actin-associated proteins. An important family of proteins are the actin-associated tropomyosins, which control access of other actin-associated proteins to actin filaments. Two isoforms of tropomyosin are known to be enriched in the postsynaptic compartment and associated with the postsynaptic density: Tpm3.1 and Tpm4.2. Both prevent binding of actin depolymerizing factor, therefore having an actin stabilising action. We hypothesised that enhancing actin stability will augment mature dendritic spine formation and increase synaptic function.
Whole-cell patch clamp recordings of mEPSCs in cultured hippocampal neurons prepared from transgenic mice overexpressing Tpm3.1 and wild-type (WT) control embryos revealed no difference in amplitude or frequency between WT and Tpm3.1 overexpressing cells. Morphometric analysis showed that dendritic spine density was decreased in Tpm3.1 overexpressing cells ($p = 0.02$; unpaired t-test, Tpm3.1 Tg $n = 33$, WT $n = 28$), but the proportions of spine types was unaltered.
Hippocampal field excitatory postsynaptic potentials (fEPSPs) were recorded in acute brain slices prepared from male transgenic mice and littermate controls. Synaptic potentiation induced by high frequency stimulation (100 Hz 1s) was greater ($p = 0.04$; RM-ANOVA) in Tpm3.1 transgenic mice ($n = 16$) than controls ($n = 15$), suggesting that Tpm3.1 overexpression improves synaptic plasticity.

Hippocampal cultures prepared from Tpm4.2 knockout mice had reduced mEPSC amplitude ($p = 0.001$) and frequency ($p = 0.002$) compared to WT controls (unpaired t-test, Tpm4.2 n = 16, WT n = 17). This shows that Tpm4.2 is critical for normal baseline synaptic transmission.
Our results highlight the importance of these tropomyosin isoforms and the actin cytoskeleton in synaptic function.

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Poster

462. Postsynaptic Organization and Structure

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Program #/Poster #: 462.15/D31

Topic: B.06. Synaptic Transmission

Support: R01-MH100561

Title: Expression of the GABA-A receptor α4 subunit is selective for specific spine types in female mouse hippocampus at puberty

Authors: *J. PARATO[1], S. S. SMITH[2]
[1]SUNY Downstate, Brooklyn, NY; [2]Dept Physiol Pharmacol, SUNY Downstate Med. Ctr., Brooklyn, NY

Abstract: Adolescent synaptic pruning occurs in multiple brain regions and is thought to be necessary for normal post-pubertal brain function. We have previously shown that extrasynaptic GABA-A receptors containing the α4 subunit trigger pubertal pruning in the CA1 and CA3 hippocampus (Afroz and Parato et al., 2016), when the density of the mushroom ("memory") and stubby spines decreases by half. These α4βδ receptors increase tonic inhibition, which prevents NMDA receptor activation leading to decreased expression of kalirin-7, a spine protein which is necessary for spine maintenance (Ma et al., 2003). In the absence of pruning, behavioral flexibility in a spatial learning task is impaired, likely due to the abundance of the mushroom spines (Afroz and Parato et al., 2016), emphasizing the importance of pubertal pruning of the mushroom spines. Although α4 has been localized to the dendritic spine at puberty (Shen et al., 2010), it is not yet known whether pubertal α4 expression is selective for certain spine types. Therefore, for this study we tested the hypothesis that α4 expression at puberty is more prevalent on mushroom and stubby spines than on thin spines in the female mouse hippocampus. To this end, we employed a novel Golgi-immunohistochemistry protocol (Sebastian et al., 2013) that allows for visualization of spine types and co-localization of α4 staining (Santa Cruz sc7355). Puberty was identified by vaginal opening (~PND 35). Z-stack images (0.1 um) were taken of pyramidal cells from CA1 and CA3 hippocampus on an Olympus FluoView TM FV1000

confocal inverted microscope. Reconstruction of the Golgi-stained dendrite and 3D colocalization of α4 to spine volumes was performed with Imaris software. In comparing the number of spines of each type which express α4 per 10um segment, there were significantly more mushroom spines which express α4 compared to the thin spines (2.8+/-1.4, mushroom vs 1.4+/-1.3, thin, P<0.002) in CA1 hippocampus as well as in CA3 hippocampus (3+/-1.2, mushroom vs. 1.2+/-1.1, thin, P<0.02). There were also more stubby spines expressing α4 compared to the thin spines (3.4+/-1.9, stubby vs. 1.4+/-1.3, thin, P<0.002, CA1; 3.2+/-1.7, stubby, vs. 1.2+/-1.1, thin, P<0.003, CA3). Thus, α4 localization to the mushroom spines at puberty may explain how these receptors trigger pruning of this spine type which is essential for normal learning flexibility in adulthood.

Disclosures: J. Parato: None. **S.S. Smith:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.16/D32

Topic: B.06. Synaptic Transmission

Support: ALW-VENI 863.13.020
ALW-VIDI 171.029
Graduate Program of Quantitative Biology and Computational Life Sciences
ERC-StG 716011
NARSAD Young Investigator Award

Title: Resolving the functional organization of postsynaptic glutamate receptors

Authors: *N. SCHEEFHALS, H. D. MACGILLAVRY
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Abstract: The spatial organization of neurotransmitter receptors at neuronal synapses critically determines the efficiency of synaptic transmission. At excitatory synapses, ionotropic AMPA-type glutamate receptors (AMPARs) mediate the majority of fast synaptic transmission, while metabotropic glutamate receptors (mGluRs), including the group I mGluRs (mGluR1/5), modulate synaptic efficacy on much slower time scales. Interestingly, while AMPARs concentrate in the core of the postsynaptic density (PSD) that directly opposes the presynaptic vesicle release site, mGluRs are enriched in the perisynaptic domain surrounding the PSD. The spatial segregation of these functionally distinct receptor types is thus predicted to allow for precise temporal control of synaptic transmission and plasticity, yet we know little about the mechanisms that underlie the subsynaptic organization of different glutamate receptor types. Here, we used complementary super-resolution imaging approaches to resolve the dynamic

distribution of AMPARs and mGluRs in dissociated hippocampal neurons. Using STED imaging and single-molecule localization microscopy we confirmed early EM studies showing that mGluRs and AMPARs are spatially segregated in subsynaptic domains. We found that while AMPARs are enriched in the PSD, mGluR5 is almost completely excluded from the synapse, but rather accumulates in nanoscale domains at perisynaptic sites. Moreover, using single-molecule tracking we found that compared to the synaptic pool of AMPARs, which is largely immobile, mGluR5 is relatively mobile and is only transiently confined at perisynaptic sites. To start understanding how mGluR5 is attracted and trapped at perisynaptic sites, but remains excluded from the core of the synapse, we set out to delineate whether specific protein-protein interactions control this particular distribution of mGluR5 at synapses. Surprisingly, the distribution of mutated versions of mGluR5 suggest that the intracellular tail of mGluR5 is not required for the observed perisynaptic distribution, but rather prevents the accumulation of receptors in the core of the synapse. Based on these findings we propose that at excitatory synapses functionally distinct glutamate receptor types are spatially segregated in subsynaptic domains, in part via intracellular interactions that can either promote or hinder the entry of receptors into the PSD. These findings suggest novel mechanisms by which synaptic receptor complexes are spatially segregated to efficiently modulate synaptic transmission and plasticity.

Disclosures: N. Scheefhals: None. **H.D. MacGillavry:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.17/D33

Topic: B.06. Synaptic Transmission

Support: NIH Grant DA039533

Title: Targeting histone deacetylation for recovery of maternal deprivation-induced changes in BDNF and AKAP150 expression in the VTA

Authors: *F. S. NUGENT[1], S. GOUTY[2], B. M. COX[3], H. KASSIS[1], A. BERENJI[2], W. ZHU[2], R. HAMMACK[2], R. D. SHEPARD[1]
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Abstract: Severe early life stressors increase the probability of developing psychiatric disorders later in life through modifications in neuronal circuits controlling brain monoaminergic signaling. Our previous work demonstrated that 24hr maternal deprivation (MD) in Sprauge Dawley rats modifies dopamine (DA) signaling from the ventral tegmental area (VTA) through changes at GABAergic synapses in the VTA that were reversible by in vitro histone deacetylase (HDAC) inhibition through restoration of the scaffold A-kinase anchoring protein (AKAP150)

signaling (Authement et al., 2015). Using this model in male rats with in situ hybridization, Western blots and immunohistochemistry we confirmed that MD-induced epigenetic modifications at the level of histone acetylation was associated with an upregulation of HDAC2. MD also increased Akap5 mRNA levels in the VTA. Western blot analysis of AKAP150 protein expression showed an increase in synaptic levels of AKAP150 protein in the VTA with accompanying decreases in synaptic levels of protein kinase A (PKA). Moreover, the levels of mature brain-derived neurotrophic factor (BDNF) protein of VTA tissues from MD rats were significantly lower than in control groups. In vivo systemic injection with a selective class I HDAC inhibitor was sufficient to reverse MD-induced histone hypoacetylation in the VTA for 24hr after the injection. Furthermore, HDAC inhibition normalized the levels of mBDNF and AKAP150 proteins at 24hr. Our data suggest that HDAC-mediated targeting of BDNF and AKAP-dependent local signaling within VTA could provide novel therapeutics for prevention of later-life psychopathology.

Disclosures: F.S. Nugent: None. **S. Gouty:** None. **B.M. Cox:** None. **H. Kassis:** None. **A. Berenji:** None. **W. Zhu:** None. **R. Hammack:** None. **R.D. Shepard:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.18/D34

Topic: B.06. Synaptic Transmission

Support: NIH MH080046
NIH NS090644
Kahlert Foundation

Title: Dynamic control of synaptic substructure and function by adhesion molecules

Authors: *A. M. RAMSEY[1], A.-H. TANG[2], T. BIEDERER[4], T. A. BLANPIED[3]
[1]Dept. of Physiol., Univ. of Maryland, Baltimore, Baltimore, MD; [2]Physiol., [3]Dept. of Physiol., Univ. of Maryland Sch. of Med., Baltimore, MD; [4]Dpt. of Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: The complex neural processes of information encoding, storage, and retrieval are enabled by precise and efficient regulation of synaptic strength. Recent work indicates that one critical factor likely to control synaptic strength is the nanoscale organization of proteins within the synapse. Our lab discovered that a protein called Rab3 Interacting Molecule (RIM), which is essential for neurotransmitter release, is clustered into ~100 nm subdomains within the active zone, and that vesicle exocytosis preferentially occurs where there is a higher subsynaptic density of RIM. Furthermore, these presynaptic sites of neurotransmitter exocytosis are aligned

with postsynaptic nanoclusters of receptors, which has major implications for the regulation of receptor activation and synaptic efficacy through the subsynaptic positioning of receptors. Though many mechanisms may contribute to the trans-synaptic alignment of receptors to sites of release, a particularly attractive model is that synaptic cell adhesion molecules mediate alignment through high-affinity trans-synaptic protein binding. Leucine Rich Repeat Transmembrane neuronal (LRRTM2) participates in trans-synaptic protein binding with PSD-95 and several neurexin isoforms. Using multicolor 3D dSTORM, we found that LRRTM2 is tightly enriched within PSD-95 nanoclusters and across from RIM1/2 nanoclusters. In order to test the ongoing role of LRRTM2 in established synapses, we engineered a mutant version of LRRTM2 that contains a thrombin-cleavable target sequence at an extracellular, juxtamembrane site. Using a knockdown and replacement strategy, we performed 3D multicolor dSTORM and found that acute cleavage of LRRTM2 results in rapid reduction in the nanoscale alignment of proteins at synapses. Furthermore, we performed whole-cell patch clamp of cultured hippocampal neurons to test how acute disruption of the LRRTM2 extracellular binding interaction impacts synaptic transmission. We find that acute cleavage of LRRTM2 results in a substantial decrease in the evoked AMPAR-mediated EPSC amplitude but only a slight alteration in probability of release. Together, these findings provide experimental support for the idea that trans-synaptic nanoscale organization plays an important role in maintaining synaptic strength. A structural role played by one or more specific cleft proteins provides further evidence for a molecularly guided "nanocolumn" architecture within the synapse. More broadly, these results also indicate that synaptic cell adhesion molecules can play specific and unexpected roles in regulating function at established synapses well after synaptogenesis.

Disclosures: A.M. Ramsey: None. **A. Tang:** None. **T. Biederer:** None. **T.A. Blanpied:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

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Program #/Poster #: 462.19/D35

Topic: B.06. Synaptic Transmission

Support: NIH Grant R01 MH100561

Title: α4βδ GABA-A receptors trigger pruning of mushroom spines in primary motor cortex during adolescence

Authors: M. TEKIN, H. SHEN, *S. S. SMITH
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Abstract: Pubertal synaptic pruning is thought to play a role in refining memories. Proper neurodevelopment of the primary motor cortex (M1) is essential for motor learning and

coordination yet synaptic pruning of basilar dendrites in layer 5 (L5) of M1 has not been studied. Previous research has shown that α4βδ $GABA_A$ receptors (GABARs) trigger pubertal synaptic pruning in the CA1 hippocampus (Afroz et al., 2016). Autism Spectrum Disorder has been linked to abnormalities in the α4 GABAR subunit (Collins et al., 2006) and motor deficits (Geschwind 2009). Thus, the following experiments were used to test the hypothesis that adolescent pruning of L5 pyramidal cells in M1 is regulated by α4βδ GABARs. Golgi staining was used to assess spine density and spine types in each group from z-stack projection (0.3 µm) photomicrographs taken with a Nikon DS-U3 camera mounted on a Nikon Eclipse Ci-L microscope using a 100x oil objective. Spine density across the basilar dendrites (proximal, medial and distal segments) of pubertal vs. post-pubertal mice was compared using either wild-type (P35WT vs. P56WT) or α4 knockout mice (P35α4KO vs. P56α4KO). Using an analysis of variance followed by a post-hoc Tukey's test, we found no significant difference in total spine density between P35WT and P56WT but observed a significant decrease in proximal mushroom spines (P35WT, spine density = 0.057±0.006 spines/µm, P56WT, spine density = 0.026±0.005 spines/µm, $P<0.05$), and an increase in long thin spines (P35WT, spine density = 0.053±0.008 spines/µm, P56WT, spine density = 0.101±0.014 spines/µm, $P<0.05$) in L5. These changes were not observed in L5 when comparing P35α4KO and P56α4KO mice. The functional expression of α4βδ GABARs in L5 M1 pyramidal cells in pre-pubertal wild-type (P28WT) mice and pubertal (~P35WT, identified by vaginal opening) was assessed by performing whole cell patch clamp analysis of pyramidal cell responses to 100nM gaboxadol (selective for α4βδ GABARs). The results demonstrate an 150% increase in gaboxadol response at puberty compared to pre-puberty (P28WT, 18.24±2.4 pA, P35WT, 45.12±3.9 pA, $t(8) = 5.9$, $P=0.00019$) reflecting a significant increase in α4βδ GABAR expression at puberty. These results suggest that selective pruning of mushroom spines in the proximal region of M1 L5 pyramidal cells occurs during puberty, and that α4βδ GABARs are responsible for this pruning.

Disclosures: M. Tekin: None. **H. Shen:** None. **S.S. Smith:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.20/D36

Topic: B.06. Synaptic Transmission

Support: NINDS intramural funds

Title: FAM81A protein, a component of the postsynaptic density in adult brain

Authors: *A. DOSEMECI[1], H. K. LOO[1], C. A. WINTERS[1], T. S. REESE[1], J.-H. TAO-CHENG[2]
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Abstract: Proteomic analysis of affinity-purified PSD-95 complexes had previously identified a 'hypothetical protein', product of the gene FAM81A (Dosemeci et al 2007). Recent data mining reveals that FAM81A mRNA and protein expression are highest in brain tissue (Human Protein Atlas). Here we show that FAM81A protein in brain is expressed late in development, with a post-natal gradual increase in levels that parallels the expression of PSD-95. Comparison of subcellular fractions from adult brain show that the distribution of FAM81A is similar to PSD-95, with a drastic enrichment in the postsynaptic density fraction. Immuno-electron microscopy of adult brain tissue reveal specific immunogold labeling for FAM81A at a subpopulation of postsynaptic densities. The label for FAM81A is concentrated at the outer edge of the postsynaptic density core, within 30-40 nm from the postsynaptic membrane. While nuclear localization of FAM81A has been reported for certain cell lines (Human Protein Atlas) immuno-electron microscopy studies on adult brain tissue are so far inconclusive. On the other hand, size and sequence considerations indicate that the protein can potentially localize to the nucleus, as well as the cytoplasm, and NCBI Conserved Domain search reveals a sequence similar to the SMC_N (N-terminus of Structural Maintenance of Chromosomes) domain. Further studies are focused on testing the presence of FAM81A at the neuronal nuclei, which may point to a potential function in communication between synapse and nucleus.

Disclosures: A. Dosemeci: None. **H.K. Loo:** None. **C.A. Winters:** None. **T.S. Reese:** None. **J. Tao-Cheng:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.21/D37

Topic: B.06. Synaptic Transmission

Support: SNSF Grant PP00P3_176968

Title: Rapid modulation of transsynaptically aligned glutamate receptor nanocluster rings during homeostatic plasticity

Authors: P. FREI, *M. MUELLER
Univ. of Zurich, Zurich, Switzerland

Abstract: Subtle changes in the organization of synaptic proteins may have profound effects on synaptic transmission and animal behavior. The *Drosophila* neuromuscular junction (NMJ) has emerged as a powerful model system to explore the 'sub-synaptic' molecular architecture of presynaptic active zones using super-resolution light microscopy approaches. However, little is known about a corresponding postsynaptic organization and its relationship to presynaptic architecture. Using dual-color super-resolution stimulated emission depletion (STED)

microscopy, we here uncovered that postsynaptic glutamate receptors are arranged in distinct, sub-diffraction 'nanoclusters' at the *Drosophila* NMJ. Interestingly, around six of these clusters form rings with an average diameter of ~200 nm. Moreover, these receptor rings precisely align with rings formed by the C-termini of the presynaptic cytomatrix protein Bruchpilot (Brp), suggesting transsynaptic co-alignment. While postsynaptic *neto* RNAi expression results in more pronounced receptor rings due to predominant loss of 'extrasynaptic' receptors, postsynaptic knock down of *ankyrin* leads to diffuse receptor-cluster organization and larger Brp rings. Finally, preliminary data suggest a rapid expansion of these transsynaptic ring modules on the minute time scale during presynaptic homeostatic plasticity. These findings provide evidence for ring-like, transsynaptic nanomodules that undergo rapid changes during synaptic plasticity.

Disclosures: P. Frei: None. **M. Mueller:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

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Program #/Poster #: 462.22/D38

Topic: B.06. Synaptic Transmission

Support: NIH Grant R00MH102244
NIH Grant R01MH113545

Title: Multiprotein complexes containing synapse-associated proteins are differentially sensitive to lysis buffer detergent

Authors: *S. E. SMITH, J. LAUTZ, E. A. BROWN, E. P. GNIFFKE
Ctr. for Integrative Brain Res., Seattle Childrens Res. Inst., Seattle, WA

Abstract: Proteins do not act in isolation, but assemble into large multi-protein complexes to perform diverse cellular functions. In response to neuronal stimulation with KCl, glutamate, or agonists, multiprotein complexes containing proteins typically associated with the post-synaptic density rapidly change their composition. These activity-dependent dynamics may be a mechanism by which the cell responds to activity, both by activating intracellular signal transduction cascades and by changing the composition of the postsynaptic membrane (Lautz et al, 2018). However, the study of synaptic multiprotein complexes is complicated by the need to solubilize complexes when preparing cell lysates for co-immunoprecipitation. Typical preparations of the "postsynaptic density" involve solubilizing synaptic fractions in TritonX100, then recovering the insoluble portion and solubilizing it in a high-pH buffer containing the harsh detergent deoxycholate. This treatment would be expected to destroy many protein-protein interactions that may exist at the native synapse. However, it is unclear if, or to what extent, less harsh detergent conditions will solubilize protein complexes associated with the electron-dense

post synaptic density. In this study, we used immunoprecipitation-flow cytometry (IP-FCM) to examine the solubility of several synaptic proteins, as well complexes containing multiple proteins; targets included Homer1, Shank1 and 3, PSD95, SynGAP, and representative members of the GRIA, GRIN and mGluRs receptor families. We find that protein solubility and complexes are greatly affected by detergents. For example, SynGAP and PSD95 show much greater solubility in deoxycholate, and lower solubility in Triton and NP40-contianing buffers. Detection of a protein complex containing PSD95 and SynGAP by IP-FCM follows the same pattern. In contrast, Homer1 shows similar solubility in all detergents, but a shared complex containing Homer and mGluR5 is detected only in NP-40 or Triton-containing buffers. Homer in complex with Shank proteins (detected by a pan-Shank antibody) follows a similar pattern. Thus, it seems that Shank and Homer interactions are disrupted by deoxycholate buffers; in fact, SynGAP and Shank3 are detected in a shared complex only in Triton lysis buffer, despite SynGAP detection being several-fold higher in deoxycholate. We therefore conclude that, for the study of many activity-dependent interactions, non-traditional solubilization protocols can result in the detection of a greater number of proteins in shared complexes that respond to synaptic activity.

Disclosures: S.E. Smith: None. **J. Lautz:** None. **E.A. Brown:** None. **E.P. Gniffke:** None.

Poster

462. Postsynaptic Organization and Structure

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Program #/Poster #: 462.23/D39

Topic: B.06. Synaptic Transmission

Support: NIH Grant 5T32GM008203-28

Title: Spontaneous and evoked neurotransmission are partially segregated at inhibitory synapses

Authors: *P. M. HORVATH[1], L. M. MONTEGGIA[2], E. T. KAVALALI[2]
[2]Neurosci., [1]UT Southwestern Med. Ctr., Dallas, TX

Abstract: Neurotransmission can be classified into two broad types: spontaneous and evoked. Much of the work examining these types of neurotransmission and their properties has been done in excitatory synapses. Previous work has shown a segregation of AMPA receptors which respond to spontaneous and evoked neurotransmission at excitatory synapses in both the central nervous system as well as the drosophila neuromuscular junction. Additionally, central nervous system NMDA receptors also show a near complete segregation of spontaneous and evoked neurotransmission. Although inhibitory synapses also transmit both spontaneous and evoked neurotransmission, they differ from excitatory synapses in both structure and function. Therefore, it has been unclear if the same principle of segregation holds true at inhibitory

synapses. Addressing this question previously had been inhibited by a lack of well-characterized use-dependent $GABA_A$ receptor blockers. Here, we evaluated picrotoxin's ability to function as a use-dependent $GABA_A$ receptor blocker in dissociated hippocampal cultures. Indeed, picrotoxin is able to block both spontaneous and evoked neurotransmission in a use-dependent manner. By making use of this tool, we show that there is partial, but not full, segregation of spontaneous and evoked neurotransmission at inhibitory synapses. These data indicate that while the principle of segregation of spontaneous and evoked neurotransmission still applies at inhibitory synapses, it is not as complete as at excitatory synapses.

Disclosures: P.M. Horvath: None. **L.M. Monteggia:** None. **E.T. Kavalali:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.24/D40

Topic: B.06. Synaptic Transmission

Support: 1ZIANS003140-04

Title: Functional differences of neuroligins: 4x vs. 4y

Authors: *T. A. NGUYEN, M. A. BEMBEN, Y. LI, K. W. ROCHE
NINDS, Bethesda, MD

Abstract: Autism Spectrum Disorders (ASDs) are a diverse set of cognitive developmental disorders that result in a wide range of behavioral deficits. Interestingly, ASDs have long been reported to affect many more males than females. This sex bias in ASDs has been a puzzle in the field. Neuroligins (NLs) are postsynaptic cell adhesion molecules involved in synapse formation and modulation. There are five NLs (NLGN1, NLGN2, NLGN3, NLGN4X, NLGN4Y) encoded in the human genome, whereas in rodent there are four (NLGN1, NLGN2, NLGN3, NLGN4-like). NLGN4X and NLGN4Y are of particular interest because they are sex-linked genes located on the X and Y chromosome, respectively. In addition, multiple mutations in both the extracellular domain (ECD) and the intracellular domain (ICD) of NLGN4X have been shown to associate with ASDs. NLGN4X and NLGN4Y are highly conserved with only fourteen amino acid differences in the ECD and five in the ICD. Here, we show that while having approximately 97% sequence similarity, NLGN4Y does not have the same functions as NLGN4X. Overexpressing NLGN4Y in heterologous cells or in neurons shows that NLGN4Y does not traffic well to the surface, and due to this deficiency in trafficking, NLGN4Y cannot induce synaptogenesis. Chimeras of NLGN4X and NLGN4Y demonstrate the lack of surface expression is due to the ECD of NLGN4Y. Swapping NLGN4Y ECD with NLGN4X rescues NLGN4Y surface expression and synapse formation. Aside from forming synapses, the strength of

synapses can be modified through protein phosphorylation. NLGN4X has been shown to be phosphorylated by protein kinase C (PKC) at threonine 707 (T707) with a profound impact on the synaptogenic properties of NLGN4X. Surprisingly, I observed that PKC cannot robustly phosphorylate NLGN4Y. To screen for new phosphorylation residues specific to NLGN4X or NLGN4Y, I used in vitro kinase assays in conjunction with mass spectrometry. I found that NLGN4X can be phosphorylated by protein kinase A (PKA) but not at the analogous residue on NLGN4Y. Interestingly, a single amino acid difference between NLGN4X and NLGN4Y is responsible for the lack of phosphorylation in NLGN4Y. Using differentiated human neurons from induced pluripotent stem cells, I show that endogenous NLGN4X is phosphorylated by PKC and PKA. Therefore, using a variety of assays, I've identified important functional divergence between NLGN 4X vs 4Y. Taken together, my data indicate that functional deficits in NLGN4Y may contribute to the ASD gender-bias, because NLGN4X mutations will have a dominant effect in males.

Disclosures: T.A. Nguyen: None. **M.A. Bemben:** None. **Y. Li:** None. **K.W. Roche:** None.

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.25/D41

Topic: B.06. Synaptic Transmission

Title: Proteomic analysis of trio and kalirin interactomes

Authors: *J. PASKUS, M. BEMBEN, Y. LI, K. W. ROCHE
Natl. Inst. of Hlth., Bethesda, MD

Abstract: Rho family GTPases regulate many synaptic processes including, but not limited to, actin cytoskeleton and spine remodeling. Guanine nucleotide exchange factors (GEFs) are crucial regulators of Rho protein signaling through catalyzing the exchange of GDP for GTP. Kalirin and Trio are essential RhoGEFs of the postsynaptic density, regulating local spine dynamics, synaptic transmission, and plasticity. Intriguingly, Kalirin and Trio are paralog proteins, sharing ~60% total homology, with ~90% conservation of their respective GEF1 domains. Consequently, it has been suggested that Kalirin and Trio may be effectively redundant. However, total and brain-specific deletions of Trio are largely fatal in mice, whereas Kalirin knockout animals are viable. Moreover, recent whole-exome sequencing data have implicated Trio, but not Kalirin, as an ASD-associated gene, together suggesting potential divergence in their developmental and synaptic function. It is not known whether these proteins share discrete or intersecting protein-protein interaction networks, and defining unique or common interactors may aid in elucidating their respective synaptic roles. To establish the interactomes of Kalirin and Trio, we first generated antibodies to Kalirin-7, the major brain-

specific isoform, and Trio using non-conserved epitopes to eliminate cross-reactivity between these paralog proteins. We next immunoprecipitated endogenous Kalirin-7 and Trio from crude synaptic fractions of mouse brain and used liquid chromatography-tandem mass spectrometry to screen for Kalirin-7 and Trio interactors. Comparative analysis of these GEF interactomes revealed distinct and intersecting protein-protein interactions between Kalirin-7 and Trio involving synapse-adhesion, excitatory neurotransmission, and GTPase signaling. Of potential convergent interactors, members of the Neuroligin (NLGN) family of cell adhesion proteins were of particular interest given their overlapping phenotype with Kalirin-7 and Trio, namely their ability to regulate spinogenesis and excitatory transmission. We further validated these interactions *in vitro* and *in vivo*, demonstrating that Trio and Kalirin-7 indeed interact with neuroligin isoforms. Our findings establish interactome networks for two important GEFs of the postsynaptic density, revealing distinct, yet overlapping, interaction networks. We further establish neuroligins as common interactors, which has implications for both the basic biology of synaptic transmission, and in neurodevelopmental and degenerative disorders.

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

Poster

462. Postsynaptic Organization and Structure

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 462.26/D42

Topic: B.06. Synaptic Transmission

Title: PKA phosphorylation of NLGN1 regulates trafficking and PSD-95 binding

Authors: *J. JEONG, M. A. BEMBEN, Y. LI, K. W. ROCHE
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Abstract: The NLGN gene family encodes single-pass transmembrane postsynaptic cell adhesion molecules that are important for synapse assembly and function. Five NLGN genes (NLGN1, 2, 3, 4X, and 4Y) are identified in humans and four genes (Nlgn1 to Nlgn4) in mice. While all isoforms show high similarity in amino acid sequence, each of the NLGN isoforms displays distinct expression patterns and subcellular localization. NLGN1 is mostly localized to glutamatergic excitatory synapses and is critical for excitatory synapse assembly and function. The large extracellular domain of NLGN1 is responsible for transsynaptic binding with neurexin, a presynaptic cell adhesion molecule. The short cytoplasmic tail of NLGN1 is exposed to a variety of intracellular regulation.
Importantly, NLGN1 binds to PSD-95 via the PDZ ligand. PSD-95 is a scaffolding protein at excitatory synapses and interacts with a large number of channels, receptors, and membrane proteins to organize glutamatergic postsynaptic signaling. PSD-95 and NLGN1 have been investigated together in many studies for their physiological roles in the glutamatergic signaling

pathway. Several studies have shown a functional correlation between NLGN1 and PSD-95. However, PDZ ligand-dependent and -independent NLGN1 function has also been investigated. All these studies suggest an important physiological interplay between NLGN1 and PSD-95. In this study, we found protein kinase A (PKA) phosphorylates NLGN1 on S839, near the PDZ ligand. Interestingly, a phosphomimetic mutation of NLGN1, S839E, significantly reduced the interaction between NLGN1 and PSD-95 in vitro and in situ. Also, when the NLGN1 and PSD-95 interaction was disrupted, surface expression of NLGN1 was reduced in cultured neurons. We further observed that impaired NLGN1 and PSD-95 interactions reduced synaptic NLGN1 expression and NLGN1-dependent synaptic enhancement, as well as reduced increases in spine density. Our results establish a molecular mechanism that regulates NLGN1 and PSD-95 binding in a phosphorylation-dependent manner, which provides novel insights into excitatory synapse development and function.

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

Poster

463. Network Interactions and Synaptic Integration II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 463.01/D43

Topic: B.06. Synaptic Transmission

Title: Quantification of the input-output relationship in an interneuron of *C. elegans* under natural noise

Authors: *K. ASHIDA[1], K. HOTTA[1], K. OKA[2]
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Abstract: A dendrite receives variable and separate inputs from presynaptic neurons, and neurons show sporadic neuronal activity even under natural states on the different neuronal sub-compartments, neurite. To investigate the effects of fluctuating neurotransmitter-release on postsynaptic neuronal activity is crucial in vivo. Here, we focused on AIY interneurons in a nematode, *Caenorhabditis elegans*. They receive sensory information as glutamate inputs throughout the neurite, and integrate environmental information. Moreover, AIY shows a sporadic Ca^{2+} response with and without stimulation; on the other hand, sensory neurons show responses in a deterministic manner. For identification the relationship between input and output in natural state, the simultaneous imaging of glutamate inputs and Ca^{2+} responses in AIY was performed. Furthermore, the relationship between the regional specificity of inputs and neuronal responses were also investigated. For further analysis, we employed Shannon's information theory, which allows measuring the amount of information transfer between sender and receiver and quantifying the reliability of signal transduction in biological systems. Finally, we measured

the Ca^{2+} and membrane potential simultaneously to investigate their relationship. From these results, we showed that input fluctuations are necessary and sufficient to explain Ca^{2+} response fluctuations in AIY regardless of odor stimulation to worms. Furthermore, we found that odor modulates the regional specificity of the information transfer by Shannon's information theory. Finally, we found that Ca^{2+} spikes directly correspond to the depolarization of the membrane potential. As far as we know, this is the first report identifying the region-specific relationship of fluctuations between input and output in vivo under natural environmental noise.

Disclosures: K. Ashida: None. **K. Hotta:** None. **K. Oka:** None.

Poster

463. Network Interactions and Synaptic Integration II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 463.02/D44

Topic: B.06. Synaptic Transmission

Support: PhD fellowship "Cognitive Sciences and Technologies Council", University of Tehran
BMBF FKZ 01GQ1502

Title: Coincidence detection within the excitable olfactory bulb granule cell spines

Authors: S. AGHVAMI[1], M. MÜLLER[2], *M. LUKAS[3], H. SEYED-ALLAEI[4], B. N. ARAABI[1], V. EGGER[2]
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Abstract: In the mammalian olfactory bulb, the inhibitory axonless granule cells (GCs) feature reciprocal synapses that interconnect them with the principal neurons of the bulb, mitral and tufted cells. These synapses are located within large excitable spines that can generate local action potentials (AP) upon synaptic input. Moreover, GCs are capable of firing global APs that propagate throughout the entire dendrite. Strikingly, local postsynaptic Ca^{2+} entry was shown to summate linearly or even supralinearly with Ca^{2+} entry triggered by coincident global APs, even though the underlying conductances would be expected to overlap. We investigated this phenomenon by constructing a compartmental GC model to simulate the spine membrane potential, the ionic currents and the intracellular dynamics of Ca^{2+} in response to coincident local and global signals as a function of their temporal separation Δt. These simulations yielded strongly sublinear summation of spine Ca^{2+} entry for the case of perfect coincidence $\Delta t = 0$ ms. Summation efficiency sharply rose for both positive and negative pairing intervals Δt. The increase was more pronounced and eventually supralinear for positive Δt, and less pronounced

for negative Δt, i.e. when the global AP preceded the synaptic input. This dip was dependent on the presence of voltage-gated sodium channels in the spine head while NMDA receptors or either T-type or high-voltage activated Ca^{2+} channels were not essential. We tested these predictions experimentally by pairing two-photon uncaging of glutamate at spines and somatically evoked APs at Δt = -10 ms, 0 ms, +10 ms (n = 9 spines). The respective spine Ca^{2+} signals were recorded with two-photon imaging and showed significant differences in summation efficiency, with sublinear summation around 0 ms (nonlinearity NL = 0.76 ± 0.15), slightly sublinear summation at -10 ms (NL = 0.86 ± 0.27) and supralinear summation at +10 ms (NL = 1.13 ± 0.28, P < 0.01 vs 0 ms), in close overlap with the simulations. Finally, analysis of response latencies of synaptically evoked global APs yielded a mean Δt = 9.6 ± 8.4 ms (n = 20), explaining the earlier finding of roughly linear summation of synaptic local and global signals. We conclude that these simulations and experiments provide another proof for the existence of the GC "spine spike". In the wake of a synaptic global AP the substantial summation of Ca^{2+} entry within a previously activated reciprocal spine might contribute to an increase in release probability. Such a coincidence mechanism might foster the synchronization of principal neuron and GC network activity within gamma and beta oscillation cycles.

Disclosures: S. Aghvami: None. **M. Müller:** None. **M. Lukas:** None. **H. Seyed-allaei:** None. **B.N. Araabi:** None. **V. Egger:** None.

Poster

463. Network Interactions and Synaptic Integration II

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Topic: B.06. Synaptic Transmission

Support: NIDCD grant R01 DC 00997701-06
NINDS grant NS11613

Title: Lateral inhibition and rhythmic gating by the dendrodendritic microcircuit in the olfactory bulb

Authors: *M. MIGLIORE[1,2], M. L. HINES[2], C. GREER[2], G. M. SHEPHERD[2]
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Abstract: A model for dendrodendritic interactions between mitral and granule cells in the olfactory bulb has been hypothesized to generate both lateral inhibition and rhythmic potentials in olfactory processing (Rall and Shepherd, 1968). Over the past 50 years, the model has been subjected to many tests and confirmed on anatomical, physiological and pharmacological grounds. Current questions are whether the model can account for the long distances required for lateral inhibition implied by non-topographical distributions of activated olfactory glomeruli, as

well as for rhythmic potentials. We review here the evidence that the model accounts for both these critical features.
The original model hypothesized that depolarization to activate the mitral-to-granule synapses could occur by either passive or active means. Active properties of the lateral dendrites were demonstrated by Xiong and Chen, 2002. They showed that action potential propagation occurs through the mitral cell lateral dendrites, and furthermore that direct activation of granule cells can inhibit propagation at arbitrary distances from the origin of the action potential at the mitral cell soma.
On this basis, our labs have carried out a series of anatomical studies of the dendrodendritic synapses and computational studies of the model with active dendritic properties. The propagating action potential enables the lateral dendrite to activate the mitral-to-granule cell excitatory synapses at arbitrary distances from the soma, as in the experiments. The lateral dendrites are known to spread up to 1.5 cm around the circumference of the external plexiform layer, covering virtually all the territory of the medial or lateral olfactory bulbs containing the non-topographically activated glomeruli.
With regard to rhythmic potentials, recent studies (cf. Osinski and Kay, 2016) have provided evidence that the dendrodendritic synaptic interactions are involved in generation of either beta or gamma waves, depending on the balance of excitatory drive between sensory input and centrifugal modulation.
In summary, after 50 years the original model with active properties continues to apply. We review these studies and discuss how the dendrodendritic synaptic interactions are coordinated with microcircuits at the input level to the glomeruli and the output level to the olfactory cortex to play a key role in the neural basis of olfactory perception.
References.
Osinski BL, Kay LM. 2016. J Neurophysiol 116: 522-539
Rall W, Shepherd GM. 1968. J Neurophysiol 31: 884-915
Xiong W, Chen WR. 2002. Neuron 34: 115-126

Disclosures: M. Migliore: None. **M.L. Hines:** None. **C. Greer:** None. **G.M. Shepherd:** None.

Poster

463. Network Interactions and Synaptic Integration II

Location: SDCC Halls B-H

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Program #/Poster #: 463.04/D46

Topic: B.06. Synaptic Transmission

Support: National Institute on Drug Abuse Intramural Research Program

Title: Glutamate and gaba co-transmission: Cell-types, distribution, synaptic and vesicular mechanisms

Authors: *D. H. ROOT, S. ZHANG, D. J. BARKER, J. A. MIRANDA-BARRIENTOS, B. LIU, H.-L. WANG, M. F. MORALES
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Abstract: Glutamate-GABA neurons within the ventral tegmental area (VTA) are capable of synaptically releasing both glutamate and GABA in the adult mouse. We aimed to identify populations of glutamate-GABA neurons outside VTA and determine the synaptic and vesicular mechanisms that underlie glutamate and GABA co-transmission.
We performed dual *in situ* hybridization for the detection of neurons co-expressing VGluT2 mRNA and GAD mRNA in rats. We found six brain structures containing concentrated populations of neurons co-expressing VGluT2 mRNA and GAD mRNA: the VTA, entopeduncular nucleus (EPN), supramammillary nucleus (SUM), lateral habenula (LHb), posterodorsal tegmental nucleus (PDTg), and caudal pontine reticular nucleus (PNC). By triple *in situ* hybridization for the detection of neurons co-expressing VGluT2 mRNA, GAD mRNA, and VGaT mRNA we found that only the VTA, EPN, and SUM contained neurons co-expressing VGluT2, GAD, and VGaT mRNAs. In contrast, VGluT2 neurons co-expressing GAD mRNA in LHb, PDTg, and PNC lacked VGaT. Thus, neurons belonging to the VTA, EPN, and SUM contain the molecular machinery to synthesize and vesicularly package both glutamate and GABA. However, neurons belonging to the LHb, PDTg, and PNC are capable of vesicularly packaging glutamate and synthesizing GABA, but are incapable of canonical vesicular packaging of GABA by VGaT.
By viral labeling of projections from VTA to LHb, EPN to LHb, and SUM to dentate gyrus in rats, we found that glutamate-GABA neurons establish a common synaptic architecture involving distinct asymmetric (putative excitatory) and symmetric synapses (putative inhibitory) from single axon terminals. These data suggest that glutamate-GABA neurons co-transmit glutamate and GABA from separate synaptic vesicles. We explored this possibility within rat LHb, which receives co-transmitted glutamate and GABA from VTA or EPN in mice. Consistent with results from mice, we found that both VTA and EPN pathways to LHb co-transmitted glutamate and GABA in GAD::Cre rats. To determine if glutamate and GABA are co-transmitted from the same or different synaptic vesicles, we purified synaptic vesicles from LHb. By co-immunoprecipitation and co-immunolabeling of LHb purified synaptic vesicles, we found that VGluT2 and VGaT are distributed on separate synaptic vesicles. We conclude that 1) neurons co-transmitting glutamate and GABA by their expression of VGluT2, VGaT, and GAD, are found in VTA, EPN, and SUM; and 2) VTA, EPN, and SUM axon terminals co-transmit glutamate and GABA via distinct synaptic vesicles at independent synapses within single axon terminals.

Disclosures: S. Zhang: None. **D.J. Barker:** None. **J.A. Miranda-Barrientos:** None. **B. Liu:** None. **H. Wang:** None. **M.F. Morales:** None.

Poster

463. Network Interactions and Synaptic Integration II

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Program #/Poster #: 463.05/D47

Topic: B.06. Synaptic Transmission

Support: NIH-NIDA R01 DA085321

Title: Mapping somatodendritic circuits of midbrain dopamine neurons

Authors: *S. ZYCH, C. P. FORD
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Abstract: Midbrain dopamine (DA) neurons in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) largely innervate a single terminal region, such that DA neuron populations are distinct and non-overlapping. In addition to terminal dopamine release, these cells locally modulate the excitability of neighboring DA neurons via somatodendritic dopamine release. This leads to activation of D2 autoreceptors (D2R) located on the soma and dendrites of DA neurons, evoking an inhibitory postsynaptic current (D2-IPSC) mediated by G-protein coupled inward rectifying potassium channels. However, the local somatodendritic circuitry between midbrain DA neuron populations has yet to be elucidated. It remains unclear whether DA neurons that project to distinct terminal sites provide somatodendritic inhibition to differentially-projecting DA populations. Using electrical or optogenetic stimulation of midbrain DA neurons to evoke dendritic DA release, we performed whole cell recordings in *ex vivo* brain slices to measure D2R-mediated inhibition between DA cell populations. We found that electrical stimulation and non-selective photoactivation of DA neurons in the VTA and SNc resulted in a post-synaptic D2-IPSC, which was abolished by sulpiride (200nM), confirming that electrical and optogenetic stimulation both cause sufficient DA release to evoke a D2-IPSC. To examine local midbrain circuitry, we injected a retrograde virus encoding channelrhodopsin (ChR2) into the nucleus accumbens (NAc) and the dorsal striatum (DStr). Thus, ChR2 expression in midbrain DA neurons labelled these target-specific populations. We observed that photoactivation of the DStr-projecting population evoked a D2-IPSC in half of recorded SNc DA cells, indicating that the local circuitry of the SNc enables somatodendritic modulation of neighboring neurons. We are further investigating preferential regulation within the SNc between DA populations that project to the medial versus lateral subdivisions of the DStr. We observed that photoactivation of the NAc-projecting population in the VTA resulted in no detectable D2-IPSC in both NAc-projecting and non-projecting DA cells. We are examining whether the activity of another DA population or multiple populations is necessary to evoke D2 IPSCs and mediate local regulation in the VTA.

Disclosures: S. Zych: None. **C.P. Ford:** None.

Poster

463. Network Interactions and Synaptic Integration II

Location: SDCC Halls B-H

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Program #/Poster #: 463.06/D48

Topic: B.06. Synaptic Transmission

Support: Grants-in-Aid for Science Research on Innovative Areas "Brain Information Dynamics" (18H05114)

Title: Depolarization-induced sensitization and synaptic properties of layer 2/3 pyramidal cells in mouse granule retrosplenial cortex

Authors: *M. GAO, Y. IKEGAYA
Grad. Sch. of Pharmaceut. Sci., The Univ. of Tokyo, Tokyo, Japan

Abstract: The retrosplenial cortex (RSC) is a cognitive hub that is involved in a variety of cognitive functions, including spatial memories, head direction, and context fear memories with interval delays. Consistent with this fact, the RSC has reciprocal synaptic connections with various brain regions, including the visual cortex, the hippocampus, the medial entorhinal cortex, and the subiculum. Thus, the RSC is likely to conduct synaptic integrations in different levels of neural information. However, there is only limited knowledge concerning about the basic properties of individual RSC neurons. A previous study has demonstrated that small pyramidal cells in the layer 2/3 of the rat RSC exhibit late-spiking properties through activity of a series of Kv channel subtypes (Kurotani et al, Brain Struct Funct, 2013), but it remains unclear how RSC neurons react to diverse synaptic inputs or how these features influence the computational properties of RSC neurons. Here, we used whole-cell patch-clamp recordings to examine the spiking properties of RSC layer 2/3 neurons and found that RSC layer 2/3 late-spiking neurons tend to produce spikes with shorter latencies after current injection-induced depolarization, and this tendency was more evident when the prior current injection had longer durations, larger depolarizations, or shorter intervals between the current injection and spike-evoking stimulation. These properties were in the opposite direction to that observed for RSC layer 5/6 neurons, anterior cingulate layer 2/3 neurons, and hippocampal CA1 neurons. Optogenetic stimulation of excitatory afferents projected from the subiculum reproduced similar results. We will further examine the synaptic properties of RSC layer 2/3 neurons to reveal a possible role of RSC in the integration of information flow.

Disclosures: M. Gao: None. **Y. Ikegaya:** None.

Poster

463. Network Interactions and Synaptic Integration II

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Program #/Poster #: 463.07/D49

Topic: B.06. Synaptic Transmission

Support: NIH Grant NS093866
NIH Grant NS105200

Title: Voltage imaging reveals gap junction enhancement of inhibitory interneuron synchrony in layer II/III of mouse cortex

Authors: *K. S. SCHEUER[1], P. O. BAYGUINOV[2], M. B. JACKSON[1]
[1]Neurosci., Univ. of Wisconsin-Madison, Madison, WI; [2]Washington Univ., St Louis, MO

Abstract: Neurons fire action potentials when the summation of excitatory inputs exceeds a threshold. The time window within which input can be integrated has a strong impact on the temporal fidelity of neural firing; over longer time spans, neurons are able to sum more excitatory inputs and consequently exhibit reduced selectivity and lower temporal resolution. When the time window is narrower, however, inputs must be tightly synchronized to trigger an action potential. Under these conditions, neurons can act as coincidence detectors and transmit information at a temporal resolution of 2 msec or less with sub-millisecond variability. Inhibitory interneurons (INs) are critical for narrowing this summation time window; in rat hippocampal pyramidal cells, $GABA_AR$ antagonists increase the integration window nearly 10-fold and nearly triple the variability in spike timing. To investigate the factors which influence IN activity and thereby gain insight into spike timing in local cortical circuits, we used hybrid voltage optical sensors (hVOS) to measure voltage changes in murine LII/III INs. This technique allowed us to study ten or more INs simultaneously in an area of approximately 500-1000 μM with a time resolution of 0.5 msec. We used Cre-lox recombination to target a genetically-encoded hVOS probe either generally to GABAergic INs with a glutamic acid decarboxylase 2 Cre driver, or specifically to parvalbumin (PV) INs with a PV-Cre driver. Cortical slices prepared from the offspring of these crosses contained many hVOS probe-labeled INs, most of which responded with optically-reported voltage changes to electrical stimulation. Responses to electrical stimulation were visible in a single trial, and revealed significant trial-to-trial variations in latency of 1-2 msec. However, in many pairs of INs, these latencies were highly correlated and varied in concert. To test the role of gap junctions in this correlation, we used quinine or mefloquine to block the primary neuronal connexin (Cx36) and two additional connexins present in PV+ IN gap junctions (Cx32 and Cx43). Most of the IN pairs previously identified as correlated in response latency became uncorrelated following the addition of connexin blockers. This study indicates that the gap junctions known to couple INs serve to synchronize their

responses and give IN circuits greater temporal power in controlling the timing and integration windows of local cortical circuits.

Disclosures: K.S. Scheuer: None. **P.O. Bayguinov:** None. **M.B. Jackson:** None.

Poster

463. Network Interactions and Synaptic Integration II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 463.08/D50

Topic: B.06. Synaptic Transmission

Title: Localization of inhibitory interneurons integrating central amygdaloid inputs to locus coeruleus neurons using virus mediated cell type specific wheat germ agglutinin tracing method

Authors: *J.-C. HSIEH[1], M.-Y. MIN[2], C.-C. CHEN[3], H.-W. YANG[4]
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Abstract: It has been reported that neurons in the central amygdala (CeA) and locus coeruleus (LC) increase their activity when predictive relationships between events are first noticed or altered, and electrical stimulation of CeA causes phasic response in LC neurons. Nevertheless, the underlying mechanism remains unknown. Given the majority of projecting neurons in CeA outputs are GABAergic, we hypothesize that CeA inputs might trigger LC phasic response through with inhibition of local GABAergic interneuron synapsing on LC neurons. To test this hypothesis, we first examined local GABAergic interneuron by producing a serotype 2 adeno-associative virus (AAV2), carrying floxed stop codon followed by sequence encoding wheat germ agglutinin (WGA), a commonly used transneuronal tracer. Second, we choosed AAV-Syn-ChrimsonR-tdT (addgene, plasmid#59171) as a marker to examine the input from CeA. After injecting AAV2-CMV-floxed stop-WGA into LC and AAV-Syn-ChrimsonR-tdT into CeA of cross bred transgenetic mouse line of tyrosine hydroxylase-cre(TH-cre) and glutamic acid decarboxylase-green fluorescent protein (GAD-GFP). This resulted in localization of a population that is WGA-immunoreactive (WGA-ir) within LC and the surrounding peri-LC areas. We further observed that, while most of these WGA-ir neurons are also TH-ir, a few of them are not. We reason that these WGA-ir but non-TH-ir neurons represented WGA transneuronal transportation from TH-ir neurons basing on two arguments. First, there are no catecholamine neurons other than LC NAergic neurons in the dorsal potine area; second, we have validated that there is no leak-out cre expression in LC of TH-cre mice, as cre-dependent expression of eYFP was only found in TH-ir neurons in TH-cre mouse injected AAV2-floxed-eYFP in LC. Basing on analysis from 2 animals with precise injection, about 20% of WGA-ir but non-TH-ir neurons also expressed GFP, showing they are GABAergic neurons. Furthermore, we have observed in one case that a WGA-ir, non-TH-ir and GFP^+ neuron received tdT labeled

fiber. The above observations support our hypothesis that disinhibiting of local GABAergic neurons is involved in trigger of phasic activation of LC neurons by CeA inputs.

Disclosures: J. Hsieh: None. **M. Min:** None. **C. Chen:** None. **H. Yang:** None.

Poster

463. Network Interactions and Synaptic Integration II

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Program #/Poster #: 463.09/D51

Topic: B.06. Synaptic Transmission

Support: ANPCyT PICT2013-0182
ANPCyT PICT2015-0364
FOCEM-Mercosur (COF 03/11)

Title: Cholinergic modulation reorganizes dentate gyrus microcircuits

Authors: M. B. OGANDO, D. M. ARRIBAS, L. G. MORELLI, *A. MARIN-BURGIN
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Abstract: Neurogenesis in the adulthood continuously provides the dentate gyrus (DG) of the mouse hippocampus with pools of granule cells (GC) that integrate into the preexisting network. We have previously showed that immature GC have lower thresholds of activation than the rest of the mature GC, are less selective in their responses to afferent inputs and respond to a wider range of frequencies of afferent activity. The differences in the activation profile of immature and mature neurons are dictated by the inhibitory circuits. These results suggest that mature and immature granule cells could then represent two different codes coexisting in the same structure: A sparse-code of mature neurons with low firing rates and high selectivity, and a dense-code of immature neurons in which most neurons are active at any moment and information is encoded by variations in firing rate. In this work we wanted to evaluate how neuromodulators, in particular acetylcholine, affects processing of inputs in both mature and immature GC. Using both pharmacologic and optogenetic tools combined with electrophysiological recordings, we observed that in presence of cholinergic activation, mature neurons increase their spiking response to stimulation of medial perforant path (mPP) inputs, whereas no significant changes were seen for immature 4 week old neurons. Then we recorded from individual neurons in a whole cell configuration, isolating the evoked excitatory and inhibitory currents (EPSCs and IPSCs) in response to mPP stimulation. We observed that Ach induced a reduction in the inhibitory component of the response, which was more prominent for mature neurons. This produced an increase in the excitation to inhibition balance that explained the differential spiking response. In addition, we observed that activating mPP at high frequency, normally insufficient to produce long term potentiation (LTP) in control conditions, produce LTP when paired with

optogenetic activation of cholinergic axons. We conclude that acetylcholine can provide a temporal window in which the information processing and plasticity rules of granule cells change, possibly allowing this brain region to adapt the encoding to the behavioral demands.

Disclosures: M.B. Ogando: None. **D.M. Arribas:** None. **L.G. Morelli:** None. **A. Marin-Burgin:** None.

Poster

463. Network Interactions and Synaptic Integration II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 463.10/E1

Topic: B.06. Synaptic Transmission

Title: The modulation of responses characteristics depending on the input frequency in hippocampal granule cells

Authors: N. NAKAJIMA, T. OINUMA, H. HAYAKAWA, E. SUGISAKI, *T. AIHARA
Tamagawa Univ., Tokyo, Japan

Abstract: The hippocampal dentate gyrus is a gate for memory association among cortexes. It was reported that the granule cells (GCs) in the dentate gyrus receives individual inputs by two different pathways from entorhinal cortex. One is spatial (place) information which is propagated through the medial perforant path to the medial dendrite (MD, at the middle molecular layer). The other is non-spatial (e.g. odor) information which is propagated through the lateral perforant path to the distal dendrite (DD, at the outer molecular layer). In addition, 4-8Hz (theta) and 20-40Hz (gamma) oscillations were observed in entorhinal cortex, an origin of pathways to MD and DD, in the rat brain during the odor discrimination task, respectively. However, the response-characteristics and the associative-interaction of two inputs on dendrites of GCs, depending on the input frequency, is still unclear. In this study, to investigate the integration of two input information propagated to hippocampal GCs, electrical regular-stimuli consisting 5 pulses were applied at 10 Hz - 40 Hz to two pathways projected to dendrites, MD and DD, of granule cells in a rat hippocampal slices and magnitudes of field excitatory-post-synaptic-potentiation (fEPSP) were measured. In our experiments, NMDA receptor and GABAergic receptor as post-synaptic factors were controlled by application of D-APV and picrotoxin, respectively, and thereby response characteristics for two inputs were analyzed paying attention to pre- and post-synaptic mechanism in the presence and absence inhibitory interneurons. As the result, magnitudes of successive fEPSP for regular electrical-stimulus to DD and MD showed transient and sustained responses, respectively. Especially, sustained responses for stimulus to DD were significantly influenced by temporal interaction between the NMDA current and the IPSP induced by inhibitory interneurons, depending on the input frequency. In addition, our previous report showed successive inputs to DD facilitated the temporal-pattern discrimination for MD input in

GCs. These results suggest that modulation of the sustained response at DD by interaction between NMDA receptors and GABAergic receptor depending on the input frequency are crucial role for the integration of two inputs in GCs.

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Poster

463. Network Interactions and Synaptic Integration II

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Program #/Poster #: 463.11/E2

Topic: B.06. Synaptic Transmission

Support: FAPESP
CNPq

Title: Changes in synaptic transmission in NTS of rats in response to acute hypoxia are not affected by previous exposure to sustained hypoxia or chronic intermittent hypoxia

Authors: *D. ACCORSI-MENDONCA[1], L. G. H. BONAGAMBA[2], B. H. MACHADO[3]
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Abstract: Peripheral chemoreflex is activated under hypoxia and produces cardiovascular and respiratory changes to keep the oxygen level in the physiological range. Neurons are highly sensitive to sustained hypoxia (SH) as well to chronic intermittent hypoxia (CIH), with implications on the synaptic transmission. Here, we evaluated the effect of previous short-term SH (FiO_2 0.1, 24 hours) or CIH (10 days, FiO_2 0.06, 8 hours/day) on changes induced by acute hypoxia (5 min) on the electrophysiological profile of NTS neurons. For this purpose, we used whole-cell patch clamp technique and brainstem slices from Wistar rats (P30). Normoxia condition was obtained by bubbling bath solution with 95% O_2 and 5% CO_2 and for the acute hypoxia the bath solution was bubbled with 95% N_2 and 5% CO_2. We observed that acute hypoxia induced a hyperpolarization (-63 ± 3.4 mV vs -73 ± 4.6 mV, n=8) and blocked the spontaneous firing frequency in NTS neurons from control rats. Acute hypoxia also decreased the RMP in neurons from CIH animals (-68 ± 3.2 mV vs -78 ± 4.7 mV, n=5) as well in SH rats (-62 ± 2.3 mV vs -68 ± 4.0 mV, n=12) and reduced the firing frequency in both groups. Acute hypoxia did not affect the R_{input} in NTS neurons from any group [(control: 1.03 ± 0.11GΩ vs 1.20 ± 0.28 GΩ, n=11)(SH: 1.15 ± 0.18 GΩ vs 0.93 ± 0.23 GΩ, n=8)(CIH: 0.95 ± 0.16 GΩ vs 0.75 ± 0.13 GΩ, n=6)]. With respect to the excitatory transmission, acute hypoxia reduced the amplitude of glutamatergic post-synaptic currents in neurons from all groups [(control: 142 ± 25 pA vs 91 ± 27 pA, n=14)(SH: 319 ± 73 pA vs 232 ± 68 pA, n=12)(CIH: 81 ± 12 pA vs 66 ± 7

pA, n=7). The data are showing that preconditioning to SH or CIH does not prevent the changes induced by acute hypoxia on the excitatory transmission and passive properties of neurons in the NTS of rats.
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Disclosures: D. Accorsi-Mendonca: None. **L.G.H. Bonagamba:** None. **B.H. Machado:** None.

Poster

463. Network Interactions and Synaptic Integration II

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Program #/Poster #: 463.12/E3

Topic: B.06. Synaptic Transmission

Title: NMDA spikes in human neocortex

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Abstract: Since the days of Golgi and Cajal, dendrites have been recognised as neuronal structures of potential relevance to information processing and storage in the brain. Yet, despite their potential significance, what we know about dendritic physiology stems, almost exclusively, from rodent research. Over the past decade, however, there has been increased interest in research on human neurons, obtained primarily from epilepsy and tumour surgeries in adult patients. In the present study, we build on this body of work to investigate whether local dendritic NMDA-dependent regenerative plateau potentials (NMDA spikes), which have been shown to play a critical role in information processing in rodent neurons, also occur in human neurons, and if so, describe their kinetics and the experimental conditions required for their generation. To address this, we recorded from supragranular tufted pyramidal cells in neocortical human slices from both epilepsy and tumour patients. Using glutamate iontophoresis, we probed excitation of basal dendrites, with our preliminary efforts illustrating linear integration in the majority of basal dendritic locations (from 50 up 250 um from the soma). In contrast, glutamate iontophoresis onto oblique dendrites routinely evoked supra-linear regenerative responses, which were abolished in the presence of APV, illustrating that human dendrites can generate NMDA spikes. To understand why these supra-linear voltage events were preferentially evoked in the oblique dendrites of human pyramidal neurons, we explored the underlying biophysical mechanisms in a morphologically realistic, active compartmental model. These results show that the dendrites of human cortical pyramidal neurons can generate NMDA spikes, as previously illustrated in rodent pyramidal neurons. Taken together, our findings suggest that human cortical

pyramidal neurons contain distinct dendritic domains, which respond differently to synaptic input.

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Poster

463. Network Interactions and Synaptic Integration II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 463.13/E4

Topic: B.06. Synaptic Transmission

Support: National Natural Science Foundation of China grant 31430038

Title: Functional autapses in neocortical pyramidal cells

Authors: W. KE[1], L. YIN[1], R. ZHENG[1], Q. HE[1], Y. ZHANG[1], J. LI[1], B. WANG[1], Z. MI[1], M. RASCH[1], T. LI[2], G. LUAN[2], *Y. SHU[1]
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Abstract: Autapses are special synapses formed in a single neuron, from the axon onto its own somatodendritic compartments. Autapses are abundant in neurons in culture systems, they have been considered as aberrant and redundant neuronal structures. However, autaptic contacts are found massive in certain types of GABAergic interneurons in the neocortex and play critical roles in regulating spike precision and network activity. In this study, we sought to determine whether neocortical pyramidal cells (PCs) form functional autapses. In acute mouse neocortical slices (postnatal 14-21 days, either sex, sex differences were not assessed), we performed simultaneous soma-axon patch clamp recording combined with axotomy or treated the preparation with $SrCl_2$ to isolate autaptic currents. We found that autapses are mainly formed by subcortically projecting layer-V PCs but rarely in cortico-cortical PCs and those in layer II/III. Autapses are not just transient structures in the developing brain. PCs in adult mouse (2 months) and human (male, 30-40 years, with intractable epilepsy) cortical tissue also show autaptic connections. Surprisingly, autapses produce giant postsynaptic responses (n=62 cells), five-fold greater than PC-PC recurrent synapses (n=10 pairs). In addition, autaptic responses are exclusively mediated by AMPA receptors. Further experiments showed that the activation of PC autapses enhances burst firing, neuronal responsiveness and coincidence detection of self-activity and incoming synaptic inputs. Together, our findings indicate that PC autapses are not aberrant structures, they are functional instead and represent an important circuit element in the neocortex.

Disclosures: W. Ke: None. **L. Yin:** None. **R. Zheng:** None. **Q. He:** None. **Y. Zhang:** None. **J. Li:** None. **B. Wang:** None. **Z. Mi:** None. **M. Rasch:** None. **T. Li:** None. **G. Luan:** None. **Y. Shu:** None.

Poster

463. Network Interactions and Synaptic Integration II

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Topic: B.06. Synaptic Transmission

Support: NIH Grant R01 MH085974

Title: Impact of layer 6 corticothalamic neurons in the prefrontal cortex

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Abstract: The cerebral cortex sends two distinct output streams to the thalamus, originating in deep layers five (L5) and six (L6). In the prefrontal cortex (PFC), both L5 and L6 corticothalamic neurons send axons to the same PFC-projecting thalamic nuclei. However, the relative contributions of these corticothalamic circuits in the PFC remain largely unexplored. Here we use transgenic mice along with optogenetics and whole-cell physiology to investigate the role of L6 in PFC-thalamus communication. We first study connections from the PFC to the thalamus to understand how the PFC shapes excitatory drive. We next explore the role of L6 inputs to the reticular thalamus in driving inhibition of thalamic nuclei. Finally, we examine L6 activity within the local circuit of the PFC. Together, our findings reveal new ways in which L6 neurons mediate PFC-thalamus communication.

Disclosures: D. Collins: None. **A.G. Carter:** None.

Poster

463. Network Interactions and Synaptic Integration II

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Program #/Poster #: 463.15/E6

Topic: B.06. Synaptic Transmission

Support: NIH R01 MH085974

Title: Ventral hippocampal inputs preferentially drive cortico-cortical neurons in the infralimbic prefrontal cortex

Authors: *X. LIU, A. G. CARTER
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Abstract: Inputs from the ventral hippocampus (vHPC) to the prefrontal cortex (PFC) play a key role in working memory and emotional control. However, little is known about how excitatory inputs from the vHPC engage different populations of neurons in the PFC. Here we use optogenetics and whole-cell recordings to study the cell-type specificity of synaptic connections in acute slices from mouse PFC. We first show that vHPC inputs target pyramidal neurons in superficial and deep layers of infralimbic (IL) PFC, but only deep layers of prelimbic (PL) PFC. We then compare connections onto different classes of projection neurons located in these layers and sub-regions of PFC. We establish vHPC inputs similarly contact cortico-cortical (CC) and cortico-amygdala (CA) neurons in layer 2/3 (L2/3) of IL, but preferentially target CC neurons over cortico-pontine (CP) neurons in layer 5 (L5) of both IL and PL. Of all these neurons, we determine that vHPC inputs are most effective at driving action potential (AP) firing of CC neurons in L5 of IL. We also show this connection exhibits frequency-dependent facilitation, with repetitive activity enhancing AP firing of IL L5 CC neurons, even with intact inhibition. Together, our findings reveal how vHPC inputs engage defined populations of projection neurons within the PFC, allowing them to preferentially activate the intra-cortical network.

Disclosures: X. Liu: None. **A.G. Carter:** None.

Poster

463. Network Interactions and Synaptic Integration II

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Topic: B.06. Synaptic Transmission

Support: National Natural Science Foundation of China grant 31430038

Title: Target cell-specific asynchronous glutamate release from neocortical pyramidal cells

Authors: S. DENG[1], J. LI[1], J. ZHU[2], Q. HE[1], Z. MI[1], *M. ZHANG[1], Y. SHU[1]
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Abstract: The arrival of action potential (AP) at presynaptic terminal usually causes immediate synchronous release (SR) of neurotransmitter within a time window of 1-2 ms. Prolonged asynchronous release (AR) that is not tightly coupled to presynaptic AP also occurs at output synapses of certain types of GABAergic interneurons in the hippocampus and neocortex upon high-intensity stimulation. Asynchronous GABA release provides long-lasting inhibition in

target cells and desynchronizes their activities. However, it remains unclear whether AR occurs at output glutamatergic synapses of pyramidal cells (PCs). We performed dual recordings from cortical PCs and neighboring inhibitory interneurons including the fast-spiking (FS) cell and the low-threshold spiking (LTS) cell in rodent cortical slices (postnatal 15-20 days, either sex, sex differences were not assessed). We found surprisingly that, in response to AP bursts in the presynaptic PC, AR occurs at its output synapses in a target cell-specific manner. In comparison with PC synapses onto FS (n=10 pairs) and neighbor PCs (n=7), those onto LTS (n=10) show the strongest AR and cause prolonged depolarization and firing in the postsynaptic cell. Intracellular application of EGTA (n=9) could abolish the occurrence of AR, indicating a dependence on residual Ca^{2+}, and Ca^{2+} influx at PC-LTS synapses is mainly mediated by P/Q-type Ca^{2+} channels. Further experiments revealed an important role of Ca^{2+} sensor synaptotagmin-7 (Syt7) in the occurrence of AR. Knocking out Syt7 (n=19) reduced both the number of AR events and the AR-induced basal currents, leading to a reduction of lateral inhibition between PCs. In conclusion, our results demonstrate that asynchronous glutamate release occurs at PC output synapses and its strength is target cell specific. The robust AR in PC-LTS synapses could induce prolonged activities in LTS cells, which may subsequently provide long-lasting inhibition and regulate dendritic integration in neocortical PCs.

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Poster

463. Network Interactions and Synaptic Integration II

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Program #/Poster #: 463.17/E8

Topic: B.06. Synaptic Transmission

Support: NIDCD: R21DC014765

Title: Non-reciprocal open-loop interactions in thalamo-thalamicreticular network

Authors: *K. PAUL[1], J. W. BROWN[2], A. TAHERI[4], R. V. KENYON[4], T. Y. BERGER-WOLF[4], D. A. LLANO[3]
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Abstract: The thalamic reticular nucleus (TRN) has well-established closed loop reciprocal connectivity with the thalamus. However, there is growing evidence of additional non-reciprocal or open loop connectivity between them, in which thalamic neurons are not reciprocally inihibited by the TRN neuron that they excite. Such an arrangement may provide a basis for the

transmission of neuronal information between thalamic nuclei, both intramodal and crossmodal. In this study, we employ experimental and computational approaches to show that information transmission may occur along the thalamus via non-reciprocal, open-loop thalamus-TRN interconnectivity. Whole-cell patch-clamp recordings were performed in colliculo-thalamocortical and somatosensory slice preparations from mice (P12-24). Recordings were obtained using standard extracellular solution and Cs based intracellular solution in the voltage clamp mode. The holding potential was kept at 0 mV or +10 mV to maximize amplitudes of the photostimulation evoked inhibitory postsynaptic potentials. MNI-caged glutamate (Tocris) was added to recirculating ACSF and stimulated using a pulsed UV laser (355 nm, DPSS) over a grid of points encompassing the TRN and several thalamic nuclei (MGB, VB, dLGN) and focal photolysis was accomplished by non-neighbor stimulation of points within the grid. Current responses were obtained in the voltage clamp configuration with the outward current amplitude representing the strength of the disynaptic connection. Pharmacological investigations showed that monosynaptic and disynaptic TRN-thalamus inhibitory maps are attenuated by local application of excitatory synaptic blockers in the TRN but not by inhibitory blockers. This suggests that open-loop interactions occur via the TRN-thalamus AMPA connectivity. We further investigated contributions of TRN-TRN electrical synapses in the non-reciprocal transmission using gap junction blockers as well as in Connexin 36 KO mice. The experimental findings were complemented with a computational model of the thalamo-reticular-cortical network to show that propagation of oscillatory activity was best supported in networks with strong closed and open loop reticulothalamic connectivity, with minimal contribution of intrareticular chemical or electrical synapses.

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Poster

463. Network Interactions and Synaptic Integration II

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Program #/Poster #: 463.18/E9

Topic: B.06. Synaptic Transmission

Support: NIH EB022903
EB017695

Title: Recruitment of neurons into neural ensembles based on dendritic plateau potentials

Authors: *P. P. GAO[1], J. W. GRAHAM[2], S. L. ANGULO[2,3], S. DURA-BERNAL[2], M. L. HINES[4], W. W. LYTTON[2,3], S. D. ANTIC[1]
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Abstract: Experimental observations have shown that glutamatergic inputs to the basal dendrites of cortical pyramidal neurons activate AMPA and NMDA receptors, which can bring the dendrites into a long-lasting depolarized state: a dendritic plateau potential. These sustained depolarizations push the cell body towards spike threshold and reduce the membrane time constant. In such a "*Prepared*" state, the pyramidal cells can respond to other sparse synaptic inputs more quickly and easily, facilitating synchronization of firing. During the plateau depolarization, a neuron can tune into ongoing network activity and synchronize spiking with other neurons to provide a coordinated "*Active*" state (robust firing of somatic action potentials), which would permit "binding" of signals through coordination of neural activity across a population. Under this scenario, *Active* cells are recruited from cells in the *Prepared* state, and therefore the transient *Active* ensemble is embedded in the longer-lasting *Prepared* ensemble of neurons. We hypothesize that "embedded ensemble encoding" may be an important organizing principle in networks of neurons, explaining how electrical signaling endows central nervous system with capacity to form large number of neural ensembles. We have developed a morphologically-detailed model reconstructed from a cortical Layer 5 prefrontal pyramidal cell in the NEURON simulator. Both synaptic AMPA/NMDA and extrasynaptic NMDA receptors are placed on basal dendrites to model the induction of plateau potentials. The active properties of the cell are tuned to match the amplitude and duration of plateau potentials recorded by voltage-sensitive dye imaging in dendrites and whole-cell patch measurements in soma. Then, the effects of input location, receptor conductance, calcium-activated potassium channels and voltage-activated calcium channels were explored in the model. These findings help us to better understand the implications of dendritic plateaus at the cellular and network level. In the future, this detailed individual cell model can be used to develop cortical meso-scale network models for exploring the hypotheses pertaining to the recruitment of neurons into neural ensembles.

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Poster

463. Network Interactions and Synaptic Integration II

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Program #/Poster #: 463.19/E10

Topic: B.06. Synaptic Transmission

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Title: Embedded ensemble encoding: A hypothesis for reconciling cortical coding strategies

Authors: *J. W. GRAHAM[1], S. ANGULO[1], P. P. GAO[2], S. DURA-BERNAL[1], S. SIVAGNANAM[1,3], M. L. HINES[4], S. D. ANTIC[2], W. W. LYTTON[1,5]
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Abstract: Applying glutamate near basal dendrites of cortical pyramidal neurons has been shown experimentally to activate AMPA and NMDA receptors, which can result in dendritic plateau potentials: long-lasting depolarizations in the dendrites which spread into the soma, bringing the cell closer to the spiking threshold and reducing the membrane time constant. When in such a "*Prepared*" state, pyramidal cells can more quickly and easily respond to synaptic inputs, facilitating synchronization of firing in this subset of cells. These "*Active*" cells thus represent another neuronal ensemble which is embedded in the ensemble of Prepared cells. We hypothesize that "embedded ensemble encoding" may be an important organizing principle in networks of neurons. Starting with a morphologically-detailed model reconstructed from a cortical Layer 5 prefrontal pyramidal cell, synaptic AMPA/NMDA and extrasynaptic NMDA receptor models were placed on basal dendrites to induce plateau potentials. The active properties of the cell were tuned to match plateau potentials recorded by voltage-sensitive dye imaging in dendrites and whole-cell patch measurements in soma (see companion poster). We then methodically simplified the model while maintaining the general behavior of the cell as well as its response to glutamate stimulation. Using the simplified pyramidal neuron model, along with a previously-published inhibitory interneuron model, we created network models to explore the behavior of subpopulations of neurons in *Prepared* and *Active* states. The network model simulations showed increased synchrony during the dendritic plateau in the subsets with AMPA/NMDA receptor activation in the basal dendrite. Dendritic plateaus induced by strong basilar dendrite stimulation can increase population synchrony produced by weak coherent stimulation in apical dendrites. These findings may help to understand the implications of dendritic plateaus at the cellular and network level, and may lead to a better understanding of ensemble synchronization and multimodal cortical information processing.

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Poster

463. Network Interactions and Synaptic Integration II

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Title: Shaping the spatiotemporal window for spiking via cell-type-specific inhibition of dendritic plateau potential in the striatal spiny projection neurons

Authors: *Y.-W. WU[1], K. DU[2], R. C. LINDROOS[3], Y. LIU[4], B. ROZSA[5], G. KATONA[6], J. HELLGREN KOTALESKI[2], J. B. DING[7]
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Abstract: Dendritic plateau potentials are supralinear synaptic integration events and are crucial for single-neuron computations. Plateau potentials could be initiated at the distal branches by activation of spatially clustered and temporally synchronized excitatory inputs in the striatal spiny projection neurons (SPNs). However, it is largely unknown how following excitatory and inhibitory synaptic activities shape the plateau potentials. Here, by using detailed SPN computational simulation, we show that plateau potentials broadened the spatiotemporal window for integrating excitatory inputs and promote spiking. By further combining two-photon imaging, optogenetics, and dual-color uncaging of glutamate and GABA, we directly tested the spatiotemporal interaction between the plateau potential and the GABAergic inhibitions. We demonstrated the temporal window of spiking was differentially tuned by GABAergic inhibition in a cell-type-specific manner. This delicate inhibitory control of the spike output is most efficient at the dendritic branch where the plateau potentials are initiated and relies on the reestablishment of NMDA receptor Mg^{2+} block. These findings provide a new insight into how spatiotemporal window of SPN spike output can be finely shaped by branch-specific dendritic inhibition.

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Poster

463. Network Interactions and Synaptic Integration II

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Title: Coincidence and sequence detection by electrically-coupled interneurons

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Abstract: Electrical synapses are ubiquitous in interneuron networks. They form intercellular pathways, allowing electrical currents to leak between coupled interneurons. I explored the impact of electrical coupling on the integration of excitatory signals and on the coincidence detection abilities of electrically-coupled cerebellar basket cells in juvenile mice and rats. Simultaneously-injected current pulses in coupled cells increased their firing rate and their probability of recruitment and they reduced the latency of action potential generation. Furthermore, action potential probability was increased and action potential latency was shortened in response to synaptic stimulations in mice lacking the protein that forms gap junctions between basket cells, connexin36, relative to wild-type controls. These results suggest that electrical synapses between basket cells decrease the probability and increase the latency of stimulus-triggered action potentials, both effects being reverted upon simultaneous excitation of coupled cells. Varying the delay at which coupled cells are stimulated revealed that the probability of action potential generation is also increased when a basket cell is stimulated shortly after a coupled cell. These findings suggest that electrically-coupled interneurons behave as coincidence and sequence detectors that dynamically regulate the impact of inhibition onto postsynaptic targets depending on the degree of input synchrony in the coupled interneuron network.

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Poster

464. Short-Term Synaptic Plasticity

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Topic: B.07. Synaptic Plasticity

Support: AA020501-01A1

Title: Binge alcohol drinking alters computing of executive and emotional information in nucleus accumbens medium spiny neurons

Authors: *G. E. MARTIN[1], J. KOLPAKOVA[2]
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Abstract: Drug addiction is a devastating neuropsychiatric disorder that affects millions of individual in the US and worldwide. Decades of research support the idea that addiction is a chronic illness of the brain caused by impaired neuronal communication. More specifically, one theory posits that uncontrolled drug use results in part from the inability of neurons in specific brain regions (e.g. hippocampus, prefrontal cortex, amygdala and nucleus accumbens) to correctly integrate and prioritize distinct (e.g. cognitive, contextual and emotional) information. Yet, despite decades of research, the experimental validation of this idea remains elusive, in great part due to technical obstacles that have precluded testing this hypothesis directly. To address the central question of neuronal computing in naïve and binge alcohol drinking mice, we have developed innovative technology that permits us, for the first time, to directly test how the nucleus accumbens computes information from distinct circuits, and how binge drinking influences this process. To do this, we recorded light-driven excitatory postsynaptic potentials in nucleus accumbens medium spiny neurons (MSNs) in fresh mouse brain slices, and used a novel optogenetic approach that we recently developed to selectively and independently activate specific neuronal populations that originate from the prefrontal cortex and the basolateral amygdala regions, and which converge onto MSNs in the nucleus accumbens. These candidate populations are responsible for processing executive and emotional information, respectively, but their role in drug and alcohol addiction is not fully understood. We show that **i)**executive and emotional information converging onto the same accumbens spiny neurons mutually control each other's strength, **ii)**binge alcohol drinking profoundly upsets this reciprocal control in male mice by favoring the processing of emotional information at the expense of cognitive ones. Importantly, we also showed that this phenomenon is sex-specific as it appears to follow different rules in females vs. males. These data offer the tantalizing hint that restoring the transmission of information between the prefrontal cortex to the accumbens may help limit alcohol consumption, a possible strategy for treating alcohol abuse in humans.

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Poster

464. Short-Term Synaptic Plasticity

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Program #/Poster #: 464.02/E14

Topic: B.07. Synaptic Plasticity

Support: Welcome DBT

Title: Form follows function: Synaptic design to account for short term plasticity at mossy fiber boutons

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Abstract: Mossy fibers (MF) provides the first entry of neuronal signals to the hippocampus and make synapses with CA3 pyramidal neurons. In contrast to other well studied synapse in the hippocampus, the CA3-CA1 synapse, the MF bouton has a large size (~8 μm^3) and hundreds of docked vesicles. Each MF bouton has an elaborate arrangement of active zones that span multiple dendritic protrusions of the CA3 neuron and operate at low vesicle release probability (Pr ~ 0.2). In response to a high frequency stimulus, fast and long-lasting increase in Pr and generation of a postsynaptic AP is seen (conditional detonation). This postsynaptic AP generation is more sensitive to the number (~6) of stimuli and not the rate of stimulus between 10-100 Hz (AP counting). Additionally these boutons are capable of an extensive range of short time plasticity profile. We investigate the causal relationship of the presynaptic components of synaptic transmission and its specialized spatial arrangement in the MF bouton to the characteristic plasticity displayed.
Our strategy here is to build a physiologically realistic computational model of the MF bouton and populate it with basic components underlying synaptic transmission with biophysical realism (concentrations, numbers, diffusion constants, reaction rates and spatial arrangement etc.). We compute calcium signals in the bouton, at the active zones, and measure activity dependent changes in vesicle release rates. We establish a relationship between presynaptic release rate and the probability of generating a postsynaptic AP at the MF-CA3 synapse. Various factors in MF boutons have been shown to individually participate in orchestrating and modulating short term plasticity. Our model elucidates the implication of elaborate active zone arrangement at this synapse and its spatial relationship to the calcium channels in altering STP. We propose an minimal synaptic design that can account for the typical plasticity attributes observed at this synapse.
MF-CA3 synapses are said to be specialized for pattern separation and make use of plasticity to differentiate between similarly encoded patterns, consequently retaining distinct memories

effectively. A clear understanding of contributions of the synaptic signaling at the MF would provide insights into changes in synaptic strength and its precise relationship to higher order computation.

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Poster

464. Short-Term Synaptic Plasticity

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Topic: B.07. Synaptic Plasticity

Support: DFG via CNMPB B1-1

Title: Increased synaptic facilitation and exploratory behavior in mice lacking the presynaptic protein mover

Authors: J. S. VIOTTI[1], F. W. OTT[2], J. M. WAGNER[2], E. M. SCHLEICHER[2], Y. BOUTER[2], T. A. BAYER[2], *T. DRESBACH[1]
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Abstract: The increase in the complexity of brains in evolution is accompanied by a surprisingly small number of new synaptic proteins. However, a few vertebrate-specific synaptic proteins arose. One of these vertebrate-specific proteins, Mover, is strongly upregulated in schizophrenia.Mover is a synaptic vesicle-attached phosphoprotein, regulated by activity, and binds the conserved Calmodulin and the vertebrate-specific protein Bassoon. Mover is differentially expressed at subsets of synapses. Knockdown of Mover in the calyx of Held leads to an increased calcium sensitivity of release.In this study, we used a Mover knockout mouse line to investigate the role of Mover in the hippocampus and its behavioral phenotype. While Schaffer collateral synapses were unchanged by the knockout, the mossy fibers showed strongly increased facilitation. The effect of Mover knockout in facilitation was both calcium- and age-dependent, having a stronger effect at higher calcium concentrations and in younger animals. Increasing cAMP levels by forskolin potentiated equally both wildtype and knockout mossy fiber synapses. However, forskolin-potentiation and Kainate receptor blockade independently occluded most of the increased facilitation observed in the knockout.Mover knockout mice show unimpaired memory but display increased willingness to persist in open arms in an elevated plus maze and spend more time in the center of open field tests. These results suggest an anxiolytic effect caused by the absence of Mover.These discoveries suggest that Mover a) has distinct roles at different synapses; b) generally acts to dampen the extent of presynaptic events; c) acts as a brake that can be released during low activity; d) promotes anxiety-like effects. We suggest a model in which Mover inhibits the Kainate receptor/cAMP pathway, which explains the

observed electrophysiological results and supports the proposed role of Mover dynamically buffering synaptic strength.

Disclosures: J.S. Viotti: None. **F.W. Ott:** None. **J.M. Wagner:** None. **E.M. Schleicher:** None. **Y. Bouter:** None. **T.A. Bayer:** None. **T. Dresbach:** None.

Poster

464. Short-Term Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 464.04/E16

Topic: B.07. Synaptic Plasticity

Support: DFG Grant SFB 889

Title: Mover promotes activity-dependent superpriming of synaptic vesicles at the Calyx of Held

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Abstract: Mover is a vertebrate-specific presynaptic protein that is attached to synaptic vesicles. It is an interaction partner with calmodulin and Bassoon, another vertebrate-specific active zone protein. The expression levels of Mover are variable throughout the brain; in some subsets of synapses it is highly expressed whereas in others it is below detection limit, indicating a modulatory function at the operation of the synapses. Additionally, Mover is highly upregulated in the brains of schizophrenic patients, specifically in the anterior cingulate cortex.
In this study we aimed to elucidate Mover's function in synaptic transmission and short-term plasticity in a central glutamatergic synapse, the calyx of Held, by using a Mover knockout (KO) mouse line. For that purpose, we stimulated bushy cell axons, which give rise to the axo-somatic calyx of Held terminal, placing a parallel bipolar electrode close to the brainstem midline. We recorded evoked excitatory postsynaptic currents (eEPSCs) from postsynaptic principal cells of the medial nucleus of the trapezoid body using a whole-cell patch clamp configuration.
We found that in Mover knockout mice the steady-state EPSC at the end of a stimulus train is increased. Moreover, the linear relationship of the initial EPSC amplitude to the steady state EPSC amplitude was enhanced in the KO, indicating a weaker short-term depression of the superprimed component of the EPSCs. By subtracting the normally-primed component of the EPSCs we calculated a significantly lower release probability of the superprimed synaptic vesicles in the knockout mice. These data suggest an activity-dependent effect of Mover on the synaptic vesicle pool and especially on the superprimed synaptic vesicles.

Disclosures: H. Pofantis: None. **T. Dresbach:** None.

Poster

464. Short-Term Synaptic Plasticity

Location: SDCC Halls B-H

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Program #/Poster #: 464.05/E17

Topic: B.07. Synaptic Plasticity

Support: NICHD Intramural Grant 1ZIAHD001205-25
NINDS Intramural Grant 1ZIANS003144-04

Title: Intrinsic plasticity associated with barrage firing episodes in rodent and human neurogliaform cells culminates in short-term potentiation of dendritic EPSP-spike coupling

Authors: *R. CHITTAJALLU[1], K. AUVILLE[1], D. CALVIGIONI[1], C. FANG[1], X. Q. YUAN[1], K. A. PELKEY[1], K. ZAGHLOUL[2], C. J. MCBAIN[1]
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Abstract: The capacity for neuronal communication within circuits to undergo dynamic modifications has been intensely studied and is mediated by a bewildering array of synaptic/cellular mechanisms. Here, we demonstrate that injections of brief supra-threshold current steps or synaptic induced action potentials (8 Hz, 30 Hz, 100Hz and theta-burst stimulation) in mouse cortico-hippocampal neurogliaform cells (NGFCs) culminates in a period of continued firing that occurs in the absence of any further input. Such slow neural integration has been described in a variety GABAergic interneuron (IN) subtypes and is termed persistent or retroaxonal barrage firing (RaBF). In our hands, RaBF in NGFCs is induced after 547 ± 27 action potentials and each RaBF episode lasted 2.6 ± 0.9 seconds (n = 128). The RaBF observed in the current study is, in general, shorter in duration than previously described and therefore the paradigms/experimental conditions employed likely constitute the minimum requirement to induce this firing mode. Interestingly, following these brief excursions into RaBF, NGFCs enter a state of augmented excitability that manifests as an increased action potential output in response to somatic depolarizing current/voltage injections. From a more physiological standpoint, subthreshold EPSPs elicited by electrical stimulation of afferent fibers are subsequently able to trigger action potentials in NGFCs after RaBF demonstrating a potentiation of dendritic EPSP-spike (E-S) coupling. RaBF can be repeatedly induced in a given NGFC and although RaBF duration is relatively consistent upon successive induction protocols, the time span of the subsequent potentiation in this intrinsic excitability is enhanced (63 ± 10 vs. 240 ± 160 seconds after 1st and 4th RaBF episode, respectively; n=39, 11), suggesting an ability to prime the circuit for this form of plasticity. In a parallel set of experiments, we recorded from layer I human cortical INs (hINs) where reelin-positive putative NGFCs reside. RaBF could also be induced in hINs possessing NGFC morphology resulting in a potentiation of intrinsic

excitability similar to that observed in rodent. Taken together these data demonstrate an activity-dependent neural plasticity mechanism that enhances NGFC recruitment potentially resulting in a temporal window of increased dendritic inhibition of pyramidal cells that is conserved across rodent and human cortical circuits.

Disclosures: R. Chittajallu: None. **K. Auville:** None. **D. Calvigioni:** None. **C. Fang:** None. **X.Q. Yuan:** None. **K.A. Pelkey:** None. **K. Zaghloul:** None. **C.J. McBain:** None.

Poster

464. Short-Term Synaptic Plasticity

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Program #/Poster #: 464.06/E18

Topic: B.07. Synaptic Plasticity

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Wellcome Trust PhD Studentship
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Title: Noradrenergic modulation of hippocampal CA3 and CA1 networks

Authors: *T. J. BACON[1,2], L. Y. PRINCE[3], K. TSANEVA-ATANASOVA[4], A. E. PICKERING[1,2], J. R. MELLOR[1,2]
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Abstract: The hippocampus encodes new memories by strengthening synaptic coupling to create ensembles of principle neurons. Release of neuromodulators within the hippocampus regulates this process and is therefore predicted to determine which memories are encoded. The locus coeruleus (LC) is a brainstem nucleus that projects diffusely throughout the cortex, releasing noradrenaline (NA) to co-ordinate multiple brain areas and mediate a variety of cognitive processes, including learning, memory, vigilance, and sleep (Kety, 1972; Sara *et al., 1994*). Within the hippocampus NA release acts as a novelty signal, with the LC switching from tonic firing in familiar spaces to burst firing when an animal enters a novel environment (Vankov *et al.,* 1995). The effects of such a switch on synaptic dynamics, ensemble recruitment and memory formation are still poorly understood.
Well-documented hippocampal effects of NA are its potentiation of LTP and inhibition of the slow afterhyperpolarisation (sAHP) current, a Ca^{2+}-activated K^+ current that plays an important role in synaptic integration. To explore the relatively understudied modulatory effects of NA on various hippocampal synaptic inputs and post-synaptic firing properties we have used a

combination of whole-cell patch-clamp recording in *ex vivo* hippocampal slices, opto- and chemogenetic manipulations and computational modelling.
At Schaffer Collateral-CA1 (SC-CA1) synapses bath-applied NA attenuated both excitatory and feedforward inhibitory responses resulting in little change in Excitatory-Inhibitory (E-I) ratio whereas at mossy fibre-CA3 (MF-CA3) synapses NA augmented excitatory whilst decreasing feedforward inhibitory inputs thereby increasing the E-I ratio. NA also caused a small depolarisation of CA1 & CA3 neurons and a minor increase in input resistance. These results suggest that at SC-CA1 synapses, NA does not alter CA1 hippocampal output through a change in synaptic input, but through changes in post-synaptic excitability. Within the CA3, the effect of NA on naturalistic granule cell firing patterns was modelled using a Tsodyks-Markram model of the MF-CA3 synapse, which suggested that an increase in baseline mossy fibre release probability underlies the enhanced MF-CA3 EPSCs. Thus, an increase in CA3 output is predicted to result from a combination of increased E-I ratio and post-synaptic excitability.

Disclosures: T.J. Bacon: None. **L.Y. Prince:** None. **K. Tsaneva-Atanasova:** None. **A.E. Pickering:** None. **J.R. Mellor:** None.

Poster

464. Short-Term Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 464.07/E19

Topic: B.07. Synaptic Plasticity

Title: Corticosterone and BDNF as possible contributors to the post-exercise priming of rat motor cortex and hippocampus

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Abstract: The priming of motor cortex to facilitate plasticity is an approach that may improve motor rehabilitation following injury. Emerging evidence supports the possibility that aerobic exercise may offer one means to achieve priming, however, the mechanisms whereby priming may occur following an acute bout of aerobic exercise are currently debated. One molecular mechanism may be related to the migration of receptors towards synaptic densities, which is a process shown to play a key role in the induction of long-term potentiation. Previous work from our lab suggested that a single event of moderately intense (20 m/min for 20 minutes) exercise significantly augments the phosphorylation of AMPA receptor (GluA1 & GluA2) and NMDA receptor (GluN2A & GluN2B) subunits. In a follow up study this phosphorylation was related to changes in the cellular distribution of these receptors within synaptic densities, which we argue signifies a novel molecular mechanism to explain the priming of motor cortex following single session aerobic exercise. However, based on these findings, the identity of the molecular

pathway that could be responsible for the priming phenomenon remains unclear. In our previous investigations we noted that aerobic exercise was a potent stimulus for the release of peripheral corticosterone (CORT) and central brain-derived neurotrophic factor (BDNF). As a result, we aimed to investigate the relative contributions that these molecules may have on the priming of motor cortex for plasticity. Specifically, we hypothesized that BDNF and CORT alone would be insufficient to mimic exercise induced priming, but that the combination of CORT-BDNF would induce similar effects to those seen following single-session exercise. Young, male Sprague-Dawley rats (n = 18) on a reverse light cycle (12h/12h) were sacrificed and tissue slices prepared from both the motor cortex and hippocampus. Slices were provided 1 hour to recover from surgery under standard conditions, before being exposed to either 30 minutes of CORT (200 nM), BDNF (20 ng/mL), or CORT-BDNF. Immediately following treatment, surface proteins were labelled by incubating slices in biotin. After homogenization, synaptoneurosomes were prepared (to enrich pre/post-synaptic terminals), and then proteins at the synaptic membrane were isolated by incubation with neutravidin beads. Next, we plan to probe surface synaptic fractions for proteins of interest by Western blotting analysis. The work in progress aims to establish that combined effects of CORT-BDNF following a single session of aerobic exercise is, in part, responsible for the "primed" state within motor cortex.

Disclosures: J.S. Thacker: None. **W. Staines:** None. **J.G. Mielke:** None.

Poster

464. Short-Term Synaptic Plasticity

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Program #/Poster #: 464.08/E20

Topic: B.07. Synaptic Plasticity

Support: University of Minnesota (UMN) CLA to LL
NIH-NINDS (R01NS097312-01) to AA
Human Frontier Science Program (Research Grant RGP0036/2014) to AA

Title: Synapse-specific regulation revealed at single synapses is concealed when recording multiple synapses

Authors: *J. W. LINES[1], A. COVELO[2], R. GOMEZ[3], L. LIU[2], A. ARAQUE[4]
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Abstract: Synaptic transmission and its activity-dependent changes are fundamental processes in nervous system function. Neurons may receive thousands of synaptic contacts, but synaptic regulation may occur only at individual or discrete subsets of synapses. While there exist several electrophysiological methods to assess synaptic transmission at distinct scales of observation,

e.g., through local field potential and individual whole-cell recordings, their experimental limitations to detect synapse-specific modulation is poorly defined. We have investigated the ability of electrophysiological recordings at different levels of analysis to detect synapse-specific short-term plasticity changes induced by endocannabinoids, which are known to regulate specific synapses (Navarrete and Araque, 2010). Using hippocampal slices, we combined local field potential and whole-cell recordings of CA3-CA1 synaptic activity evoked by Schaffer collateral stimulation of either multiple or single synapses, to test their ability to detect endocannabinoid-mediated short-term synaptic regulation. Additionally, we developed a mathematical model to perform Monte Carlo simulations assuming a bimodal distribution of regulated and unregulated synapses to simulate the experimental requirements of the different recording methods to detect discrete changes in subsets of synapses. Our results show that endocannabinoid-induced depolarization-induced suppression of excitation (DSE) and astrocyte-mediated synaptic potentiation can be observed when monitoring single or few synapses, but are statistically concealed when using gross recordings of multiple synapses. These results indicate that the electrophysiological methodology is critical to properly assess synaptic changes occurring in subsets of synapses, and that relevant synapse-specific regulatory phenomena may be experimentally undetected but nonetheless have important implications in the spatial extension of synaptic plasticity.

Disclosures: J.W. Lines: None. **A. Covelo:** None. **R. Gomez:** None. **L. Liu:** None. **A. Araque:** None.

Poster

464. Short-Term Synaptic Plasticity

Location: SDCC Halls B-H

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Program #/Poster #: 464.09/E21

Topic: B.07. Synaptic Plasticity

Support: Telethon-Italy GGP11043
Compagnia di San Paolo ROL-4318

Title: Conformational states of kainate receptors shapes short-term plasticity by controlling receptor lateral mobility at glutamatergic synapses

Authors: *A. I. POLENGHI[1], S. GUAZZI[1], P. GOROSTIZA[2], A. BARBERIS[1]
[1]Fondazione Inst. Italiano Di Tecnologia, Genova, Italy; [2]Inst. for Bioengineering of Catalonia, Barcelona, Spain

Abstract: Kainate receptors (KARs) mediate slow postsynaptic currents that significantly impact on synaptic integration and spike transmission. However, the molecular determinants responsible for the postsynaptic stabilization of KARs are poorly understood. In particular, the interactions

between scaffold proteins of the glutamatergic postsynaptic density and the different KARs conformational states have never been investigated. Here, we combine optogenetic and Quantum-Dots based single particle tracking approaches to study the role of KARs conformational states on KARs lateral mobility at synapses. For this purpose, we use engineered ionotropic kainate receptors - light-gated GluK2 receptors (LiGluK2Rs) - that can be switched in the desensitized or closed state by illumination with UV or blue light, respectively, in a precise and reliable way. We report that desensitized KARs are reversibly trapped at glutamatergic synapses through the interaction between LiGluK2-C-terminus (in particular the residues 892-908, a non-PDZ domain) and the β-catenin/N-Cadherin complex. Coimmunoprecipitation experiments revealed that desensitization of KARs increased the receptor interaction with the β-catenin/N-Cadherin complex. By using the glutamate uncaging technique we demonstrate that the immobilization of desensitized KARs at synapses leads to an increased current desensitization during repetitive glutamate uncaging applications. In AMPA/KARs mixed responses, such effect favors the fast AMPA component while lowers the slow kainate component, thus reducing the temporal window of signals integration. Finally, we demonstrate that mutants disrupting the interaction between LiGluK2 and β-catenin/N-Cadherin complex (LiGluK2Δ16 and N-CadherinΔE) abolish the trapping of desensitized KARs at synapses thus leading to a decreased current desensitization during repetitive stimulation with respect to control conditions. Overall, we show that the modulation of synaptic KARs lateral mobility by the receptor conformational states regulates the short-term plasticity of glutamatergic currents.

Disclosures: A.I. Polenghi: None. **S. Guazzi:** None. **P. Gorostiza:** None. **A. Barberis:** None.

Poster

464. Short-Term Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 464.10/E22

Topic: B.07. Synaptic Plasticity

Title: Interplay of entorhinal cortical input and local inhibitory network at the origin of slow inhibition in hippocampal granule cells

Authors: *Y. MIRCHEVA, M. R. PERALTA, III, K. TOTH
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Abstract: The perforant path (PP) conveys information between enthorhinal cortex (EC II) and the hippocampus. Cortical cells project to the molecular layer (ML) of the DG where excitatory signals initiate an interplay with local inhibition in order to achieve proper information transfer. Nearly simultaneous signalling to both glutamatergic and local GABA-ergic cells engages network interactions that will modulate input integration and firing pattern in dentate granule cells (DGCs). Fast and slow inhibitory mechanisms are major players in the selection of active

cells and precision of spike timing. We describe a slow inhibition mechanism in DGCs mediated by GABA receptors (GABA-R) and mGluRs. It results in long lasting hyperpolarization (LLH) of the membrane potential following a PP stimulation. LLH is preferentially induced by short bursts in the lower gamma frequencies (20-50 Hz) in young and adult mice, but not in juvenile pups. We demonstrate that synaptic neurotransmitter release from PP terminals is sufficient to induce LLH through feedforward inhibition in ML. We further address the functional consequences of LLH in DGCs and show that it significantly alters their firing properties during membrane depolarization induced AP firing. To investigate how LLH would affect firing in response to synaptic activity, we used single or double PP input stimulation. Stimulation protocol is based on reports of correlated theta/gamma oscillations coupling in EC II and DG. Single input 5 Hz trains (NoLLH, 3s) were applied alone or in combination with nested 50 Hz bursts (LLH) from the same input or from another input. We used an AP frequency distribution analysis in order to compare between NoLLH and LLH. NoLLH trains (0.05 ± 0.002) in combination with LLH bursts from the same input resulted in a global AP frequency decrease (0.03 ± 0.003; $p = 0.0024$). Similarly LLH induced by a second input decreased significantly AP frequency distribution in response to 5 Hz NoLLH (0.09 ± 0.01 to 0.04 ± 0.006, $p < 0.0001$). LLH created a restrained neuronal discharge in favor of shorter firing time window (2.07 ± 1.17 s). These results suggest that short bursts in the gamma frequency can significantly impact the integration of signals arriving close in time. Thus LLH represents temporal reference for upcoming signals. Moreover, stimulation of a specific PP terminal induced LLH only in a subset of DGCs. Thus LLH might also contribute to selective activation of cells in the DG.

Disclosures: Y. Mircheva: None. **M.R. Peralta:** None. **K. Toth:** None.

Poster

464. Short-Term Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 464.11/E23

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NINDS K08 NS058674
NIH R01 NS070824
NIH T32 GM086287
FAER

Title: Inhibition of astroglial glutamine synthetase decreases leucine transport across the blood brain barrier

Authors: *S. E. GRUENBAUM[1], R. DHAHER[2], K. BEHAR[3], H. ZAVERI[4], M. ERFE[2], T. EID[2]

[1]Dept. of Anesthesiol., [2]Dept. of Lab. Med., [3]Magnetic Resonance Res. Ctr., [4]Dept. of Neurol., Yale Univ. Sch. of Med., New Haven, CT

Abstract: Introduction: Astroglial glutamine synthetase (GS), which metabolizes glutamate and ammonia to glutamine, is critical several brain processes. Perturbations in the expression and activity of GS are thought to play a causative role in the pathogenesis of several conditions of abnormal neurotransmission. Although the long-term consequences of GS inhibition on amino acid homeostasis in the brain are unknown, it is thought that amino acid influx in the brain is tightly coupled with glutamine efflux via the L-type amino acid transporter (LAT_1). The objective of this study was to determine the effects of chronic GS inhibition with methionine sulfoximine (MSO) on glutamine and leucine homeostasis in the brain. **Methods:** Twelve rats were surgically implanted with microdialysis guide cannulas in the bilateral dentate gyrus. Rats were randomly divided for surgical implantation of either a MSO (n=6) or phosphate buffer saline (PBS; n=6) pump in the right dentate gyrus. After 7 days, bilateral microdialysis probes were placed under brief isoflurane anesthesia, and microdialysis flow was established and dialysate samples were collected every 30 minutes. A 113 mM ^{15}N-Leucine (3.6 mL per hour) and 2 M 2-^{13}C-sodium acetate (0.0633 μL/g/min for t = 0-5 minutes, 0.0316 μL/g/min for t = 5-10 minutes, and 0.0253 μL/g/min for t > 10 minutes) solution was infused intravenously for 300 minutes. The EZ:Faast Free Amino Acid analysis kit and ultra-performance liquid chromatography/ tandem mass spectrometry was used for quantification of amino acids in the dialysate fluid. **Results:** At baseline (t = 0h), the concentrations of glutamine were significantly lower in MSO-treated rats ($p < 0.001$) in the ipsilateral (GS-inhibited) hippocampus. There were no differences in glutamine concentrations between MSO and PBS-treated rats in the contralateral hippocampus. In PBS-treated rats, there was a significant increase in ^{15}N-leucine between t = 0h and t = 5h in the contralateral ($p < 0.05$) and ipsilateral ($p < 0.05$) hippocampus. In MSO-treated rats, there was a significant increase in ^{15}N-leucine between t = 0h and t = 5h in the contralateral ($p < 0.05$) hippocampus, but not in the ipsilateral hippocampus (p = n.s.). **Conclusions:** This study demonstrated for the first time that basal glutamine concentrations are low in areas of the brain where GS is acutely inhibited, and that leucine uptake in these brain areas are markedly decreased. Perturbations in glutamine and leucine homeostasis have been implicated in several disease processes, and the glutamine-dependent leucine influx in the brain may be a novel and important therapeutic target to treat these conditions.

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Poster

464. Short-Term Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 464.12/E24

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: Collaborative Research Fund

Title: Identification of LTP-associated CCK signal transduction pathways in a primary hippocampal cell culture

Authors: *R. JESKY[1], D. K. Y. SHUM[2], J. HE[1]
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Abstract: Keywords: Cholecystokinin; Hippocampus; Signal transduction; MAPK; CREB
Within the CNS, cholecystokinin, one of the most ubiquitous neuropeptides in the brain, facilitates an array of fundamental functions. Studies have demonstrated that cholecystokinin (CCK) is involved in everything from pain modulation, anxiety, hunger, satiation, and the brain's reward systems to neuropsychiatric disorders, and learning and memory. Early studies investigating the mechanisms of cholecystokinin (CCK) revealed that CCK was mediated by two variant G protein-coupled receptors - CCK1R and CCK2R - and further uncovered that it signaled through various pathways, but the current understanding of the mechanisms under which CCK modulates such an extensive range of functions within the CNS are limited. Research in our lab (Prof. Jufang, He's) has shown that CCK is a cardinal component of neocortical plasticity and plays a significant role in memory consolidation. In addition, evidence suggests it is requisite for long-term potentiation (LTP). This implies that it is integral to synaptic plasticity, and thus modulates plastic changes in the brain from the synapse to neuronal circuitry. As a principle correlate of learning and memory, LTP has been thoroughly investigated with results evincing that various kinases (i.e., CaMKII/IV, DAG, PKC, cAMP, PKA, MAPK, and CREB) are involved. The mechanisms by which CCK facilitates LTP are not yet fully understood, but to elicit LTP CCK must activate a coordinated array of signal transduction via second messenger phosphorylation within known canonical cellular cascades. Preliminary results show that in hippocampal neurons CCK triggers phosphorylation of c-Raf and its substrates such as MEK2 along with the downstream phosphorylation of CREB, which suggests that CCK-8s activation of CCK receptors is mediated through the MAPK pathway. With the cardinal functions of MAPK in dendritic morphogenesis and their pertinence to LTP formation, initial results suggest that CCK may act in concert with requisite growth factors or solely initiate the MAPK cascade leading to LTP formation. Further electrophysiological studies will be required to additionally clarify the full capacity of CCK-induced signaling cascades.

Disclosures: R. Jesky: None. **D.K.Y. Shum:** None. **J. He:** None.

Poster

464. Short-Term Synaptic Plasticity

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Program #/Poster #: 464.13/E25

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NSF Grant 1457079

Title: Low chloride transporter expression in vasopressin neurons as a substrate for excitatory GABA signaling

Authors: *M. O. FISHER, JR[1], J. G. TASKER[2]
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Abstract: The excitability of a neuron is dependent upon the intracellular and extracellular ionic concentrations. Several proteins function as ion pumps/transporters that work to maintain the relative ionic concentrations necessary for neuronal signaling. The potassium-chloride co-transporter two (KCC2) is a symporter that works to actively pump K^+ and Cl^- out of the cell in order to maintain a low intracellular [Cl^-], while the sodium-potassium-chloride cotransporters one and two (NKCC1/NKCC2) are symporters that actively pump Na^+, K^+, and Cl^- into the cell, opposing the actions of KCC2 on Cl^- transport. In the adult, high KCC2 expression leads to low intracellular [Cl^-], which causes $GABA_A$ receptor Cl- channels to flux Cl^- into the neuron, causing a hyperpolarization of the neuron. Early in development however, low KCC2 expression reverses the Cl^- gradient and causes $GABA_A$ receptors to flux Cl^- out of the neuron, leading to depolarization and excitation of the developing neuron. The change in the polarity of GABA signaling during development is, in part, due to a shift in KCC2 expression from low to high with maturation of synaptic circuits. Previous studies have demonstrated an excitatory $GABA_A$ receptor-mediated response due to a GABA equilibrium potential (E_{GABA}) that is shifted positive, like that seen early in development, in adult vasopressin (VP)-secreting neurons of the rat hypothalamus. In the current study, we used immunohistochemistry to compare expression levels of the main C^{l-} transporters, KCC2, NKCC1, and NKCC2, between vasopressin- and oxytocin-secreting neurons. We found that, in adult male Wistar rats, expression of all three transporters is uniformly lower in VP neurons than in adjacent oxytocin (OT)-secreting neurons within the hypothalamus. To further build on these findings, we are utilizing a Cre-dependent virus system in order to express a light-activatable chloride-fluxing channel conditionally in vasopressin-secreting neurons.

Disclosures: M.O. Fisher: None. **J.G. Tasker:** None.

Poster

464. Short-Term Synaptic Plasticity

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Program #/Poster #: 464.14/E26

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: The effect of vasopressin receptor activation on mouse locus coeruleus neuronal activity

Authors: *E. CAMPOS-LIRA[1], L. KELLY[2], V. S. HERNANDEZ[1], L. ZHANG[1], J. SWINNY[2]
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Abstract: The locus coeruleus (LC) nucleus is the main source of noradrenaline (NA) throughout and modulate a range of functions such as arousal, cognition and the stress response. Neurochemically diverse inputs, from a myriad of brain regions regulate the level of LC neuronal activity, in a behaviour dependent manner. One such afferent input contains the neuro-hormone arginine-vasopressin (AVP). The overall aim of the project was to characterise the effects specific AVP receptor subtypes on the spontaneous firing rates (FRs) of the mouse LC, using AVP receptor agonists and antagonist together with a patch clamp electrophysiology in acute brain slices of mouse.
A total of 50 cell were recorded from 15 animals. Application of the V1b and V2 agonist desmopressin (200 µM) had contrasting effects on LC spontaneous FR (n = 20) with 45% of cells showing an increased FR (1.7 to 2.8 Hz) and 55 % showing a significant decrease (1.4 to 0.8 Hz), also presenting significant changes in Tau values of the AHP in both scenarios. The application of a V1a antagonist ((d(CH2)51, Tyr(Me)2, Arg8)-Vasopressin, 30 nM) (n=16) also had contrasting effects on LC FR with 62 % of cells exhibiting an increase (1.6 to 2.1 Hz) whilst 38 % showed a decrease (2 to 1.4 Hz). For the V1b receptor antagonist (TASP 039325, 20 nM) (n = 14), 57 % responded with an increased FR (2.2 to 3.2 Hz) whilst the remaining 43% showed a decrease in activity (1.7 to 1.4 Hz). These diverse responses to LC-AVP receptor modulation suggest that different population of LC neurons express different AVP receptor profiles.

Disclosures: E. Campos-Lira: None. **L. Kelly:** None. **V.S. Hernandez:** None. **L. Zhang:** None. **J. Swinny:** None.

Poster

464. Short-Term Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 464.15/E27

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NIH Grant DA038208
VA Grant BX002525

Title: AMP-activated protein kinase activation reduces rundown of dopamine-induced current in rat substantia nigra compacta neurons

Authors: *S. W. JOHNSON[1], A. C. MUNHALL[1], K.-Z. SHEN[2], W. YANG[2]
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Abstract: Recent work has shown that AMP kinase influences the cellular expression of many ion channels and receptors. We examined effects of AMPK activators and inhibitors on whole-cell current evoked by D2 dopamine receptors in SNC neurons in slices of rat brain. During patch-clamp recordings, slices were superfused for 25 min with a high concentration of dopamine (100 μM) that was chosen to produce receptor desensitization. Sulpiride (1 μM) was added to the superfusate during the last 5 min of dopamine superfusion in order to measure the magnitude of residual dopamine D2 receptor-mediated current. Under control conditions, dopamine-induced outward current reached an average of 57 pA two min after beginning superfusion. This outward current then decayed in amplitude, typically diminishing to baseline levels within 10 min, and sulpiride revealed no residual D2-mediated current. When recording with pipettes that contained the AMPK activator A769662, peak dopamine-induced current was not significantly different from the control value. However, the rate of rundown of dopamine-induced current was significantly slowed by A769662 ($P<0.0005$, linear mixed model analysis). Moreover, the addition of sulpiride after 20 min of dopamine superfusion caused a significant inward current (16 pA). Using pipettes containing the AMPK activator ZLN024, rundown of dopamine-induced current was significantly slowed compared to rundown of the dopamine control current. Moreover, the addition of sulpiride caused a significant inward current in the presence of ZLN024 (19 pA). The AMPK inhibitors compound C and STO609 prevented the ability of A769662 to reduce rundown of dopamine-induced current. Finally, we recorded current produced by quinpirole (30 μM), which is a D2 agonist without D1 activity and not a substrate for the dopamine transporter. Quinpirole produced an average peak outward current of 59 pA two min after starting superfusion. As with dopamine, quinpirole-induced current decayed to zero over the 20 min superfusion, and sulpiride revealed no residual D2-mediated current. But unlike dopamine, A769662 produced no change in rundown of quinpirole-induced current. These

results suggest that D2 receptor stimulation alone is not sufficient to observe prolongation of current by AMPK.

Disclosures: S.W. Johnson: None. **A.C. Munhall:** None. **K. Shen:** None. **W. Yang:** None.

Poster

464. Short-Term Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 464.16/E28

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Title: UHPLC ALEXYS neurotransmitter analyzer for sensitive detection of gaba & glutamate, histamine, LNAAs and other amino acids

Authors: *H.-J. BROUWER[1], L. M. VAN HEERWAARDEN[1], M. EYSBERG[2], N. J. REINHOUD[1]
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Abstract: Ultra-High Performance Liquid Chromatography (UHPLC) is a rapidly growing separation technique based on the application of LC columns with sub-2 μm particles operating at higher linear velocities and high back pressures. UHPLC offers advantages in chromatographic resolution, analysis speed, and sensitivity over conventional HPLC systems. The combination of Electrochemical Detection (ECD) with UHPLC can be a powerful solution to increase the sample throughput and sensitivity of neurotransmitter analysis in microdialysates, brain homogenates and other sample matrices. A new versatile UHPLC ALEXYS Neurotransmitter Analyzer based on the DECADE Elite detector with SenCell has been developed. This analyzer is based on a flexible and scalable approach to offer an analysis solution for multiple different neurotransmitter applications (Biogenic amines and acidic metabolites, amino acid neurotransmitters and Acetylcholine).
A fast and sensitive method is presented for the analysis of the amino acid neurotransmitters GABA and Glutamate in microdialysates based on the new ALEXYS neurotransmitter analyzer (see figure 1). Separation and detection is achieved using a single sub-2 μm particle column and automated pre-column derivatization with o-phthaldialdehyde (OPA), respectively. A step-gradient is used for clean-up of late eluting amino acid neurotransmitters present in microdialysate samples at the end of the run. With this approach excellent detection sensitivity can be achieved with minimal sample consumption. Other Amino Acids e.g. Histamine, and Large Neutral Amino Acids (LNAAs: Tyr, Val, Met, Orn, Leu, Ile, Phe, Lys, Trp) can be analyzed too using this method.
Method features:
• Automated odorless in-needle OPA-sulphite derivatization.
• Small sample use per analysis: 5 uL only (injection volume 1.5 μL)

• Fast and efficient separation using sub-2 μm particle column
• Post separation step-gradient to eliminate late eluting components
With this approach, a high sample throughput and low detection limit of around 10 nmol/L (15 fmol, 6 pg on column) for GABA is achievable.

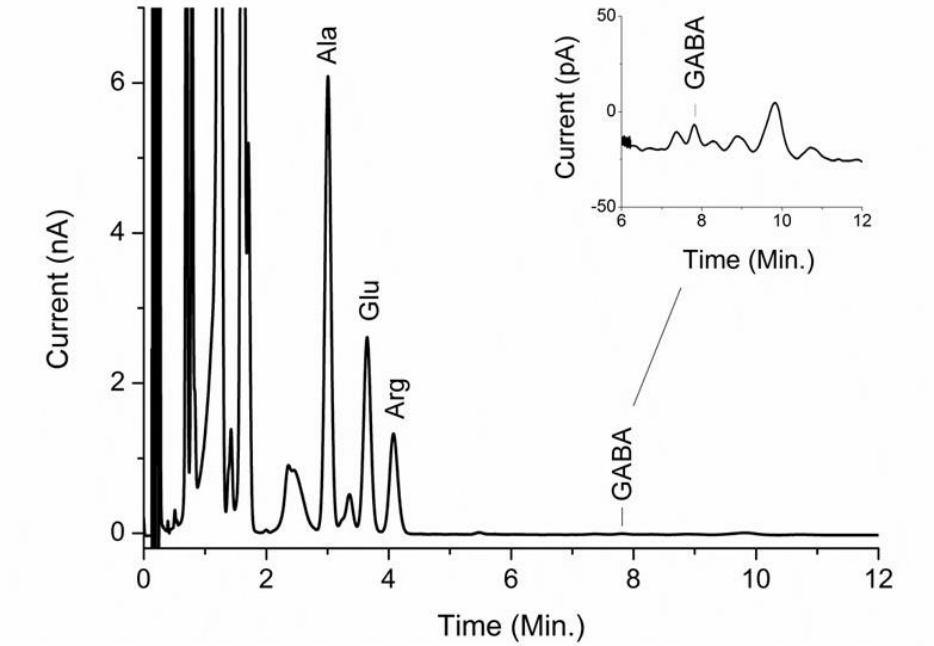

Figure 1. Chromatogram of Rat Prefrontal Cortex (insert: zoom in on GABA peak)

Disclosures: H. Brouwer: None. **L.M. van Heerwaarden:** None. **M. Eysberg:** None. **N.J. Reinhoud:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.01/E29

Topic: B.07. Synaptic Plasticity

Support: ZIA HD000713

Title: Chromatin structure of neurons and glia

Authors: *R. D. FIELDS, P. R. LEE, S. C. CLARK, R. V. CHEREJI, D. J. CLARK
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Abstract: In eukaryotes, nucleosomes are the basic DNA packing units whose positions affect all DNA-related processes within the cell. Modification of chromatin through epigenomic events

is fundamental to the function of the genome. Most environmental signals in the nervous system converge onto chromatin to control gene activation and repression. Therefore, chromatin structure and control of gene expression are tightly linked. Here we determine the basic chromatin structure, characterized by nucleosomal spacing in neurons and glia and correlate the nucleosomal maps of each cell type with gene expression data. We have obtained genome-wide nucleosome maps of cultured dorsal root ganglion (DRG) neurons, astrocytes and oligodendrocyte progenitor cells (OPCs) using micrococcal nuclease (MNase) digestion of chromatin, followed by paired-end sequencing of nucleosome core particles. Correlation of gene expression and nucleosome mapping data was carried out by sorting genes according to expression level and analyzed for nucleosome phasing relative to transcription start sites. We have determined that DRG neurons have a significantly shorter (165 base pairs) nucleosome spacing ($N=9$, $p<0.001$) across the entire genome, compared to astrocytes (182 base pairs) and OPCs (183 base pairs). However, when nucleosome distributions on transcriptionally active genes were analyzed, we observed that DRG neurons, astrocytes and OPCs have very similar nucleosomal spacing at the 5' ends of expressed genes (184, 187 and 184 base pairs, respectively). Our findings demonstrate a significant difference in genome-wide chromatin structure between neurons and glia with implications for the regulation of global gene expression and neuron-glia communication.

Disclosures: R.D. Fields: None. **P.R. Lee:** None. **S.C. Clark:** None. **R.V. Chereji:** None. **D.J. Clark:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.02/E30

Topic: B.07. Synaptic Plasticity

Support: NSF IOS 1256114
SIUE Undergraduate Research and Creative Activities

Title: The chromatin remodeling protein, Kismet, regulates presynaptic vesicle endocytosis at glutamatergic synapses

Authors: *F. L. LIEBL, K. LANE, K. BERNARD
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Abstract: Glutamatergic synaptic transmission is important for a number of behaviors including learning and memory, movement, and visual perception. This neurotransmission relies on the proper localization of cell adhesion molecules and recycling of presynaptic vesicles. We have previously shown that the chromodomain helicase DNA (CHD) binding protein, Kismet (Kis),

positively regulates the synaptic localization of glutamate receptors, neurotransmission, and the apposition between glutamate receptors and presynaptic active zones at the *Drosophila* neuromuscular junction. As a transcriptional regulator, Kis likely broadly affects glutamatergic synaptic development. Indeed, we found endocytosis of presynaptic vesicles is deficient at *kis* mutant synapses. We hypothesize that Kis regulates both activity-dependent bulk endocytosis and clathrin-mediated endocytosis as there is a significant reduction in presynaptic transcript levels of *endophilin B* and *AP180* in *kis* mutants. Further, kis mutants cannot sustain evoked amplitude responses to high frequency stimulation. Surprisingly, our knock down and rescue experiments suggest that Kis is required in postsynaptic muscles for proper presynaptic endocytosis. We are currently investigating whether Kis affects synaptic function by suppressing Polycomb Group repression.

Disclosures: F.L. Liebl: None. **K. Lane:** None. **K. Bernard:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.03/E31

Topic: B.07. Synaptic Plasticity

Support: NIA T32 AG052374

Title: CRC regulates presynaptic neurotransmitter release at the *Drosophila* neuromuscular junction

Authors: *L. GRAY, G. KAUWE, P. HAGHIGHI
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Abstract: The highly conserved integrated cellular stress response depends on a cellular program that regulates translation through the phosphorylation of eif2a by stress-sensing kinases. While general translation is dampened through this pathway, a small subset of stress-responsive genes is upregulated. Among these genes, perhaps the most prominent is activating transcription factor 4 (ATF4), a critical regulator of the cellular stress response that facilitates an array of functions, from cellular repair to apoptosis. In addition to the stress response, ATF4 is also implicated in long term memory formation via regulation of CREB; however, details of the underlying mechanisms remain unclear. We have begun an investigation of the role of ATF4 in the regulation of neurotransmitter release, using a combination of genetics and electrophysiology at the Drosophila neuromuscular junction (NMJ). Our preliminary findings suggest that CRC, the Drosophila homologue of ATF4, plays a critical role in the regulation of neurotransmitter release at the NMJ. Furthermore, we are conducting bioinformatics analysis of candidate transcriptional

targets of CRC in motorneurons to understand the cellular programs under the control of ATF4 at the presynaptic level. Results of our experiments will be presented.

Disclosures: L. Gray: None. **G. Kauwe:** None. **P. Haghighi:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.04/E32

Topic: B.07. Synaptic Plasticity

Support: PRIN 2015

Title: Identification and characterization of the promoter and of regulatory elements on the cerebral sodium/calcium exchanger isoform 2, NCX2, gene in rat pheochromocytoma cells

Authors: A. SERANI[1], P. MOLINARO[2], N. GUIDA[4], S. NATALE[2], L. FORMISANO[2], G. DI RENZO[2], *L. ANNUNZIATO[3]
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Abstract: The isoform 2 of sodium-calcium exchanger (NCX2) is selectively expressed in CNS, where it participates in the regulation of Na^+ and Ca^{2+} homoeostasis. Under physiological conditions, NCX2 increase neuronal Ca^{2+} clearance after spike potentials, and its knock-out increases spatial-learning and memory performance. In addition, under some pathophysiological conditions, such as stroke, NCX2 exerts a neuroprotective effect. Although the relevance of the regulatory mechanisms involved in the expression of this antiporter under physiological and pathophysiological conditions is easily conceivable, no studies have been reported on the characterization of its promoter and on the identification of the transcription factors (TFs) involved in its regulation.We identified, in PC12 cells, a region of 1200 bp named S3 and located upstream the slc8a2 gene, encoding for NCX2, containing several conserved TF binding sites. Interestingly, many of these sequences are target of regulatory proteins that are expressed in CNS and participate to synaptic plasticity. The identified putative promoter S3 induced the transcription of a luciferase reporter gene in two different neuronal cell lines, PC12 and SHSY, expressing the endogenous NCX2 gene. Interestingly, S3 failed to induce luciferase activity in BHK and U87 cell lines that do not express NCX2 under control conditions. Moreover, among the putative TFs involved in NCX2 transcriptional regulation, the overexpression of Sp1, Sp4 or CREB exerted a stimulatory effect, whereas SREBP1 exerted an inhibitory action, on both endogenous NCX2 transcription and luciferase activity of S3. These results reinforced the hypothesis that the identified S3 region contains the promoter of NCX2 gene and share the same mechanisms of transcriptional regulation. In addition, by using site-directed mutagenesis and

ChIP assay, we identified the regulatory binding sites of Sp1, Sp4, CREB and SREBP1 on the S3 region. Notably, these TFs and NCX2 expression, regulate synaptic plasticity and neurotransmission, thus, it is conceivable to hypothesize that the antiporter might represent one of their downstream effectors.In addition, we found that in U87 cells, not expressing NCX2 under control conditions: (a) Sp1, Sp4, or CREB failed to increase the expression of the endogenous NCX2 gene and the luciferase activity of the identified S3 promoter, and (b) 5 nM of 5'-azacytidine for 72h, by impairing DNA methylation, restored NCX2 expression and its transcriptional regulation by the above-mentioned TFs. These results suggested the presence of an additional regulation of NCX2 expression by DNA methylation as it occurs in glioblastoma cells.

Disclosures: A. Serani: None. **P. Molinaro:** None. **N. Guida:** None. **S. Natale:** None. **L. Formisano:** None. **G. Di Renzo:** None. **L. Annunziato:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.05/E33

Topic: B.07. Synaptic Plasticity

Support: AG012694-16
AG000538
AG034667

Title: A SUV39H1selective inhibitor enhances synaptic plasticity by prolonging ERK activation

Authors: *L.-Q. TONG[1], A. IONESCU[1], C. BUTLER[1], S. SNIGDHA[1], K. TSEUNG[2], L. OVERMAN[1], C. W. COTMAN[1]
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Abstract: Epigenetic regulation of genes and proteins is fundamental to the aging process and the associated decline in learning and memory. We reported previously that pharmacological inhibition of SUV39H1 using ETP69, a novel and selective inhibitor of SUV39h1, decreased levels of H3K9me3 (a repressive mark) in the hippocampus of aged mice, promoted spine formation, and improved memory performance (Snigdha et al., 2016, J Neurosci, 36(12): 3611-3622). However, the mechanism underlying the beneficial effects of ETP69 on neuronal function remains an unexplored area of research. In the present study, we evaluated the effects of ETP69 on signal transduction pathway associated with neuronal activity-dependent synaptic plasticity. ETP69 treatment induced a prolonged (24 h) increase in the phosphorylation of ERK1/2, which plays an important role in memory consolidation, in primary cultures of hippocampal neurons. The effects of ETP69 racemic enantiomers on ERK1/2 phosphorylation were also examined.

Both L-1721 and L-1722 increased ERK1/2 phosphorylation. Further, the ETP69-induced PSD-95 expression was blocked by PD98059, an inhibitor of ERK. These data suggest that SUV39H1 inhibition-mediated downregulation of H3K9me3 acts through enhancement of synaptic function by ERK activation.

Disclosures: L. Tong: None. **A. Ionescu:** None. **C. Butler:** None. **S. Snigdha:** None. **K. Tseung:** None. **L. Overman:** None. **C.W. Cotman:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.06/E34

Topic: B.07. Synaptic Plasticity

Support: CDMRP Grant W81XWH-08-2-0136 to MJF

Title: Synaptic conditioning frequency, temporal pattern and plasticity outcome effect gene expression in visual cortex

Authors: *Q. S. FISCHER[1], M. CHAUDHRY[2], D. KALIKULOV[1], M. A. FOX[1], M. J. FRIEDLANDER[1]
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Abstract: Deep brain stimulation studies have shown a variety of stimulation parameters, including frequency and patterning of conditioning stimulation, influence the efficacy of treatment. However, little is known about the changes in gene expression produced by varying these parameters. We examined whether frequency, temporal pattern, or plasticity outcome of synaptic conditioning influence gene expression. Acute visual cortical slices were prepared from 10-13 week-old male LE rats. For recording, slices were perfused with artificial cerebrospinal fluid at 32-34^{o}C. A stimulating rake electrode was placed in layer 4, and a field potential recording electrode was placed in layer 2/3. All recordings had: 15 mins pre-conditioning, 15 mins conditioning, and 15 mins post-conditioning. Pre- and post-conditioning had 0.1Hz stimulation. Conditioning was either: 1) 10 Hz discontinuous stimulation (9 epochs of 100 stimuli each, divided by 8 equal rest periods) with regular (equal) interstimulus intervals (ISIs), 2) 10 Hz discontinuous stimulation with irregular ISIs (described by a Poisson distribution), 3) 100 Hz discontinuous regular stimulation, or 4) no stimulation. Groups 1-3 were subdivided based on plasticity outcome (i.e. those showing long term potentiation - LTP, verses long term depression - LTD). Three hrs after the recording experiments, layer 2/3 above the stimulation electrode was isolated. RNA was extracted using a Bio-Rad Aurum Total RNA kit. At least 5 samples from each treatment group were processed with RNAseq. Sequences were aligned via

Tophat2 and counted via HTSeq. Relative expression of mRNA was tested for significance using the Benjamini-Hochberg corrected Wald Test in DESeq2. We identified 18,377 genes, 298 of which showed a significant change in expression across treatments. Subsequently, we selected the 12 genes with a greater than 1.5 fold change in expression, and known relevance to synaptic structure/function (e.g. cell adhesion, receptor expression/clustering, ion channel coding, or second messenger signaling). In slices exhibiting LTD verses those with no stimulation, Ak8, Htr2c and Rasa4 were downregulated, while Kcnj10 was upregulated. In contrast, for slices showing LTP verses those with no stimulation, Nyap2 and Slc9a9 were upregulated. In slices exhibiting LTP verses those showing LTD, Ak8, Gpr84, Hspa8, Nid2 and Nptx1 were upregulated, while Htr2c and Snx1 were downregulated. Finally, in slices with regular conditioning verses those with Poisson conditioning, Nid2 was upregulated, while Gpr84 and Pcp4 were downregulated. These results suggest stimulation pattern and plasticity outcome influence gene expression.

Disclosures: Q.S. Fischer: None. **M. Chaudhry:** None. **D. Kalikulov:** None. **M.A. Fox:** None. **M.J. Friedlander:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.07/E35

Topic: B.07. Synaptic Plasticity

Support: San Paolo

Title: A role for REST in adult ocular dominance plasticity

Authors: *C. G. ELEFTHERIOU[1], E. CARMINATI[1], F. CESCA[1], L. MARAGLIANO[1], F. BENFENATI[1,2], J. MAYA-VETENCOURT[1]
[1]Italian Inst. of Technol. (IIT), Genova, Italy; [2]Dept. of Exptl. Med., Univ. of Genova, Genova, Italy

Abstract: The repressor element 1 (RE-1) silencing transcription factor (REST) is considered to be a master regulator of neural development and has recently been demonstrated to play crucial roles in the adult brain under both physiological and pathological conditions. So far, however, the role of REST in adult ocular dominance (OD) plasticity remains to be explored. We addressed this issue by using the monocular deprivation (MD) paradigm. This widely used model of plasticity demonstrates a shift of OD following brief MD (≤3 days) only during early life but not in adulthood. We infected the binocular primary visual cortex of adult mice with a constitutive construct either meant to block the binding of REST to the RE-1 DNA sequence (active) or not to block this binding (sham). Following 6 weeks of infection, the

electrophysiological assessment of OD plasticity was performed after 3 days of MD of the contralateral eye, using visually evoked potentials (VEPs) recorded with 16 micro-wires chronically implanted in the infected hemisphere. Contralateral over Ipsilateral (C/I) VEP ratios were calculated on days 1 and 3 using full-field white flashes in freely moving animals. Adult mice infected with the active construct displayed a significant shift of ocular dominance after 3 days of MD whilst uninfected mice and mice infected with the sham construct did not. Moreover, we observed a significant increase in the expression of two plasticity genes (BDNF and NPAS4) in the visual cortex of mice infected with the active construct but not in control animals. These two factors have previously been implicated in the physiological processes underlying experience-dependent plasticity in adult life. Together, our data suggest that a decrease of REST activity enhances juvenile-like plasticity in the adult visual cortex.

Disclosures: C.G. Eleftheriou: None. **E. Carminati:** None. **F. Cesca:** None. **L. Maragliano:** None. **F. Benfenati:** None. **J. Maya-Vetencourt:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

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Program #/Poster #: 465.08/E36

Topic: B.07. Synaptic Plasticity

Support: Pew Charitable Trust Grant 00028631
Searle Scholars Program Grant 14-SSP-184
NIMH Grant F32MH110141
NINDS Grant 1DP2NS097029-01

Title: Communication of pathway-specific circuit activity to the genome by the immediate early gene Npas4

Authors: *S. BRIGIDI[1], M. HAYES[2], P.-A. LIN[3], A. HARTZELL[3], S. HEINZ[2], B. L. BLOODGOOD[1]
[1]Div. of Biol. Sciences, Neurobio. Section, Univ. of California San Diego, LA Jolla, CA; [2]Med., [3]Neurosci. Grad. Program, Univ. of California San Diego, La Jolla, CA

Abstract: Mechanisms that govern plasticity are executed over many time scales and the most enduring forms of plasticity require regulation of the genome. Inducible transcription factors (ITFs) are a subset of immediate-early genes that support learning by linking transient molecular signals with long-lasting changes in cellular function through activity-dependent changes in gene expression. Npas4, a bHLH-PAS domain ITF, is undetectable in quiescent neurons but is rapidly induced in response to membrane depolarization *in vitro* and learning-related sensory experiences *in vivo*. Experience-dependent Npas4 expression dramatically reorganizes inhibitory

synapses along the somato-dendritic axis of CA1 pyramidal neurons (PNs), increasing somatic and decreasing dendritic inhibition. This suggests that Npas4 regulates neuronal functions immediately linked to excitation by recalibrating inhibition in discrete domains of the PN. However, the nature of excitatory signals that lead to Npas4 induction, and whether the genome is capable of differentiating between excitatory signals that originate from distinct regions of the PN remains unknown.
Here we identify two independent pathways that lead to Npas4 expression in PNs within the CA1 microcircuit that have distinct kinetics and functional consequences. Action potentials (APs) lead to the accumulation of Npas4 in the nucleus through a signaling pathway that requires Ca^{2+} influx through L-type voltage-gated Ca^{2+} channels, transcription, and translation. However, sub-threshold transmission at Schaeffer Collateral synapses triggers rapid local translation of a pool of Npas4 mRNA localized to PN apical dendrites, requires NMDA receptor signaling, and results in the protein trafficking to the nucleus to regulate gene expression. Using CRISPR to manipulate Npas4, we identified regions of the 3' and 5' UTR of Npas4 mRNA that control dendritic trafficking and activity-dependent translation, respectively. Surprisingly, Npas4 forms distinct heterodimers with other bHLH-PAS transcription factors in response to APs or synapse activation. As activity recruits each heterodimer to preferred sites along chromatin genome-wide, we predict stimulus-specific heterodimers facilitate communication of pathway-specific information to the nucleus in order to regulate unique aspects of Npas4's cellular phenotype. Together, our findings suggest that Npas4 communicates the activity history of the cell to its genome by executing an excitation-to-inhibition transfer function that distinguishes APs from input-specific synaptic activity.

Disclosures: S. Brigidi: None. **M. Hayes:** None. **P. Lin:** None. **A. Hartzell:** None. **S. Heinz:** None. **B.L. Bloodgood:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

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Program #/Poster #: 465.09/E37

Topic: B.07. Synaptic Plasticity

Support: Samsung Science and Technology Foundation under Project Number SSTF-BA1602-11

Title: Real-time imaging of endogenous mRNA in the live mouse brain

Authors: *J. SHIM, B. LEE, H. MOON, H. PARK
Dept. of Physics and Astronomy, Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: A memory is represented by the simultaneous activation of an ensemble of neurons referred to as 'engram.' The storage of long-term memory is mediated by the enduring changes in the engram cells and their connections, which requires activity-dependent transcription and local protein synthesis. However, the spatio-temporal regulation of gene expression during memory encoding, storage, and retrieval processes in the live brain are poorly understood. To investigate the dynamics of transcription in the hippocampus and the cortex of a live animal, we implemented real-time imaging of mRNA in the mouse brain using two-photon microscopy. We used our transgenic mice in which the endogenous β-actin or Arc mRNAs are fluorescently labeled by the MS2 or PP7 system. We performed glass-covered cranial window surgery to make optical access, which enabled us to find transcription sites in the hippocampus and the visual cortex of a live mouse. For the next step, we are conducting contextual fear conditioning experiments to investigate the transcriptional dynamics of Arc mRNA in the hippocampus during fear memory formation and retrieval. This study will contribute to understanding the dynamics of gene expression in the engram cells and their roles in learning and memory *in vivo*.

Disclosures: J. Shim: None. **B. Lee:** None. **H. Moon:** None. **H. Park:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

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Program #/Poster #: 465.10/E38

Topic: B.07. Synaptic Plasticity

Support: 5R01MH101491-05
3R01AG051807-02S1
John Templeton Foundation
George E. Hewitt Foundation

Title: The effect of CPEB3 ribozyme self-scission on mRNA maturation in the mouse hippocampus

Authors: *C. CHEN[1], T. J. HEMSTEDT[2], C.-K. LAU[1], M. A. WOOD[2], A. LUPTAK[3]
[2]Neurobio. and Behavior, [1]Univ. of California Irvine, Irvine, CA; [3]Pharmaceut. Sci., Univ. of California, Irvine, Irvine, CA

Abstract: Synaptic strengthening is a prominent feature of memory formation and reconsolidation. Oligomerization of a translation regulator, cytoplasmic polyadenylation element-binding protein 3 (CPEB3), has been shown to occur during stable long-term memory formation in the hippocampus. The aggregation of this functional prion-like CPEB3 regulates polyadenylation-induced mRNA translation and synaptic protein synthesis, which is crucial for persistence of memory. Given that a single nucleotide polymorphism (SNP) in the human

CPEB3 ribozyme has been suggested to increase ribozyme self-scission rate and to impact human episodic memory, the ribozyme self-scission likely mediates pre-mRNA processing and consequently translational control. Intronic ribozymes have previously been shown to modulate the levels of spliced mRNAs in *cis* and the case of the CPEB3 ribozyme provides a unique opportunity for control of the CPEB3 mRNA production through modulation of the ribozyme activity. To study the mechanism by which the self-cleaving CPEB3 ribozyme affects the mRNA's processing, we inhibited the CPEB3 ribozyme *in vivo* using antisense oligonucleotides (ASOs). ASOs against CPEB3 ribozyme were injected bilaterally into the CA1 region of the dorsal hippocampus of C57/BL6J mice. Results suggested that ASOs inhibited CPEB3 ribozyme activity, which led to an increase in CPEB3 mRNA expression. Together, this work provides new insights into the role of CPEB3 ribozyme activity and downstream gene expression regulation in memory formation.

Disclosures: C. Chen: None. **T.J. Hemstedt:** None. **C. Lau:** None. **M.A. Wood:** None. **A. Luptak:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.11/E39

Topic: B.07. Synaptic Plasticity

Support: NIH grant NS083085
Samsung Science and Technology Foundation under Project Number SSTF-BA1602-11

Title: Real-time imaging of transcription and transport of labeled-endogenous Arc mRNA in live neurons

Authors: *H. MOON[1], S. DAS[2], R. H. SINGER[2,3], H. PARK[1]
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Abstract: Orchestration of synaptic plasticity encodes memories. An immediate early gene Arc is known to be deeply involved in the modulation of synaptic plasticity. Arc mRNAs are transcribed in response to neuronal activity and transported to the desired destinations including distal parts of dendrites for local translation. We have developed Arc-PBS KI mouse for single mRNA imaging in live cells by knocking in 24 tandem arrays of PP7 binding site (PBS) in the 3′ untranslated region (3′ UTR) of the Arc gene. Using the Arc-PBS KI mouse, we investigated the dynamics of transcription and the transport of Arc mRNAs in live primary neuron cultures. First, we simultaneously imaged somatic Ca^{2+} activity and Arc mRNA transcription after stimulation

by bicuculline. Whereas synchronized bursts of Ca^{2+} activity was induced in all neurons, Arc transcription was induced only in a subpopulation of neurons during 30 min of observation after stimulation. To determine the factor governing this selection of Arc transcribing neurons, we performed immunostaining of Ser-133 residue phosphorylated CREB and single molecule FISH of Arc mRNA together. We found that neurons with higher level of CREB phosphorylation (Ser-133) had higher probability of Arc transcription. Next, we investigated transport of Arc mRNAs along the dendrites after stimulation. Most of the Arc mRNAs were in the rest phase (~77%) during one-minute observation time, and even the directed motions of Arc mRNAs were frequently interrupted by rests, similar to the previously reported behavior of β-actin mRNAs. The active movements of Arc mRNAs were bidirectional with almost equivalent occurrence of anterograde and retrograde steps and with a speed of ~1.5 μm/s in both directions. We also assessed the effect of neuronal activity on Arc mRNA transport dynamics by inhibiting global neuronal activities with pharmacological reagents. However, no significant differences were observed on Arc mRNA movement with global silencing of neuronal activity. In summary, this study presents new perspectives about the dynamics of transcription and transport of endogenous Arc mRNA, which plays important roles in synaptic plasticity at the molecular level.

Disclosures: H. Moon: None. **S. Das:** None. **R.H. Singer:** None. **H. Park:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.12/E40

Topic: B.07. Synaptic Plasticity

Support: Samsung Science and Technology Foundation under Project Number SSTF-BA1602-11

Title: Upf1-dependent decay of Arc transcripts studied by live-cell imaging

Authors: *M. R. VIEIRA[1], Y. PARK[2], Y. KIM[2], H. PARK[1]
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Abstract: The Arc gene is crucial in regulation and consolidation of long-term memory and its expression is tightly related to synaptic plasticity. The impact of Arc expression in memory may depend on its molecular mechanisms of mRNA metabolism that are now beginning to be elucidated. Nonsense-mediated mRNA decay (NMD) is a surveillance mechanism by which mRNAs with premature termination codons are degraded. Arc mRNA is thought to be a natural target of NMD process due to the two conserved introns in the 3' untranslated region (3'UTR). We aim to characterize the Arc gene NMD process in fibroblasts as well as in neurons to

understand the impact of Arc mRNA decay in synaptic plasticity. To visualize the endogenous Arc mRNA in live cells, we utilize the Arc-PBS knock-in mouse model in which 24 repeats of PP7 binding sites (PBS) are inserted between the stop codon and the first intron in the 3'UTR of the Arc gene. Mouse embryonic fibroblasts (MEFs) were isolated from the Arc-PBS mouse and immortalized by SV40 T antigen. In the Arc-PBS MEF cell line, we expressed PP7 coat protein (PCP) fused with green fluorescent protein (PCP-GFP) using lentiviral transfection. Live-cell imaging revealed transcriptional burst of Arc gene in MEFs upon serum induction. The amount of Arc mRNA increased to 30-fold at 30 minutes after induction and decreased back to only 10-fold at 1 hour compared to the Arc mRNA level in the steady state. Then we knocked down Upf1, which is a key NMD factor, using short-hairpin RNAs (shRNA) targeting the coding sequence (CDS) and 3'UTR of Upf1. Knocking down of Upf1 in MEFs resulted in the accumulation of Arc mRNA to a 50-fold increase at 1 hour after serum induction. Our results suggest that Upf1 has a role in regulation and degradation of Arc transcripts. Our future studies involve understanding Arc NMD process and its role in synaptic plasticity in neurons.

Disclosures: M.R. Vieira: None. **Y. Park:** None. **Y. Kim:** None. **H. Park:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.13/E41

Topic: B.07. Synaptic Plasticity

Support: NMRC grant OFIRG/0019/2016

Title: Arc is a master regulator of gene transcription: Relevance for Alzheimer's disease

Authors: *A. VANDONGEN, H. VANDONGEN, H.-W. LEUNG, N. OEY, Y. JIANG, J. YIN, G. FOO
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Abstract: Alzheimer’s Disease (AD) is a devastating neurodegenerative disorder characterized by the progressive loss of both synaptic function and long-term memory formation. There is currently no therapy that prevents, stabilizes or reverses the progression of this disease, which is projected take on epidemic proportions as the world population ages. Arc is a master regulator of synaptic plasticity and is required for memory (re)consolidation. One of Arc’s functions is homeostatic regulation of synaptic strength, a process that is dysregulated in AD. Several previous studies have revealed an association between Arc and AD. A landmark study published in 2011 showed that Arc protein is required for the formation of Amyloid-beta (Aβ) plaques, the pathological hallmark of AD, which appears long before patients’ symptoms begin to show. Moreover, Arc protein levels are aberrantly regulated in the hippocampus of AD patients, and are

locally upregulated around amyloid plaques, whereas a polymorphism in the Arc gene confers a decreased likelihood of developing AD. Most recently, it has been shown that spatial memory impairment is associated with dysfunctional Arc expression in the hippocampus of an AD mouse model. The precise role that Arc plays in AD pathogenesis is still, however, unclear. Recently published data from our laboratory indicate that Arc associates with the histone-acetyltransferase Tip60 and epigenetically regulates H4K12Ac, a memory-associated histone mark which declines with age, suggesting a role for Arc in mediating age-related memory deterioration. We will present deep sequencing data of Arc knockdown experiments that establish a novel function for Arc in the nucleus, where it epigenetically regulates the transcription of many activity-dependent genes involved in a wide range of neuronal functions. The genes affected by Arc knockdown include several AD susceptibility genes, suggesting that Arc may contribute to the pathogenesis of AD. This hypothesis is being tested using a triple-transgenic AD mouse model, as well as cerebral organoids derived from Induced Pluripotent Stem Cells (IPSCs) from familial AD patients and controls.

Disclosures: A. VanDongen: None. **H. VanDongen:** None. **H. Leung:** None. **N. Oey:** None. **Y. Jiang:** None. **J. Yin:** None. **G. Foo:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.14/E42

Topic: B.07. Synaptic Plasticity

Support: MoST Grant 102-2628-B-001-007-MY3
MoST Grant 105-2311-B-001-078-MY3

Title: CPEB3 knockout mice are susceptible to develop PTSD-like behavior

Authors: *Y.-S. HUANG, H.-W. CHAO, W.-H. LU, P.-Y. LIN, M.-F. WU
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Abstract: Cytoplasmic polyadenylation element binding protein 3 (CPEB3) regulates target RNA translation in neurons. Our previous study found that CPEB3-knockout (KO) mice exhibited enhanced consolidation of spatial memory in the Morris water maze, but their ability to rapidly acquire new spatial information during the reversal learning when the platform was relocated to a new position was obviously impaired (Chao et al 2013, *J Neurosci* 33:17008-17022). Moreover, CPEB3-KO neurons have increased spine rigidity and reduced synaptic flexibility as evidenced by slow morphological and biochemical responses to the c-LTD condition and defective depotentiation in the hippocampal SC-CA1 synapses (Huang et al 2014, *Front Cell Neurosci* 8: e367). Because of aberrant synaptic plasticity observed in CPEB3-

depleted neurons, we examined whether CPEB3-KO mice are prone to develop post-traumatic stress disorder (PTSD)-like symptoms using a context-dependent fear conditioning and extinction paradigm. CPEB3-KO mice with normal renewal fear response in the conditioning context showed increased spontaneous recovery fear in the extinction context compared to their wild-type littermates. The molecular and cellular changes accounted for the PTSD-like behavior in CPEB3-KO mice are currently investigated.

Disclosures: Y. Huang: None. **H. Chao:** None. **W. Lu:** None. **P. Lin:** None. **M. Wu:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.15/E43

Topic: B.07. Synaptic Plasticity

Support: HI17C2665
NRF-2017R1A2B4006535
NRF-2015M3C7A1031395

Title: Hippocampal synaptic plasticity in FKBP5-deficient mice

Authors: *S. ZHANG, M. CHEON, C. CHUNG
Konkuk Univ., Seoul, Korea, Republic of

Abstract: FK506 binding protein51 (FKBP5) is a prolyl isomerase which serves as a co-chaperone of heat shock protein 90 (hsp90). Previous studies have shown that during glucocorticoid receptor (GR) activation, FKBP5 expression increases in various brain regions including the hippocampus, the amygdala and the prefrontal cortex. FKBP5 regulates the sensitivity of GR by inhibiting translocation of activated GR. FKBP5-knockout (KO) mice are reported to be resilient to stress exposure compared to wild-type (WT). However, it is unknown what are the consequences of FKBP5-deficiency in synaptic functions. We found that FKBP5 KO mice exhibited a decreased level of basal synaptic transmission and a reduced synaptic efficacy in the hippocampus. Interestingly, when we examined the synaptic plasticity of the Schaffer collateral pathway, we observed successful LTP but completely impaired LTD in FKBP5 KO mice. Our observations suggest that basal synaptic transmission has been reduced upon FKBP5 deficiency although the reduction was not enough to alter the induction of LTP. Further studies are required to reveal the role of FKBP5 in the LTD and the implication of LTD impairment in the absence of FKBP5 in stress resiliency of this mice.

Disclosures: S. Zhang: None. **M. Cheon:** None. **C. Chung:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.16/E44

Topic: B.07. Synaptic Plasticity

Support: CIHR/ PJT-153312

Title: Investigating translational machinery and regulation of local translation in healthy and pathologic hIPSC-derived neurons

Authors: *J. J. LANGILLE[1], W. S. SOSSIN[2]
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Abstract: The ability to spatiotemporally regulate the production of proteins, termed translational control, is crucial for normal neuronal function (homeostasis, memory) and its aberration is the basis of pathology (Fragile X, Tubular Sclerosis). Polysomes, stalled post-initiation by ribonucleic acid (RNA) binding proteins— dissociable by downstream effectors of synaptic plasticity inducing stimuli— confer the space-time regulation of protein synthesis. Our exploratory research investigates the translational machinery and regulation of local translation in healthy and pathologic hIPSC-derived neurons. Specifically, we sought to assess whether hIPSC-derived neurons possess stalled polysomes, whether these stalled polysomes are regulated by stimuli implicated in synaptic plasticity, and their aberration in human disease models. Elucidation of the mechanistic basis for aberrant translation seen in pathologies such as Fragile X would provide novel avenues for therapeutic intervention. Ribopuromycylation was used to visualize aforementioned stalled polysomes and was combined with metabotropic glutamate receptor (mGluR)-agonism via dihydroxyphenylglycine (DHPG) to assess regulation by plasticity (mGluR long-term depression (LTD)) associated signaling cascades. hIPSC-derived neurons showed dendritically localized, initiation inhibitor (homoharringtonine) resistant, puromycin puncta. Interestingly, our findings suggest puromycylated polysomes may exist in two distinct populations which differ in their inclusion of ribosomal protein S6. We are investigating whether these populations are differentially regulated by plasticity (long-term potentiation vs LTD); we will also investigate if increased translation following DHPG application, shown here, derives from the reactivation of stalled polysomes as would be evidenced by a decrease in puromycylated polysome number after DHPG treatment. In sum, these findings suggest hIPSC-derived neurons contain stalled polysomes regulated by plasticity implicated stimulation. We can now see whether this process is perturbed in hIPSC neurons derived from patients with neurodevelopmental disorders such as Fragile X. These findings have been corroborated in rodent hippocampal neurons using the aforementioned techniques as well as sun-tagging live imaging (Graber et al, PNAS. 2013 Oct 1; 110(40):6205-16210). Experiments

sampled ~ 10 - 250 neurites per condition across multiple cultures; all appropriate controls were included. Age and sex differences were not quantified.

Disclosures: J.J. Langille: None. **W.S. Sossin:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.17/E45

Topic: B.07. Synaptic Plasticity

Support: NHMRC grant 631057
NHMRC grant 1067137

Title: Ribosome profiling reveals excitation of neuronally differentiated sh-sy5y cells induces distinct programs of mrna translation and post-transcriptional regulation

Authors: *D. J. KILTSCHEWSKIJ[1,2], M. J. CAIRNS[1,2,3]
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Abstract: Modifications to neuronal structure and function in response to excitatory stimuli are driven by a cascade of transcriptional, translational and post-translational events. A major dimension of this system is mRNA translation, which is thought to exhibit distinct and swift changes following neuronal activity. Despite this, profiles of translation, the identity of mRNAs involved and the degree of post-transcriptional regulation in this system are still poorly understood, particularly in short time-frames following neuronal excitation. In the current study, we consequently sought to profile and explore immediate and early (1 and 2 hours post stimulus) patterns of mRNA translation on a global scale by conducting ribosome profiling (Illumina) on neuronally differentiated SH-SY5Y cells subjected to 4 successive cycles membrane excitation (K+, 100mM). The extent of post-transcriptional regulation was concurrently investigated by analysing mRNA and microRNA expression using conventional RNAseq and small RNAseq, respectively (Illumina). Differential expression analysis of ribosome profiling data identified a total of 1813, 269 and 568 differentially translated genes at all 3 respective time-points after application of statistical (fdr < 0.05) and fold change (fc > 1.5) thresholds, revealing an extensive remodelling of translational profiles following membrane excitation. Gene-set enrichment analysis of these groups uncovered enrichment of gene ontologies relating to neuronal activity and extra cellular matrix interaction immediately after excitation. By contrast, later time-points were overrepresented for genes associated with transcriptional regulation, suggesting a spatiotemporal partition exists between immediate and early programs of excitation-induced

translation. Integrative analysis of mRNA translational status and abundance (RNAseq) revealed a fascinating time-based lag between these factors, wherein correlation was initially weak (r = -0.042), yet progressively strengthened (1hr: r = 0.224, 2hrs: r = 0.419), implying a layer of post-transcriptional regulation. Supporting this finding, a number of mRNAs subjected to downregulation at the translational level at all 3 stages were enriched for binding sites of upregulated neuronal microRNA, particularly miR-1271-5p and miR-125b-5p. Together, these results suggest unique programs of mRNA translation are induced in immediate and early time-points following neuronal excitation. We additionally suspect a key role for post-transcriptional regulation, particularly by microRNA, in the remodelling of mRNA translational status during these time-periods.

Disclosures: D.J. Kiltschewskij: None. **M.J. Cairns:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

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Program #/Poster #: 465.18/E46

Topic: B.07. Synaptic Plasticity

Support: ARC DECRA DE170100112
ARC Grant DP170102402
University of Queensland Graduate School Scholarship

Title: Ubiquitination of m6A-demethylase FTO regulates its protein stability and localization

Authors: *J. WIDAGDO[1,2], T. ZHU[1,2], X. L. H. YONG[1,2], V. ANGGONO[2,1]
[1]Queensland Brain Inst., St Lucia, Australia; [2]The Univ. of Queensland, Brisbane, Australia

Abstract: As the most prevalent internal modification on eukaryotic RNA, methylation of adenosine residue or N^6-methyladenosine (m6A), affects various aspects of RNA metabolism. m6A is catalyzed by a multi-protein complex of m6A-methyltransferase and reversed by the m6A demethylating enzymes. Dynamic regulation of m6A plays important role during development and learning and memory. Our recent study demonstrates that in the medial prefrontal cortex, upregulation of m6A was induced by a fear conditioning paradigm. The activity-dependent regulation of m6A highlights the dynamic nature of m6A-enzymes. However, little is known of how these proteins are regulated. Here, we report that the m6A-demethylase, fat mass and obesity-associated (FTO) undergoes post-translational ubiquitination on Lys-216. Knock-in HeLa cells harboring the ubiquitin-deficient K216R mutation displayed a slower rate of FTO turnover, resulting in an increase in the level of FTO as well as enhanced phosphorylation of the ribosomal S6 kinase. Given the strong association of FTO and energy metabolism, we showed that amino acid starvation induced nuclear translocation of FTO, but

markedly affected in the K216R mutant. Collectively, our results reveal the functional importance of ubiquitination in controlling FTO expression and localization, which may be crucial for determining body mass and composition, as well as synaptic plasticity, learning and memory.

Disclosures: J. Widagdo: None. **T. Zhu:** None. **X.L.H. Yong:** None. **V. Anggono:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

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Topic: B.07. Synaptic Plasticity

Support: NIH Grant EY011261
NIH Grant EY027437
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NSF Grant DGE-1232825

Title: Functional roles of membrane-bounded uncapped 20S proteasomes in regulating neuronal activity *in vivo*

Authors: *H. HE[1], K. V. RAMACHANDRAN[2], E. G. CARLSON[1], S. S. MARGOLIS[3], H. T. CLINE[1]
[1]The Scripps Res. Inst., La Jolla, CA; [2]Dept of Cell Biol., Harvard Med. Sch., Boston, MA; [3]Dept. of Biol. Chem., the Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: New roles for the proteasome in the nervous system are emerging, especially the roles that the proteasome plays in regulating neuronal activity. Recent studies in mouse neuronal cultures show that uncapped 20S core subunits of proteasomes specifically bind to the neuronal plasma membrane and modulate neuronal activity (Ramachandran and Margolis, 2017). The in vivo significance of these neuronal membrane-specific proteasomes (NMPs) is unknown. Here, we showed that the core proteasome subunits (α1-7) are abundantly expressed in Xenopus laevis tadpole brain, and are associated with membrane preparations, giving us an opportunity to investigate the functional role of NMPs in a powerful in vivo system. Biotin-Epoxomicin (Bio-Epox) is a membrane-impermeable proteasome inhibitor that covalently inhibits the activity of NMPs. After injection of tadpole brains with Bio-Epox, biotinylated 20S catalytic subunits were only recovered in the membrane preparation. Western blots of subcellular preparations showed that Bio-Epox remained in the membrane preparation for up to 6 hours with no detection in the cytosol, validating the use of Bio-Epox as a NMP-specific inhibitor in vivo. We then used in vivo calcium imaging in the optic tectum of tadpoles to study the role of NMPs in regulating spontaneous neuronal activity. Interestingly, blocking NMPs in tectal neurons with Bio-Epox

significantly increased spontaneous neuronal activity in a dose-dependent manner. The increase in spontaneous activity was observed as soon as 5 min post-injection and lasted for at least 30 min. In the presence of BMI (bicuculline methiodide), when spontaneous neuronal activity was already heightened, blocking NMPs further increased neuronal activity. Based on unpublished data showing that NMP targets intracellular substrates that are being newly synthesized, we used bio-orthogonal metabolic labeling (BONCAT) to label newly synthesized proteins (NSP) and studied the function of NMPs in tadpole brains. In BONCAT, azidohomoalanine (AHA) is incorporated into NSPs and then tagged with biotin alkyne by click chemistry to allow specific detection of NSPs (Liu et al., 2018). Using BONCAT, we found that BMI increases NSPs and that blocking NMPs with Bio-Epox in the presence of BMI further increased NSPs. Bio-Epox alone did not increase NSPs, suggesting that NMPs actively degrade NSPs in response to increased neuronal activity. Taken together these data are consistent with findings observed in cultured mouse neurons. Our findings presented here are the first to demonstrate NMPs actively modulate neuronal activity in vivo and may function in part by regulating expression of activity-induced NSPs.

Disclosures: H. He: None. **K.V. Ramachandran:** None. **E.G. Carlson:** None. **S.S. Margolis:** None. **H.T. Cline:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

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Program #/Poster #: 465.20/E48

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R01MH112766

Title: The neuronal protein Arc acts as a repurposed viral Gag protein that mediates cell-to-cell communication

Authors: *E. D. PASTUZYN, R. B. KEARNS, J. N. EINSTEIN, J. D. SHEPHERD
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Abstract: The neuronal gene Arc is crucial for consolidation of long-term memories, and Arc knockout (KO) mice are deficient in multiple forms of synaptic plasticity. Arc mediates synaptic plasticity via trafficking of AMPA receptors to and from the postsynaptic membrane. However, the molecular biology of Arc is not well-characterized. Recently, Arc was discovered to have structural homology to Gag, a critical component of retroviruses like HIV that is sufficient to form an infectious particle. This suggested that Arc may exhibit viral-like properties: the ability to self-assemble into proteinaceous shells or capsids, interaction with lipid membranes, encapsulation of nucleic acids, and release from cells. We found that Arc performs all of these

key functions associated with viral Gag. Electron microscopy shows that purified Arc protein forms capsids similar to HIV. Immunoprecipitation of Arc protein from brain tissue pulls down *Arc* mRNA, suggesting the two are directly interacting or forming a complex. Neurons release extracellular vesicles, which contain RNA and are thought to be important in cell-to-cell communication or transfer of material. The extracellular vesicle fraction from cultured cortical neurons contains both Arc protein and *Arc* mRNA. Incubation of cultured Arc KO neurons with either the extracellular vesicle fraction from wildtype (WT) neurons, or purified Arc protein alone, results in transfer of both Arc protein and *Arc* mRNA into KO neurons. Furthermore, transferred *Arc* mRNA is available in the cytoplasm for activity-induced translation into new Arc protein. Extracellular vesicles are a heterogeneous population that can be differentiated by membrane surface markers, such as receptors, as well as potentially by their cargo. We purified Arc vesicles using differential ultracentrifugation and density gradients to determine which subpopulation of extracellular vesicles Arc is associated with. We then performed proteomic and deep RNA sequencing of purified Arc vesicles to determine the composition of cargo, which will provide insight into the function of this form cell-to-cell communication. These studies show that Arc serves as a novel intercellular messenger in neuronal networks and can regulate neuronal function in a non-cell autonomous manner.

Disclosures: E.D. Pastuzyn: None. **R.B. Kearns:** None. **J.N. Einstein:** None. **J.D. Shepherd:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.21/E49

Topic: B.06. Synaptic Transmission

Support: NIH-NINDS: NS051401-42

Title: Functional presynaptic ribosomes in the mammalian brain, and presynaptic effects of inhibiting protein synthesis

Authors: *K. G. PARADISO[1], M. S. SCARNATI[2], R. KATARIA[1], M. BISWAS[1]
[1]Cell Biol. and Neurosci., Rutgers Univ., Piscataway, NJ; [2]Dept. of Neurosci. and Cell Biol., Rutgers-Robert Wood Johnson Med. Sch., New Brunswick, NJ

Abstract: To determine if ribosomes are present and functional in presynaptic terminals in the mammalian brain, we used the SUrface SEnsing of Translation (SUnSET) technique to detect the location of active ribosomes in mouse brain slices. In this assay, puromycin becomes incorporated into nascent polypeptide chains, and is detected by antibody labelling. We find clear evidence of ribosomal activity in calyx of Held presynaptic terminals, based on

colocalization of puromycin with the vesicular glutamate transporter VGLUT1 which specifically labels the calyx nerve terminal. Addition of anisomycin to inhibit translation completely blocks the presynaptic and postsynaptic puromycin signal, demonstrating the specificity of this assay. In separate immunocytochemistry experiments, we find 5.8s ribosomal RNA, a major component of ribosomes, is also present in the presynaptic terminal. These results demonstrate that calyx of Held presynaptic terminals in the mammalian brain contain functional presynaptic ribosomes capable of presynaptic protein synthesis. This suggests that active presynaptic translation could affect presynaptic activity. In separate experiments, we inhibited translation and examined the effects on synaptic transmission. We find an increase in spontaneous release frequency, demonstrating that presynaptic vesicular release is affected by ongoing protein synthesis. In contrast, the amplitude and shape of spontaneous release events were not affected by inhibiting protein synthesis, demonstrating that postsynaptic activity is not affected. In response to evoked stimulation after inhibiting protein synthesis for ~1 hour, we find a decrease in the initial probability of release with increased levels of release during sustained stimulation at 100 Hz and 200 Hz. This is accompanied by an increased level of vesicle recycling at 100Hz and 200 Hz when protein synthesis is inhibited. These results indicate that ongoing protein synthesis is necessary to maintain specific levels of vesicular release. Overall levels of release are increased when protein synthesis is inhibited. Given that normal levels of release are sufficient to produce an adequate postsynaptic response, this indicates that ongoing protein synthesis acts to limit excess neurotransmitter release. Ongoing protein synthesis therefore acts to limit excess energy consumption that is required for vesicle recycling. This suggests that ongoing protein synthesis increases the efficiency of the presynaptic terminal by limiting excess vesicle release.

Disclosures: K.G. Paradiso: None. **M.S. Scarnati:** None. **R. Kataria:** None. **M. Biswas:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

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Program #/Poster #: 465.22/DP03/E50

Topic: B.07. Synaptic Plasticity

Support: NIH Grant NS083085

Title: Imaging transcription dynamics of neuronal activity-regulated genes in hippocampal neurons

Authors: *S. DAS, R. H. SINGER
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Abstract: Spatio-temporal control of gene expression in a neuronal network is an essential element of memory formation. However, it has not been possible to follow the dynamics of memory-associated mRNAs in living neurons in response to neuronal activity in real time. We generated transgenic mouse models where the endogenous Arc (Arg 3.1) and β-actin genes are tagged in their 3'UTR with stem loops that bind different fluorescent coat proteins, allowing simultaneous visualization of two different mRNAs in the same neuron in real time. The physiological response of the tagged genes to neuronal activity is identical to the endogenous wild-type and faithfully captures the true dynamics of the mRNAs. Real time transcription dynamics of immediate early gene Arc reveals: i) a robust transcriptional burst with a prolonged ON-state after stimulation, and ii) reactivation of transcription at the same allele even after the initial stimulation is removed. This is quite distinct from how β-actin responds to neuronal activity with more stochastic bursting. The tagging and imaging of endogenous genes, one inducible and other constitutive, provide an important tool to investigate how individual neurons transduce activity into regulation of gene expression with unprecedented temporal resolution.

Disclosures: S. Das: None. **R.H. Singer:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.23/E51

Topic: B.07. Synaptic Plasticity

Support: HHMI

Title: Direct administration of osteocalcin into the dentate gyrus affects contextual fear memory via a CPEB3 mediated mechanism

Authors: *S. KOSMIDIS, L. HARVEY, E. KANDEL
Neurosci., Columbia Univ., New York, NY

Abstract: Recent studies highlight the contribution of several sites in the aging process, illustrating the importance of blood-derived factors in memory. One such humoral factor is the bone-derived hormone Osteocalcin (OCN). Injection of OCN into the dentate gyrus enhances discrimination memory via the GPR158 protein. Subsequent RNA seq analysis upon direct administration of OCN in the dentate gyrus after fear memory recall, demonstrated that OCN enhances translation of several memory-related genes. We therefore hypothesized that the cytoplasmic poly-adenylation element binding protein 3 (CPEB3) could be involved in the translational regulation of OCN signaling. Here we demonstrate that OCN signaling via GPR158 leads to phosphorylation of CPEB3, which in turn exerts control over translation. Using RNA-immuno-precipitation coupled with deep sequencing, we further found that CPEB3 binds to

several mRNAs involved in the recall of fear memory. Finally we find that overexpression of CPEB3 phosphorylation mutants in the dentate gyrus differentially affects fear memory.

Disclosures: S. Kosmidis: None. **L. Harvey:** None. **E. Kandel:** A. Employment/Salary (full or part-time):; HHMI.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.24/F1

Topic: B.07. Synaptic Plasticity

Support: NS034007
NS047384
HD082013
T32MH01952425

Title: Characterization of the mTORC1 effector PDCD4 in activity dependent translation

Authors: *I. KATS[1], E. KLANN[2]
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Abstract: Translation initiation, regulated by mechanistic target of rapamycin 1 (mTORC1) and its effectors eIF4E and p70 S6 kinase 1 (S6K1), is relevant to both normal memory function and disease. Either increased expression of eukaryotic initiation factor 4E (eIF4E) or deletion of its repressor eukaryotic factor 4E binding protein 2 (4E-BP2) causes autistic endophenotypes in mice. Moreover deletion of S6K1 can cause deficits in various types of memory. Inhibitors of either the interaction of eIF4E with eukaryotic initiation factor 4G (eIF4G) or the eukaryotic initiation factor 4A (eIF4A) have also been shown to affect protein synthesis in brain slices and to disrupt long-term potentiation. eIF4A1, the DEAD box helicase in the cap-dependent translation initiation complex, has proven to be important for translation in cancer cells where it is often upregulated. The inhibitor of eIF4A1, PDCD4 is phosphorylated and broken down by the proteasome pathway in cancer cells to permit protein synthesis and cell growth. Our preliminary data show that PDCD4 is down regulated by neuronal stimulation and that the pathway responsible for this regulation is S6K1- and proteasome-dependent. Moreover, in contract to non-neuronal cell types, PDCD4 is present in the cell body as well as dendrites and its overexpression in neurons causes a decrease in dendrite complexity. The localization and regulation of PDCD4 implicates the importance of PDCD4 and eIF4A1 as mTORC1 effectors in not only activity-dependent translation but also synaptic plasticity and memory function. To test this idea we have begun to examine synaptic function and memory processes in PDCD4

knockout mice. In summary, our findings indicate that PDCD4 acts as a downstream effector of mTORC1 in neurons, and thus, is an important regulator of activity-dependent translation.

Disclosures: I. Kats: None. **E. Klann:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.25/F2

Topic: B.07. Synaptic Plasticity

Support: NIH R01 NS086933-01
Alzheimer's Association MNIRGDP-12-258900
Linda Crnic Institute
NIH T32 MH016880

Title: Investigating non-canonical protein synthesis in neurons

Authors: *H. WONG[1], J. LEVENGA[1], C. HOEFFER[1,2]
[1]Inst. for Behavioral Genet., [2]Integrative Physiol., Univ. of Colorado Boulder, Boulder, CO

Abstract: Protein synthesis is required for persistent forms of synaptic plasticity such as long-term potentiation and long-term depression, which are thought to be cellular substrates of memory. The primary pathway for protein synthesis is canonical translation, which initiates with binding of the small ribosomal subunit and associated translation initiation factors to the 5' cap of eukaryotic mRNAs. While this pathway is well-studied and known to support synaptic plasticity and memory, protein synthesis can also occur to a lesser extent through non-canonical pathways. In one mode of non-canonical translation, protein synthesis initiates from an internal ribosome entry site (IRES) in the mRNA transcript. An IRES is an element within the mRNA that recruits the ribosome by various mechanisms different from canonical initiation. Very little is known about the contribution of this IRES-mediated mode of translation to neural function. However, a few proteins associated with synaptic plasticity have been reported to contain an IRES in their mRNA. We hypothesized that IRES-mediated translation may play a role in the protein synthesis supporting persistent forms of synaptic plasticity. To explore this idea, we have developed bicistronic translation reporters to measure cap- and IRES-mediated protein synthesis in neurons. Using these reporters in addition to complementary approaches, we are examining translational activity in hippocampal neurons following different stimulation and treatment conditions. These studies may provide new insight into the translation mechanisms underlying synaptic plasticity and how their dysfunction could be involved in memory disorders.

Disclosures: H. Wong: None. **J. Levenga:** None. **C. Hoeffer:** None.

Poster

465. Transcription and Translation in Synaptic Plasticity

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 465.26/F3

Topic: B.07. Synaptic Plasticity

Support: JSPS Grant 22650066, 23300121

Title: Detection of native RNAs dynamics in living neurons by fluorescence correlation spectroscopy

Authors: *H. FUJITA[1], S. KAMIZONO[1], R. OIKAWA[2], M. HAYAKAWA[2], F. TOMOIKE[2], S. TSUNEDA[1], H. ABE[2], T. INOUE[1]
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Abstract: Peripheral localization of transcripts mediates many neuronal processes, the dynamics of which are the key to understanding development, cellular signaling and synaptic plasticity. While several techniques have been used to visualize mRNAs in live cells, dynamics of endogenous and non-engineered mRNAs in living neurons have been difficult. We developed a method to analyze the behavior of native mRNAs without modifying their sequences in living neurons. In order to fluorescently label native RNAs, we used reduction-triggered fluorescence (RETF) probes, of which fluorescence emission was chemically activated after a pair of probes hybridize to the target RNA side by side. We chose activity-regulated cytoskeleton-associated (Arc) and inositol 1,4,5-trisphosphate receptor type 1 (IP3R1) mRNAs as targets.Fluorescence signal deriving from the RETF probe increased and spread over the cytosol after loading to cultured hippocampal neurons by a whole cell patch clamp method. Fluorescence correlation spectroscopy (FCS) was applied to discriminate bound and unbound probes by the difference in diffusion coefficients. The slower diffusing component reflected RNA-bound probes and the faster one reflected unbound probes presumably due to RNA degradation. The balance between the faster and slower diffusion components was different when IP3R1 mRNA probes were used, suggesting a difference in the turnover rates between Arc and IP3R1 mRNAs. Neuronal activation drastically increased concentrations of the both diffusion populations within 40 min, which was interpreted as the production and degradation of Arc mRNA. Simulation of diffusive RNA within the dendritic space using the obtained diffusion coefficient of Arc mRNA (1.0 $\mu m^2/s$) showed that RNA does not reach distal dendrites by diffusion within reasonable time, supporting the notion that the active transport mechanism is necessary to deliver mRNA to the distal dendrite.

Disclosures: H. Fujita: None. **S. Kamizono:** None. **R. Oikawa:** None. **M. Hayakawa:** None. **F. Tomoike:** None. **S. Tsuneda:** None. **H. Abe:** None. **T. Inoue:** None.

Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 466.01/F4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: U01AG032984
R01AG033193
U54HG003273
U54HG003067
U54HG003079

Title: Machine learning tech for neural omics

Authors: *B. R. MONK[1], A. RAJKOVIC[3], R. MALINOW[2]
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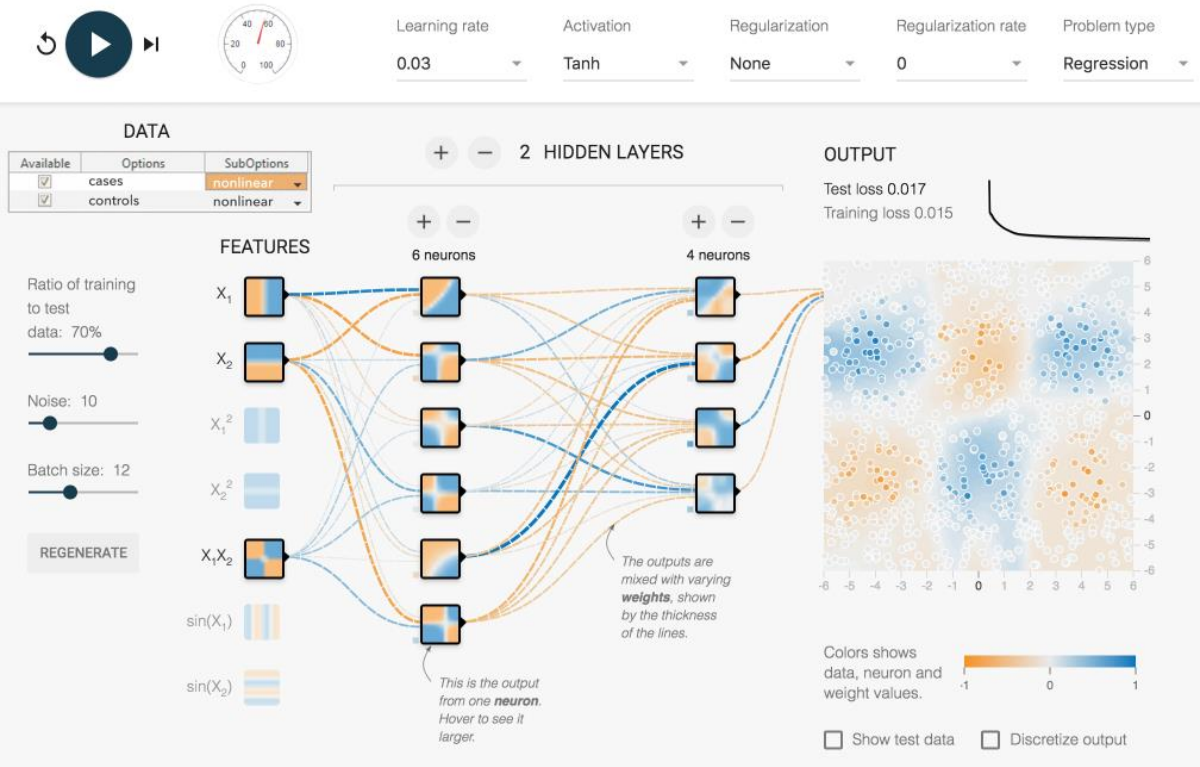
Abstract: We have developed a computational framework for informing neural disease-related diagnostics. This framework integrates and leverages powerful machine learning libraries (e.g. Google Tensorflow) to perform regression based and artificial neural network based computations that can, for example, inform dementia diagnoses. In one use-case our platform could correctly diagnose Alzheimer's Disease patients with 75-80% accuracy, after training a neural net classifier on whole exome sequences from 5k patients and 5k controls. This prediction accuracy generalized to individuals never seen by the machine classifier. The platform can also output a confidence level for each prediction; for individuals returning highly confident predictions the classifier can reach upwards of 85% accuracy. Our data also suggests there remain substantial gains to be had in prediction accuracy (and precisely how these can be achieved). We think such a platform could be adapted for use in both a clinical setting and for aiding primary research, and we are interested in collaborating with other parties in further developing this tech. (Figure: Example Custom Tensorflow interface)



Disclosures: B.R. Monk: None. **A. Rajkovic:** None. **R. Malinow:** None.

Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 466.02/F5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Dept of Biomedical Science, FSU College of Medicine

Title: A multi-omic analysis of the pre-histopathological and sex-biased molecular pathology in the hippocampus of the 5XFAD mouse model of Alzheimer's disease

Authors: *R. S. NOWAKOWSKI[1], J. L. BUNDY[2], C. M. VIED[3]
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Abstract: Alzheimer’s disease is a progressive neurodegenerative disorder and is the most common form of dementia. Like many neurological disorders, Alzheimer’s disease has a sex-biased epidemiological profile, affecting approximately twice as many women as men. To

identify the molecular mechanism of this sex bias at its earliest onset, we investigated the molecular changes in females and males using the 5XFAD genetic mouse model of Alzheimer's disease at 3 different ages. The 5XFAD model contains two mutated human transgenes (*APP* and *PSEN1*) associated with familial Alzheimer's disease co-inserted into the mouse genome. We profiled the transcriptome, the miRNAome and proteome of the mouse hippocampus during early stages of disease development (one, two, and four months of age). At one month, only the transgenes are differentially expressed. At two months of age, which is prior to observable plaque deposition, our analysis reveals 42 genes that are differentially expressed between transgenic and control animals In four month old animals, we detect 1316 differentially expressed genes between transgenic and control mice, many of which are associated with immune function. Additionally, we find that some of these transcriptional differences are correlated with altered protein levels in four month old transgenic animals. Importantly, our data indicate that female 5XFAD mice exhibit more profound molecular pathology than their male counterparts as measured by differences in gene expression. In addition to the transcriptome and proteome analyses, we will present miRNA expression data generated from the same RNA used to produce the transcriptomic data. The three omics datasets will be correlated and the pathways containing the significantly changed genes analyzed to produce a comprehensive profile of the molecular changes that occur due to Alzheimer's disease in the 5XFAD mouse model.

Disclosures: R.S. Nowakowski: None. **J.L. Bundy:** None. **C.M. Vied:** None.

Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 466.03/F6

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Early apoptosis in Alzheimer's disease 5XFAD mouse model is induced through multiple pathways: A comparative transcriptomics study on *in vivo* neuron-microglia interaction phase

Authors: *F. XUE, Q. WANG, H. CHEN, Z. XUAN, L. GUO, H. DU
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Abstract: Alzheimer's disease (AD) is a devastating neurodegenerative disorder, characterized by progressive cognitive decline. Neuronal death and neuroinflammation are featured AD brain pathology closely associated with the toxicity of a key AD mediator, Amyloid beta (Aβ). Microglia has both neuron protection and neuroinflammation functions, and may play different roles at early or later stage of amyloidopathy. Therefore, the examination on neurons and microglia separated from AD-sensitive brain tissues has paramount importance to address the "cause and effect" question. In this study we used an AD mouse model (5xFAD) overproducing human form Aβ. Experiments were conducted on young 5xFAD mice, which mimic mild brain

amyloidopathy, neuronal injury and cognitive deficits in early AD. Experimentally, we modified brain tissue dissociation, fluorescence-activated cell sorting (FACS), high integrity RNA purification, and moderate depth RNAseq methods, and revealed the steady transcriptomic changes in neuron and microglia from 5xFAD mice in comparison with those from the age- and gender-matched wildtype littermates. The robust gene upregulations in MAPK, Toll-like receptor, JAK-STAT, and Insulin signaling pathways in neurons sorted from 5xFAD mouse cortex and hippocampal tissue indicated that the initiation of apoptosis was induced through multiple pathways. However, the downregulation of several key actors in apoptosis pathways as well as the activation of several anti-apoptosis pathways (eg. Focal adhesion, Wnt) seem to suggest a balance between pro- and anti-apoptosis in neuron population. Surprisingly, the CD11b+ microglia from 4 months old 5xFAD mice did not exhibit significant inflammatory response, which is different from previous inflammation activation results. Such discrepancy may be explained by a more rigorous sample preparation that we used in current study. In addition, our RNAseq data also verified recently reported single-cell RNAseq markers of disease-associated microglia (DAM), which suggests a potential protective effect of microglia on neurons against Aβ in young 5xFAD mice. In summary, our results suggest that the early neuron apoptosis in Alzheimer's Disease (AD) 5XFAD mouse model was induced through multiple pathways, but not through inflammatory response in microglia.

Disclosures: **F. Xue:** A. Employment/Salary (full or part-time):; The University of Texas at Dallas. **Q. Wang:** None. **H. Chen:** None. **Z. Xuan:** A. Employment/Salary (full or part-time):; The University of Texas at Dallas. **L. Guo:** A. Employment/Salary (full or part-time):; The University of Texas at Dallas. **H. Du:** A. Employment/Salary (full or part-time):; The University of Texas at Dallas.

Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 466.04/F7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Basic Research Program of China (973 Program) Grant 2014CB910204
The National Key Research and Development Program (2016YFA0501900)
National Natural Scientific Foundation of China (81571043)

Title: Decoding competing endogenous RNA regulations in Alzheimer's disease

Authors: ***Y. CAI**[1], Z. SUN[2], H. JIA[2], J. WAN[2,3]
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Abstract: Leverging the fast developing sequencing technology, large amount of non-coding RNA (ncRNA) have been discovered involving in diseases and health. Alzheimer's disease (AD) is a heterogeneous neurodegenerative disease. Recent studies have identified ncRNAs influentially involved in AD pathogenesis. Competing endogenous RNA (ceRNA) regulation is one of the most important mechanism. Briefly, ceRNAs can compete with other endogenous RNAs by microRNA response elements (MREs) and manipulate biological processes, such as tumorigenesis. Abundant of studies have reported miRNAs in AD pathogenesis, as well as ceRNA regulations and networks in tumorigenesis. Although few, the studies of ceRNAs in AD pathogenesis is growing.
In the first session of this study, we constructed the first ceRNA network based on APPswe/PS1ΔE9 transgenic mice model, leveraging whole transcriptome sequencing and miRNA-seq of cortex samples from AD and wild type mice. Differentially expressed lncRNAs were identified, then input into bioinformatics batabases, such as LncBase, TarBase, DIANA web server v.5, mining for ceRNA interactions. In this network, 1091 nodes and 1171 edges were constructed. Four hub lncRNAs (C030034L19Rik, Rpph1, A830012C17Rik, and Gm15477) and five hub miRNAs (miR-182-5p, miR-330-5p, miR-326-3p, miR-132-3p, and miR-484) are enriched in nine AD-associated pathways and an AD-related gene pool.
In the second part of this study, one of the ceRNA pathway Rpph1-miR330-5p-Cdc42 were studied with molecule biology verification and cell biology functional assays. The underlying ceRNA interactions were validated using molecular biology approaches, such as Dual Luciferase Reporter Assay, quantitative RT-PCR and Western blotting; cell biology approaches, such as primary neuronal culture for dendritic spine and neurites morphological examination. Long non-coding RNA Ribonuclease P RNA component H1 (Rpph1) is upregulated in the cortex of APPswe/PS1ΔE9 mice compared to wild type controls. Rpph1 binds to miR326-3p/miR-330-5p and causes the release of their downstream target Cdc42, which leads to CDC42 upregulation. This effect was disrupted upon mutation of the MRE on Rpph1. Moreover, overexpression of Rpph1 increased dendritic spine density in primary cultured hippocampal pyramidal neurons, whereas knocking down of Rpph1 had the reverse effect. This pathway may represent a compensatory mechanism in the early stage of the AD pathogenesis.
In the third part of this study, we focus on the advanced strategies in ceRNA regulations based on evidence in neurodegenerative disorders, mainly summarized five miRNA and ceRNA hierarchies in cross regulations.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 466.05/F8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: DP5-OD017908-01
UR009601 Faculty Research Fellowships

Title: A longitudinal analysis of hippocampal metabolomic alterations following cognitive decline in aged mice and APP/PS1 Alzheimer's disease mice

Authors: *H. C. HUNSBERGER[1,2], A. KITAYEV[2], C. HILL[2], N. NARAIN[2], M. KIEBISH[2], C. A. DENNY[1]
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Abstract: Alzheimer's disease (AD), a progressive and debilitating neurodegenerative disorder, stands alone as one of the ten leading causes of death in the United States that cannot be prevented, slowed, or cured. However, research suggests that the brain changes associated with AD often begin 20 or more years before symptoms appear, which makes this a critical time window for possible preventative treatments. Therefore, it is essential to discover early biomarkers in those at risk for AD. Because aging is the greatest risk factor for the development of AD, it is also important to examine age-related changes in the brain and age-related cognitive decline (ARCD). Metabolomics represents one of the best omics platforms for the diagnosis and prognosis of neurodegenerative diseases, as the metabolome is a reflection of genetics, protein profiles, and environmental influences. Furthermore, metabolic decline is one of the earliest symptoms detected in patients with mild cognitive impairment (MCI). Here in, we used metabolomics to define system-level alterations following cognitive decline in aged and APP/PS1 mice. At 6, 12, and 24 months of age, both AD and aged-match control (Ctrl) mice were tested for cognitive impairment in a 3-shock contextual fear conditioning (CFC) paradigm. Brain tissue (i.e, hippocampus, hypothalamus, PFC, and cerebellum) and biofluid (i.e., plasma) metabolomic analysis was performed. By examining behavior across ages in these animals, we aimed to determine if early metabolomic changes could associate with cognitive decline observed following natural aging and AD development. Furthermore, since metabolomics pathways are largely conserved between species, these results could improve the translation of preclinical research. Our results confirmed that AD mice exhibit memory deficits in the CFC paradigm compared to controls at 6, 12, and 24 months of age. However, aged-match Ctrl mice also exhibited cognitive decline across ages. These memory impairments were correlated with metabolome changes in both the left and right hemispheres of the hippocampus. Specifically, in AD mice, metabolome changes were left lateralized, meaning there were greater changes in the left hemisphere of the hippocampus compared to the right. These data support human literature showing greater grey-matter atrophy in the left hippocampus of Alzheimer's patients. Ctrl mice exhibited equal metabolome changes in both hemispheres, which highlights the differences in ARCD and AD progression. Our future directions are to further analyze other brain regions and to determine the role of peripheral organs through metabolic signaling.

Disclosures: H.C. Hunsberger: None. **A. Kitayev:** None. **C. Hill:** None. **N. Narain:** None. **M. Kiebish:** None. **C.A. Denny:** None.

Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 466.06/F9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant U01AG046170
NIH Grant U01AG046139
NIH Grant U01AG046152

Title: Sex specific Alzheimer's disease heterogeneity identified through cross study integrative analysis of RNA-seq data from the AMP-AD consortium

Authors: *B. LOGSDON[1], T. M. PERUMAL[1], V. SWARUP[2], C. FUNK[3], M. ALLEN[4], M. WANG[5], C. GAITERI[6], X. WANG[4], S. SIEBERTS[1], L. OMBERG[1], E. DAMMER[7], S. AMBERKAR[8], W. HIDE[8], J. M. SHULMAN[9], T. E. GOLDE[10], D. BENNETT[6], B. ZHANG[5], E. SCHADT[5], P. L. DE JAGER[11], N. PRICE[3], L. M. MANGRAVITE[1]
[1]Sage Bionetworks, Seattle, WA; [2]Neurol., Univ. of California Los Angeles Dept. of Neurol., Los Angeles, CA; [3]Inst. for Systems Biol., Seattle, WA; [4]Mayo Clin., Jacksonville, FL; [5]Mount Sinai Sch. of Med., New York City, NY; [6]Rush Univ., Chicago, IL; [7]Emory Univ., Atlanta, GA; [8]Univ. of Sheffield, Sheffield, United Kingdom; [9]Baylor Univ., Houston, TX; [10]Dept. of Neurosci., Col. of Medicine, Univ. of Florida, Gainesville, FL; [11]Columbia Univ., New York City, NY

Abstract: Background: The systemic failure to develop successful treatments for Alzheimer's Disease (AD) is in part driven by an incomplete understanding of the multi-factorial and heterogeneous biological processes that underlie this disease. To address this challenge, the AMP-AD Target Discovery Project has identified transcriptional endophenotypes that characterize AD-altered processes in the postmortem brain and, using these, evaluated common sources of heterogeneity in their manifestation across 2114 samples collected from 3 studies and 7 brain regions. **Methods:** To identify AD transcriptomic endophenotypes that are robustly observed across data sets and methodologies, we apply five distinct network methodologies (MEGENa, metanetwork, WINA, SpeakEasy, and rWGCNA) to learn coexpression modules within each tissue type and combine these modules with a meta-analysis of differential expression signatures of AD to produce consensus modules for each tissue via a graph clustering algorithm. **Results:** Thirty disease-associated transcriptomic networks were consistently observed across brain regions and independent of analytical method. Many of the conserved AD-altered transcriptional networks show strong enrichment for known AD pathway signatures including evidence of neuroinflammation and synaptic dysfunction. Others represent potentially new insights into AD biology and may suggest sex specificity of transcriptional endophenotypes.

For example, there is strong evidence of female specific neuronal, vascular, and myelination dysfunction and male specific changes in DNA damage repair and response to unfolded proteins. **Conclusions:** These results, which require further replication, may suggest sex-specific disease pathways or rates of AD pathophysiology progression. In women cell type specific transcriptional dysregulation appears to be more prominent, whereas in men, failure of various proteostatic pathways may be more instrumental in pathophysiology. Neuroinflammatory pathways reveal transcriptional changes in both sexes. Furthermore, these observations provide a set of AD transcriptional endophenotypes that can be used to identify causal factors that modulate changes in biological processes that lead to or propagate AD pathophysiology. Some of these transcripts and their protein products are being evaluated as potential drug targets.

Disclosures: B. Logsdon: None. **T.M. Perumal:** None. **V. Swarup:** None. **C. Funk:** None. **M. Allen:** None. **M. Wang:** None. **C. Gaiteri:** None. **X. Wang:** None. **S. Sieberts:** None. **L. Omberg:** None. **E. Dammer:** None. **S. Amberkar:** None. **W. Hide:** None. **J.M. Shulman:** None. **T.E. Golde:** None. **D. Bennett:** None. **B. Zhang:** None. **E. Schadt:** None. **P.L. de Jager:** None. **N. Price:** None. **L.M. Mangravite:** None.

Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 466.07/F10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Good Ventures (Foundation)

Title: Microbial profiling on human Alzheimer’s brain samples using Whole Genome Metagenomic Sequencing approach in comparison with different age groups

Authors: *N. NAVALPUR SHANMUGAM[1], D. VIJAYA KUMAR[2], W. A. EIMER[3], F. ZAMUDIO[4], R. E. TANZI[5], R. D. MOIR[6]
[1]Dept. of Neurol., Massachusetts Gen. Hospital/Harvard Med. Sch., Charlestown, MA; [2]Genet. & Aging Res. Unit, Massachusetts Gen. Hosp. & Harvard Med. Sch., Charlestown, MA; [3]Genet. and Aging Res. Unit, [4]Neurol., Massachusetts Gen. Hosp., Charlestown, MA; [5]Massachusetts Gen Hosp, Harvard Med. Sch., Charlestown, MA; [6]Neurology, Genet. and Aging Res. Unit, Massachusetts Gen. Hosp. and Harvard Med. Sch., Charlestown, MA

Abstract: Background: Amyloid plaques in the human brain are a pathological hallmark of Alzheimer’s disease (AD). The last three decades as seen the etiology of AD increasingly linked to chronic, low-grade, asymptomatic microbial brain infections. We recently reported Abeta is an innate immune protein and the peptide’s expression protects against fungal and bacterial infections in animal and cell culture models, doubling host survival in some cases. However,

fibrilization pathways mediate Abeta antimicrobial activities. Thus, infection can dramatically accelerate beta-amyloid deposition. Here we report on a study to determine microbes normally residing in aging human brain and how this population may change in AD. **Methods:**Human frontal cortex brain samples from different age groups were screened for microbial signal by Whole Genome Metagenomics Sequencing (WGMS) using next generation technique (NGS). Screening aimed to identify non-human nucleic acid sequences. Additional established methods were also used to confirm findings.**Results:**Initial sequencing data confirmed the presence of microbial populations in aging and AD human brain samples, with bacterial organisms being more abundant (40-60 % of total microbial populations). Organisms identified included fungi, viruses and protozoa. Bacterial genera identified include *Acinetobacter, Pseudomonas, Escherichia*,*Bacteroidetes*, as well as symbiotic bacteria, including *Eubacterium, Bifidobacterium*, *Roseburia*and *Akkermansia*. Eukaryotic microorganisms, were also present, including species from the *Plasmodium*genus. Most significantly, data suggest AD brain may have altered microbial populations compared to age-matched non-demented controls. Conclusions:Preliminary data suggest the existence of a microbial population in human brain samples whose composition changes across age and disease. Findings are consistent with a link between enhanced β-amyloid deposition in AD and a shift in the population of microorganisms in brain.

Disclosures: N. Navalpur Shanmugam: None. **D. Vijaya Kumar:** None. **W.A. Eimer:** None. **F. Zamudio:** None. **R.E. Tanzi:** None. **R.D. Moir:** None.

Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

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Program #/Poster #: 466.08/F11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG037919
NIH Grant ES024233
NIH Grant AG056371
NIH Grant AG057565
NIH Grant AG044490
Alzheimer's Association AARF-16-443213

Title: Comparative cell and nuclear isolation strategies for transcriptomic analysis of neurons, microglia and astrocytes

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Abstract: While multiple methods have already been developed for isolation of neurons or astrocytes from frozen human brain tissue for transcriptomic analysis, microglia isolation from frozen tissue is still a challenge. Here we compare standard protocols applied for cellular and nuclear isolation from fresh and frozen mouse brain tissue to our new protocol for simultaneous isolation of neuronal, astrocytic and microglial nuclei from frozen human brain. Cellular populations or nuclei from mouse brain, can be isolated and sorted by FACS to perform RNA-seq and analysis of transcriptomes. However, most of the methods for isolation of cells or nuclei from fresh or frozen mouse brain involve mechanical stress that increases cellular damage, and/or protease treatment at 37°C (as trypsin or papain) that may induce alterations in RNA and possibly sequencing data. In our method, Accutase allow an efficient cell dissociation at 4°C. Because of longer postmortem intervals or extended storage of human brains at −80°C, brain cells are more fragile or damaged and the use of standard isolation protocols results in a significant decrease of the number of cells/nuclei and therefore the quantity of RNA, and sequencing libraries impacting subsequent transcriptomic analysis. Therefore, in our protocol, the gentle manual trituration of the brain tissue with modified Pasteur pipettes that varied in tip diameter, slow centrifugations at 4°C, using cold buffers and keeping the samples on ice contribute to diminish cell damages and increase cell yield. After trituration, half of the single-cell suspension is exposed to anti-Cd11b-microbeads and processed into columns for magnetic separation. Then, the enriched microglia cell suspension and the leftover single cell suspension are fixed and permeabilized with Ethanol to extract the nuclei. Finally, the nuclei are labelled with DAPI, anti-NeuN, anti-GFAP and anti-SPI1. Using flow cytometry to estimate the percentage of each cell population in the samples, we were able to see a higher yield of nuclei obtained with our new protocol. Moreover, unlike the standard cell isolation methods, we were able to use down to 3000 neuronal, astrocytic and microglial nuclei sorted by FACS to perform RNA isolation and RNA-sequencing. This new protocol has been optimized to ensure a high quality of RNA for transcriptomic analysis purpose, the possibility to study simultaneously the transcriptome of neuronal, astrocytic and microglial nuclei from the same tissue and to reduce the amount of initial frozen material. This method for human frozen brain should facilitate and optimized the use of frozen tissue for Human brain transcriptomic research.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 466.09/F12

Topic: C.02. Alzheimer's Disease and Other Dementias

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1RF1AG057443-01
RF1-AG057452
7R01NS091251-03

Title: Mechanistic and directional transcriptional regulatory networks in Alzheimer's disease

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Abstract: Background Standard approaches to understand gene expression and regulation in the brain include identification of differentially and co-expressed genes. The Accelerating Medicines Partnership Alzheimer's Disease (AMP-AD) consortium has produced multiple, large RNA-seq datasets from several postmortem brain regions. The ENCODE project has produced DNAse Hypersensitivity (DHS) samples for various brain regions. We have integrated these large datasets into transcriptional regulatory networks (TRN), providing a directional and mechanistic list of putative transcription factors for nearly all expressed genes in the brain. **Methods** We reprocessed all ENCODE brain DHS samples at scale, generating footprints—signatures of occupancy by DNA binding proteins—using the Wellington and HINT algorithms. We assembled motifs from JASPAR2016, HOCOMOCO, UniPROBE, and SwissRegulon, removing redundant motifs with Tomtom and intersecting our footprints with all possible overlapping motifs. This resulted in a total of 1,530 motifs mapping to 1,515 different transcription factors. We developed and utilized Transcriptional Regulatory Network Analysis (TReNA), available as an R Bioconductor package. Gene regulatory regions in our model were obtained through Genehancer, enabling inclusion of all known enhancer regions. TReNA utilizes an ensemble of machine learning techniques, including lassopv, square root lasso (flare) and randomForest to prioritize transcription factors based on the expression levels in RNA-seq for each target gene. All resulting scores are scaled and normalized into a composite score, ranking transcription factors for each target gene. **Results** Our TRNs contain a prioritized list of putative transcription factor regulators for all genes. The footprints (and their genomic locations) allow us to integrate genetic information from GWAS or eQTL analysis to generate testable hypotheses around the functional annotation of variants. We have done this for all primary AD-associated loci from identified in GWAS. We have also identified putative targets for the AD-associated transcription factor MEF2C. We have identified multiple microglia-enriched transcription factors that regulate many differentially and co-expressed genes in AD, in particular, the AD-associated transcription

factor SPI1. **Conclusions** These resulting models can be applied to other datasets that generate lists of differentially or co-expressed genes as well as provide testable hypotheses for non-coding variants of interest. We are actively engaged in testing several hypotheses through experimental means and have made these TRNs publically available.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG030753
DOD Grant W81XWH-09-1-0107

Title: A multi-omic analysis of preclinical late-onset Alzheimer's disease: Integrating metabolomic, proteomic, and transcriptomic biomarkers from human peripheral blood

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Abstract: Late-onset Alzheimer’s disease (LOAD) is an age-related neurodegenerative disorder associated with progressive dysfunction of learning and memory. There are currently no validated clinical laboratory tests that prospectively assess risk of developing LOAD. Although specific biomarkers have been proposed, few discovery efforts have explicitly leveraged a systems biology, multi-omic approach to discovery and validation. Here, we report such an analysis of peripheral blood, contrasting cognitively healthy controls (Control = 50) with initially cognitively healthy individuals who developed memory impairment over a five-year observational study period (Converter = 26). We collected peripheral venous blood at entry to the study and analyzed blood plasma fractions for protein and small metabolite content using proteomic aptamer microarrays and targeted metabolomic mass spectrometry, respectively. We sequenced RNA obtained from buffy coat leukocytes. We modelled disease state (Converter vs. Control) as a function of the quantified biomolecules using the mixOmics DIABLO algorithm. Phosphatidylcholines (PCs) were depleted in the plasma of Converter samples compared to

controls, as previously reported from this cohort. Depletion of PCs correlated with altered transcripts that survived thresholding at the $r = .70$ level. Specifically, we found negative correlations between PC levels and two differentially expressed transcripts in Converter and Control samples. Considered individually, each -omics module submitted to analysis demonstrated highly favorable performance in its ability to distinguish Controls from Converters (ROC $AUC_{Protein} = 0.88$, ROC $AUC_{RNA} = 0.97$, ROC $AUC_{Metabolites} = 0.97$). These results expand upon our previous findings from this cohort in which we reported alteration of PC metabolism in preclinical AD. Here, we find that changes in the plasma metabolome are accompanied by relatively robust, disease-associated alterations in the blood transcriptome and proteome. Integration of these -omic levels may reveal biologically cohesive pathways underlying the pathobiology of preclinical LOAD. Further work is necessary to identify and validate causative factors driving these relationships.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

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Program #/Poster #: 466.11/F14

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: PO1 AG014449
RO1 AG043375
PO1 AG107617
R01 NS21072
R01 AG025970
Alzheimer's Association

Title: BDNF and TrkB hippocampal gene expression predict neurofibrillary tangle and neuritic plaque pathology during the progression of dementia

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Abstract: The neurotrophin brain-derived neurotrophic factor (BDNF) and its cognate neurotrophin receptor, TrkB, regulate several key brain functions involved in neuronal survival, neuroplasticity, and learning and memory. Defects in the expression of BDNF or activity of TrkB are found in several neurodegenerative disorders including mild cognitive impairment (MCI) and Alzheimer's disease (AD). Specifically, downregulation of BDNF and TrkB have been observed during the progression of dementia. However, whether alterations in BDNF and/or TrkB interact with AD pathological lesions, including neurofibrillary tangles (NFTs), neuritic plaques (NPs), and diffuse plaques (DPs) remains unknown. To determine the relationships between changes in Bdnf and TrkB mRNA with AD lesions, gene expression data was accrued from hippocampal CA1 pyramidal neurons and regional hippocampal and entorhinal cortex dissections from participants in the Rush Religious Orders study (RROS) who died with a premortem clinical diagnosis of no cognitive impairment (NCI), MCI, or AD. Negative binomial (NB) regression analysis revealed that downregulation of Bdnf was independently associated with increased hippocampal CA1 NFTs, whereas TrkB downregulation was independently associated with increased entorhinal cortex NFTs during the progression of dementia. A significant interaction was found between Bdnf and APOE e4 status with NPs indicating that e4 carriers with greater NFT pathology had lower Bdnf expression. DPs did not correlate with cognitive decline, consistent with the Bdnf and TrkB findings. Taken together, these results indicate that BDNF and TrkB dysregulation may be upstream of hallmark AD neuropathology, most notably hippocampal and entorhinal cortex NFTs. This study provides proof-of-concept that individual transcripts within a functional gene ontology group (e.g., neurotrophins and neurotrophin receptors) can be used to predict (or be the outcome measure) associated with AD neuropathology. The significance of the possible temporal sequence of BDNF/TrkB deficits preceding neuropathological accumulation lies in its therapeutic potential. Several research laboratories, including our group, hypothesize that BDNF signaling deficits lead to selective vulnerability of specific neuronal populations, including hippocampal CA1 pyramidal neurons and cholinergic basal forebrain neurons within nucleus basalis subfields. These data suggest attenuating BDNF/TrkB signaling deficits either at the level of BDNF, TrkB, or downstream of TrkB signaling may potentially abrogate NFTs and/or NPs.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

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Program #/Poster #: 466.12/F15

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: RO1 AG043375

PO1 AG107617
PO1 AG014449

Title: Quantitative assessment of endosomal characteristics within basal forebrain cholinergic neurons (BFCNs) in trisomic mice following maternal choline supplementation (MCS)

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Abstract: Down syndrome (DS) is the most common non-lethal chromosomal disorder in humans. By early middle age most DS individuals develop the pathological hallmarks of Alzheimer's disease (AD). These include the formation of amyloid-beta plaques, neurofibrillary tangles, and the presence of abnormally enlarged early endosomes. The Ts65Dn mouse model of DS/AD recapitulates key aspects of DS and AD pathology, including cognitive deficits in learning and memory, aberrations within the endosomal-lysosomal system, and degeneration of basal forebrain cholinergic neurons (BFCNs). We hypothesize that BFCN degeneration is due to deficient neurotrophic support within the septohippocampal circuit. We have previously reported that maternal choline supplementation (MCS) was able to improve neuronal size, shape, and density of septohippocampal neurons in young and aged Ts65Dn mice, as well as attenuate the overexpression of several genes involved in endosomal-lysosomal pathways. We therefore postulate that MCS will improve the efficiency of septohippocampal endosomal transport. To determine whether MCS treatment can significantly improve endosomal defects in BFCNs, we are conducting unbiased regional surveys of early endosomes in Ts65Dn mice and their normal disomic (2N) littermates at two time-points: 3-4 months of age and 10-12 months of age. BFCNs within the medial septal nucleus (MSN) and the vertical limb of the diagonal band (VDB) are dual labeled with antibodies directed against choline acetyltransferase (ChAT) and rab5, a cholinergic marker and an early endosomal marker, respectively. To determine whether MCS has an effect on early endosome pathology, quantitative analysis of vesicular attributes such as rab5-immunoractive endosomal area and cellular localization are performed in three-dimensional (3D) space using Imaris 9.1 software (Bitplane). Morphometric analysis of BFCN size and shape, as well as unbiased neuronal counts and density measurements will be performed using 3D reconstruction of z-stacks encompassing the entire soma of ChAT-immunoreactive MSN/VDB BFCNs to assess the impact of MCS treatment on the structure and function of the septohippocampal circuit. Preliminary results support the use of this quantitative scheme for accurate assessment of endosomal counts and volume within these vulnerable neurons that may respond to the nontoxic, well tolerated nutrient choline. MCS treatment may prove useful as an intervention for cognitive deficits and neuropathological alterations within the septohippocampal circuit associated with DS and AD, and we posit that this benefit is due in part to normalizing early endosome abnormalities.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

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Topic: C.02. Alzheimer's Disease and Other Dementias

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PO1 AG014449
BrightFocus Foundation
R01 AG21912
U01 AG051412
R01 HD065160

Title: Differential expression signature in cortical p-tau-containing pyramidal neurons between demented and non-demented Down syndrome subjects

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Abstract: Down syndrome (DS) is a genetic disorder characterized by intellectual disability and accompanied by phosphorylated tau protein (p-tau) containing neurofibrillary tangles (NFTs) and amyloid-beta (Aβ) plaques by the third decade of life. But not all middle-aged to aged individuals with DS will develop Alzheimer's disease (AD) type dementia. Recently, we found that DS subjects with dementia displayed a significant increase in the phosphorylated NFT burden in frontal cortex compared to those without dementia, while Aβ plaque load was similar in both groups, suggesting that p-tau plays a pivotal role in the onset of dementia in DS. However, molecular mechanisms underlying cortical NFT formation and its association with dementia in DS remain unknown. Here, we assessed the genetic signature of frontal cortex glutamatergic pyramidal neurons containing the p-tau pre-tangle maker pS422 in layers V-VI obtained from DS subjects with AD-like dementia (DS-AD; n=10) and without dementia (DS; n=5) using a combination of laser capture microdissection and custom-designed microarray analysis. Quantitative analysis revealed that the DS-AD group showed significantly lower transcript expression of genes related to APP/Aβ/tau metabolism [β-secretase (*Bace1*), γ-secretase (*Ncstn, Psenen, Aph1a*), α-secretase (*Adam10*)] and tau (*Mapt5*) than DS without dementia. Glutamatergic gene transcripts encoding several subtypes and subunits of glutamate receptors [glutamate receptors (*Grm1, Grm5*), NMDA receptors (*Grin2b, Grin2d*), ionotropic receptors (*Grik2, Gria3*), glutamate receptor interacting proteins (*Grip1, Grip2*)] and mRNAs

related to cholinergic neurotransmission [acetylcholinesterase (*Ache)*, butyryl cholinesterase (*Bche*), muscarinic (*Chrm2, Chmr4*) and nicotinic receptors (*Chrna2, Chrna3, Chrna4, Chrna7*)] were downregulated in DS-AD compared to DS without dementia. In addition, gene related to cell death [TNF-1 (*Tradd*), tumor protein p53 (*Tp53*), caspase 6 (*Casp6*), BCL2-associated X (*Bax*), several cell cycle proteins (*Ccnb1, Ccnd1, Ccnd2*)], G-protein signaling (*Rgs2, Rgs3, Rgs4, Rgs9, Rgs10*), adenylate cyclase (*Adcy1, Adcy6*), homeobox 2 (*Emx2*), autophagy protein 5 (*Atg5*), proto-oncogene c-fos, *Jun* and factor EB (*Tfeb*) transcripts were downregulated in DS-AD compared to DS. Conversely, expression of the epigenetic gene *Sirt6* in DS-AD was greater than in DS. These data suggest that cortical pyramidal p-tau containing projection neurons display different genetic signatures between age-matched demented and non-demented DS, where glutamatergic, cholinergic and APP/Aβ/tau metabolism are critically compromised in demented individuals with DS.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

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PO1 AG107617
PO1 AG014449
R01 AG055328

Title: Single population RNA sequencing (RNA-seq) analysis of basal forebrain cholinergic neurons (BFCNs) within the medial septal nucleus in the Ts65Dn mouse model of Down syndrome and Alzheimer’s disease identifies unique transcriptional mosaics following maternal choline supplementation (MCS)

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Abstract: Individuals with Down syndrome (DS) develop basal forebrain cholinergic neuron (BFCN) and hippocampal CA1 pyramidal neurodegeneration along with synaptic loss, neurofibrillary tangles, and amyloid plaques similar to Alzheimer’s disease (AD) by the third

decade of life. Both AD and DS patients exhibit selective vulnerability of septohippocampal neurons during disease progression. Unfortunately, therapeutic intervention has thus far failed, likely due to the number of pathways affected and the information gap underlying the mechanism(s) driving this selective vulnerability. The Ts65Dn mouse model recapitulates cognitive and morphological deficits of DS and AD, including BFCN degeneration. Perinatal maternal choline supplementation (MCS) delivers increased choline to disomic (2N) and trisomic offspring through the dam during the entire brain development period. MCS improves behavioral phenotypes associated with DS/AD and protects BFCNs from neurodegeneration in the Ts65Dn model. However, changes in gene/encoded protein expression due to MCS within vulnerable septohippocampal neurons have not been characterized. We utilized high-throughput, single population RNA sequencing (RNA-seq) to assess expression level changes due to MCS treatment in BFCNs from the medial septal nucleus (MSN). Expression profiles from MSN BFCNs were generated by laser capture microdissection (LCM) to isolate ~500 choline acetyltransferase (ChAT)-immunoreactive neurons in adult Ts65Dn and 2N littermates from choline normal and choline supplemented dams. Successful cDNA library construction from this small input RNA source enabled RNA-seq on individual populations for downstream transcriptional analysis. This procedure allowed for quantitative analysis of mRNAs and noncoding RNAs (ncRNAs) to help understand mechanism(s) underlying neurodegeneration, and link these expression level changes to established pathological hallmarks and cognitive decline for therapeutic development in human DS and AD. Results showed that ~500 BFCNs is sufficient for cDNA library preparation for RNA-seq and we identified unique transcriptomic profiles for MCS and choline normal animals independent of genotype. We demonstrate expression level changes in several relevant gene ontology (GO) pathways within single populations of LCM-captured MSN BFCNs in the Ts65Dn model of DS and AD in conjunction with a noninvasive, nontoxic treatment, MCS. We will utilize these profiles to further understand the molecular and cellular underpinnings of selective vulnerability and resilience with the goal of preserving the septohippocampal circuit in DS and AD.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

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Bruce Ford and Anne Smith Bundy Foundation
AG005131

PRAP from Ministry of Science and Technology, Taiwan. 105-2917-I-564-085

Title: Mosaic APP genomic structural alterations in sporadic and familial Alzheimer's diseases

Authors: *M.-H. LEE[1], B. SIDDOWAY[1], G. E. KAESER[2], I. SEGOTA[1], W. J. ROMANOW[1], R. RIVERA[1], C. S. LIU[2], G. KENNEDY[1], T. LONG[1], J. CHUN[1]
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Abstract: Genomic mosaicism (GM) in human brains has been revealed in different forms including aneuploidy, DNA-content variation (DCV), copy-number variation (CNV), and single-nucleotide variation (SNV). The function of these somatic DNA variations is still largely unknown. Alzheimer’s disease (AD) is a devastating neurodegenerative disease leading to memory loss and cognitive decline. Inheritable mutations and gene dosage of amyloid precursor protein gene (*APP*) have been shown to cause familial AD (FAD). However, the etiology of sporadic AD (SAD), representing the vast majority of AD cases, is not fully understood. Previously, we reported somatic neuronal DCV and specifically, APP CNV increases in SAD frontal cortices. In this study, we further identified novel APP genomic structural alterations in AD frontal cortical neurons by a range of PCR-based and targeted genomic DNA pull-down methodologies. Enriched mosaic presence of *APP* structural variants in both SAD and FAD, compared to age-matched non-diseased brains, was explicitly demonstrated by genomic DNA *in situ* hybridization. These data indicate APP genomic structural alteration, a novel form of GM, is associated with SAD, and raise the possibility that GM may also play a functional role in FAD.
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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

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Program #/Poster #: 466.16/F19

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: P01AG 14449

Title: Cortical regional specific telomere length reduction during the progression of AD

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Abstract: Telomeres are a special protective cap located at the terminal end of a chromosome, their DNA is highly conserved cross species and prevents chromosomal fusion, recombination and degradation. In humans, telomeres which contain a series of DNA repeats (5'-TTAGGG-3') are considered as a potential biomarker of aging. Several studies reported shorter telomere length in peripheral blood mononuclear cells, T-cells and leukocytes in Alzheimer's disease (AD) compared to normal controls. Reports indicate that telomere length differ between brain region in AD. For example, telomere length is longer in the hippocampus but not change in the cerebellum in AD compared to normal controls. To explore alterations in telomere length, we examined frozen tissue from forty-eight precuneus cases with a premortem clinical diagnosis of no cognitive impairment (NCI) (n=23, M/F=12/11, age: 86.69 ± 5.64), mild cognitive impairment (MCI) (n=13, M/F=4/9, age: 88.96 ± 4.22) and AD (n=12, M/F=5/7, age: 89.84 ± 6.05) and forty-three visual cortex samples (NCI: n=16, M/F=6/10, age: 87.2 ± 5.76 ; MCI: n=13, M/F=3/10, age: 89.96 ± 3.93 ; AD: n=14, M/F=4/10, age: 90.63 ± 4.61) to measure telomere (T reaction) and 36B4 (S reaction) by quantitative polymerase chain reaction (qPCR). T/S ratio was used to estimate the telomere length. The results showed that precuneus telomere length was shorter in MCI ($p<0.001$) and AD ($p=0.001$) compared to NCI. Telomere length did not change between the MCI and AD cases ($p=0.6$).Telomere length showed no significant group differences when compared with Consortium to Establish a Registry for Alzheimer's Disease diagnosis (CERAD) ($p = 0.48$) and Braak stage ($r= -0.20$, $p =0.16$). Telomere length was correlated with Mini-Mental State Examination (MMSE) ($r=0.48$, $p<0.001$), Global Cognitive Score (GCS) ($r=0.47$, $p<0.001$), Episodic Memory ($r=0.41$, $p=0.004$), Working Memory ($r=0.34$, $p=0.02$) and Perceptual Speed ($r=0.41$, $p=0.004$). By contrast, visual cortex telomere length did not differ significantly between NCI, MCI and AD groups ($p=0.25$) or by CERAD diagnoses ($p=0.11$). Visual cortex telomere length did not correlate with any cognitive test score or Braak stage. The present findings reveals that telomere length was shorter in MCI and AD compared to NCI in precuneus but not in the sensory visual cortex and the former was related to cognitive decline during the progression of Alzheimer's disease.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 466.17/DP04/F20

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association AARG-17-533458
Gerstner Family Career Development Award
the Center of Individualized Medicine at the Mayo Clinic

Title: Utilization of quantitative digital pathology and RNA-sequencing to uncover molecular underpinnings of selective hippocampal vulnerability in Alzheimer's disease variants

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Abstract: Alzheimer's disease (AD) neuropathologic patterns of neurofibrillary tangles are used to classify AD subtypes, which we termed hippocampal sparing (HpSp), typical, and limbic predominant. Utilizing a translational neuropathologic approach, we assessed the genetic contribution to selective vulnerability of the hippocampus in AD. The HpSp and limbic predominant AD cases were assessed as extreme phenotypes, which was complemented by comparison of controls and typical AD cases as enhanced phenotypes. RNA-sequencing was used to uncover gene expression changes associated with phenotype differences. We validated our findings in a larger cohort using NanoString and examined relevance to hippocampal neuropathology. RNA-sequencing was performed in 40 autopsy-confirmed AD subtypes and 15 controls. Validation with NanoString and quantification with digital pathology were performed in 158 AD cases and 32 controls. To prioritize genes, we employed bioinformatics methods to examine differential expression, enrichment of cellular process networks, and known AD target genes. We prioritized 52 genes from our RNA-sequencing studies to be validated using NanoString. We quantified digital pathology measures of early tangles (CP13), mature tangles (Ab39), amyloid-β burden (33.1.1), neuronal loss (H&E) and markers for microglia (CD68), endothelia (CD34), and astroglia (GFAP).Using a translational neuropathologic approach combined with deep learning based prediction models; the *SLC38A2* gene was nominated in the top gene using a multi-way importance model. The *SLC38A2* gene was originally prioritized in our RNA-sequencing data as it was found to be enriched in the sodium transport network and found differentially expressed between controls and typical AD (FDR=0.002, $p<0.00001$). RNA-seq gene expression measures validated well with NanoString for *SLC38A2* ($R=0.982$, $p<0.001$). Regression analysis was used to examine the contribution of demographics, tau and amyloid burden, neuronal loss and glial pathology. Early tau (Estimate=0.35, p=0.03) and late tau measures (Estimate=0.02, p=0.009) significantly predicted gene expression, but not amyloid measures or neuronal loss. Microgliosis approached significance (Estimate=0.35, p=0.03), but with no contribution from endothelial cell burden or astrogliosis. Age approached significance as a predictor of SLC38A2 gene expression (Estimate=-0.11, p=0.06), but not sex (Estimate=0.03, p=0.81) or *APOE* ε4 (Estimate=0.17, p=0.13). Our data supports consideration of intra-disease

divergence with regard to case stratification and may reveal genes previously masked by heterogeneity of cohorts.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

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Program #/Poster #: 466.18/F21

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Cure Alzheimer’s Fund
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Title: PICALM variant rs3851179^{A} has a protective role in neurons against Aβ toxicity

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Abstract: Increasing Genome wide associational studies (GWAS) have proposed phosphatidylinositol-binding clathrin assembly protein (PICALM) highly associates with late-onset Alzheimer’s disease (AD). PICALM can bind to clathrin and lipoprotein receptor-related protein 1 (LRP1). Therefore, PICALM plays a very important role in clathrin-mediated endocytosis and participate the internalization and intracellular trafficking of cell surface receptors. We have previously reported that endothelial cells derived from human iPSCs carrying homozygous *rs3851179^{A}* alleles exhibited increased PICALM expression and improved transvascular clearance of Aβ across human blood-brain barrier (BBB) *in vitro,* when compared with isogenic cells from iPSCs carrying homozygous risk *rs3851179^{G}* alleles. In order to investigate *rs3851179^{A}* allele functions in neurons in Aβ toxicity and AD, we established direct differentiation protocol to generate human cortical neurons from iPSCs carrying different *rs3851179* alleles. Interestingly, Western blot analysis showed higher PICALM expression in iPSC-derived neurons carrying protective *rs3851179^{A}* allele compared to those carrying non-protective *rs3851179^{G}* allele. Then, we treated iPSC-derived neurons with Aβ oligomers. While Aβ treatment resulted in dramatical cell death and dendritic spine loss in homozygous *rs3851179^{G}* (GG) neurons, *rs3851179^{A}* (AA) neurons displayed a strong resistance to Aβ

toxicity. Currently, our data indicate that *rs3851179*^{A} (AA) provides PICALM with a protective role in neurons against Aβ toxicity. Next, we will confirm the function of *rs3851179*^{A} (AA) in Aβ toxicity and AD and address its molecular mechanism.
Funding sources: This work is supported by the Cure Alzheimer's Fund, and National Institute of Health grants AG023084, NS034467 to B.V.Z.
Keywords: PICALM, Aβ toxicity, Alzheimer's disease, iPSC-derived neuron.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

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Topic: C.02. Alzheimer's Disease and Other Dementias

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Title: Using large scale brain eQTL meta-analysis from multiple RNA-sequencing cohorts to identify neurodegenerative and neuropsychiatric risk candidate genes

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Abstract: Background: To date, hundreds of risk loci have been associated with neurodevelopmental, neuropsychiatric and neurodegenerative diseases. When risks are mediated through gene expression, eQTL can implicate the specific genes involved through colocalizing algorithms or global tests of case-control differences in the predicted gene expression. In each

case, eQTL from the relevant tissue are necessary to understand the specific expression patterns contributing to disease, which may not be captured in readily available tissue such as blood. Recently, several large initiatives, including the CommonMind Consortium (CMC), the Accelerating Medicines Partnership for Alzheimer's Disease (AMP-AD) and GTEx, have made high-quality data available from the RNA-sequencing and genotyping of post-mortem brain collections.
Methods: Here we generate the best-powered brain eQTL resource to date which spans multiple brain regions and diseases. In total, we have collected 5 cohorts from CMC and AMP-AD, comprised of tissue from approximately 2300 individuals and representing 4 brain regions, the largest collection of which is from dorsolateral prefrontal cortex comprised of 1800 samples. A common analysis pipeline was applied to each cohort. Samples were imputed to the Haplotype Reference Consortium panel. RNA-seq data was aligned and quantitated in a manner appropriate to sequencing protocol; and quantified expression was normalized, adjusting for available known clinical and technical covariates, and hidden confounders, prior to applying a linear model to detect eQTL, adjusting for inferred genetic structure and diagnosis. Meta-analysis across cohorts was then performed. The eQTL were then used to identify candidate genes underlying GWAS peaks for Alzheimer's Disease in the IGAP cohort.
Results: We identify more than 4.2 million proximal (distance ≤ 1 Mb) eQTL at FDR ≤ 5%, for more than 18,000 genes/lncRNAs. While the replication of GTEx eQTL is high (96.5%), we identify 4 million eQTL, for 15,500 genes, not identified in GTEx. Preliminary analysis identifies potential colocalizations underlying 9 GWAS peaks.
Conclusion: We have generated a well powered eQTL brain resource which is valuable for identifying genes contributing to the risk for neurodegenerative and neuropsychiatric disease.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

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Program #/Poster #: 466.20/F23

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: U54AG054345

Title: Systems biology-based method to identify and prioritize Alzheimer's disease candidate driver genes

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Abstract: Background:Late onset Alzheimer's disease (LOAD) is a debilitating illness with no known disease modifying treatment. Identification of new AD biology will be key to finding effective treatments. To better prioritize experimental evaluation of AD drivers, we present a data driven approach to rank genes based on their probability that they drive a molecular state associated with LOAD using transcriptional data collected from postmortem brain tissue.
Methods:We developed a machine learning model that uses analytic summaries of transcriptional data collected from postmortem brain tissue across three studies (ROSMAP, Mayo RNAseq, MSBB) in AMP-AD to prioritize driver genes. The model used: 1) differentially expressed gene sets, 2) global network topological features, and 3) module specific network topological features for 42 co-expression modules. First, we learned the unique characteristics of 27 previously known drivers of AD identified from published LOAD GWAS studies. Next, we used the model to predict a new list of high confidence driver genes and re-trained the model to account for the many unknown driver genes. Then, the model was retrained in an iterative manner until we converged on a set of high confidence genes. Finally, the predicted probability of a gene being a driver and the p-value of its most significant AD specific variant (using IGAP stage 1+2) was used to create a score.
Results:This analysis identified a set of 283 high confidence driver genes. This set of new candidate AD driver genes was significantly enriched for genes containing SNPs that were marginally associated with LOAD in the IGAP GWAS (p-value: 0.05). Further, many of the top scoring predicted genes (FAT4, HLA-DPA1, MTHFD2L, RBPMS and GDA) contain known SNPs with p-values lower than 0.0001 in the IGAP study.
Conclusions:Here, we provide a generalizable framework for integration of diverse systems biology outputs to rank and identify new transcriptomic and genetic drivers of Alzheimer's disease. This provides evidence that integration of multiple systems biology resources can provide insights into new Alzheimer's disease loci, which can help researchers prioritize future experimental studies focusing on specific genes and pathways that are driving disease etiology.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

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Program #/Poster #: 466.21/F24

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Cortical regions contributing to cognitive performance in age-related genetic polymorphisms

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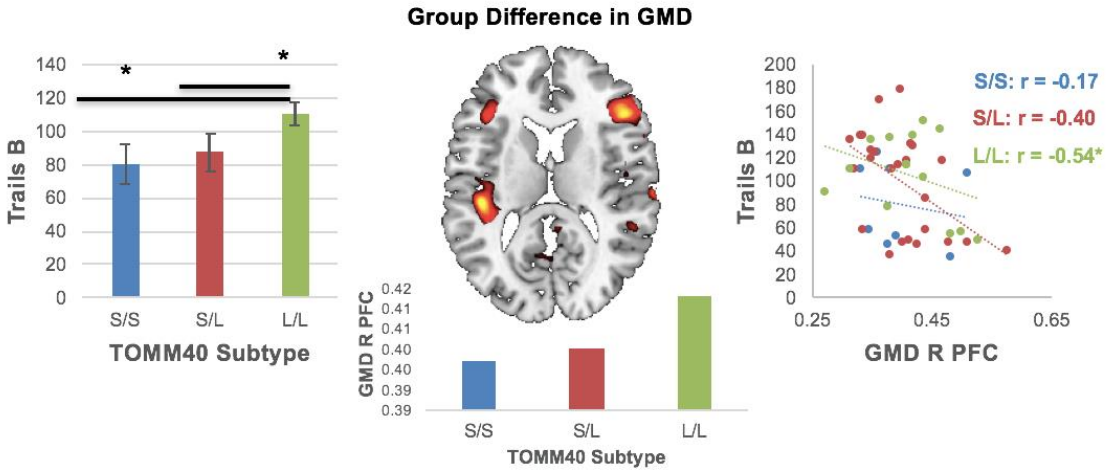
Abstract: Mitochondrial dysfunction is a fundamental characteristic of neurodegenerative diseases, including Alzheimer's disease. While the origin and underlying cause of mitochondrial dysfunction in AD has not been identified, it has been linked to specific genetic polymorphisms, including the TOMM (Translocase of the Outer Membrane) genotype. Specific TOMM40-APOE haplotypes have been associated with cognitive decline, including memory and executive decision making. However, the neural substrates underlying this selective deficit is currently unknown. We sought to address this problem by examining cognitive performance and whole-brain grey matter density (GMD) in cognitively normal individuals who were either homozygous for the VL- or L-poly T, homozygous for the short TOMM40 poly-T allele, or heterozygous individuals (controlling for APOE e3/e3 and e3/e4, age, and education). We found decreased executive function (as indexed by Trails B) in homozygous long TOMM40 individuals. GMD followed expected trends (S/S > S/L > L/L) in expected regions (e.g., PCC); surprisingly, L/L individuals showed greater GMD in a number of regions, including right prefrontal cortex (PFC). Critically, brain-behavior relationships were moderated by TOMM40 subtype, such that only L/L individuals showed a relationship between GMD and executive function. These results help to link brain-behavior relationships to specific polymorphisms to be dysfunctional in models of AD.



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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

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Program #/Poster #: 466.22/F25

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Effect of epigenetics and gender differences in mice expressing neuronal or glial aromatase

Authors: *G. AIT-GHEZALA[1], J. CUI[2], Y. SHEN[3], R. LI[2]
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Abstract: Memory dysfunction is characteristic of aging, neurodegenerative diseases such as Alzheimer’s disease, the most common dementia in elderly, is more prevalent in women than in men, Indeed, a sharp reduction of estrogen and progestins at menopause significantly increases the risk of memory decline and Alzheimer’s disease in middle-aged women relative to men. One of the risk factors is related to the in aged women. It is unknown whether epigenetics has any role in altering risk of AD in females, such as altering cognitive function. For instance, it has been shown that hippocampal memory formation is highly regulated by post-translational histone modifications and DNA methylation. In addition, Both aging and Alzheimer’s disease are illustrated by hypermethylation at specific CpG islands in the hippocampus and neocortex. However, gender differences never been established and how these epigenetic sequences affect modulatory influences, such sex hormones, on hippocampal memory never been fully investigated.
In addition, limited human studies of early pregnancy and motherhood showed alteration of cognitive functions in later life, however, researches on rodents showed a persistent improvement of learning and memory performance in females with history of giving birth compared to virgin controls. Thus, in the current study we investigated the effect of epigenetics and gender differences in mice expressing neuronal or glial Aromatase in comparison to age matched wild type mice. Our data provide valuable insight into how sex hormones employ

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

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Program #/Poster #: 466.23/F26

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Nference target identification for Alzheimer’s disease

Authors: *T. WAGNER[1], S. EBRAHIM[2]
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Abstract: Objective: Effectively treating Alzheimer’s Disease (AD) will necessitate understanding and targeting multiple distinct phenotypes. The nference Biomedical Knowledge Synthesis Platform (nferX) uses a proprietary neural network to identify significant associations between concepts in literature. nferX can be leveraged target discovery engine for such complex diseases because it can connect concepts at a large scale. Rather than looking at a single gene or pathway as a target for AD treatment, nferX can simultaneously assess all genes and all pathways. Additionally, nferX can make novel connections between concepts that may have never been explicitly linked together in literature.
Approach: A modular approach using the nferX platform identified genes significantly associated with AD phenotypes and disease terms, split into categories termed modules. A semantic score was calculated for each gene, based on the percentage of significant associations a gene had within each module. Biological datasets (i.e. gene expression studies, microarrays, and SNPs) were layered on top of these semantic results to provide additional evidence supporting potential AD targets. We applied thresholds for a significant level of association and signal within these datasets to reduce the list of targets. Clustering approaches were employed to group targets into classes. Additional filters, such as the number of articles in the literature (i.e. novelty), or alternative weights for each semantic module can be applied to prioritize other aspects of the gene-disease association. While our approach can be used to rank curated lists of targets, the primary value of nferX is providing highly actionable targets and illuminating “blind spots” in the current pre-clinical and clinical landscape. Thus, we compared the pathways enriched in our targets to those currently in clinical trials for AD.
Conclusions: we have used nferX to couple literature associations and molecular signals to arrive at a list of AD targets comprised of both known and novel genes. We have used this list to rank current clinical AD targets and identify novel targets of interest. Finally, we have identified blind spots in current AD landscape, as well as drugs that could potentially address these needs.

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holder, excluding diversified mutual funds); nference, inc. **S. Ebrahim:** A. Employment/Salary (full or part-time):; nference, inc..

Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 466.24/G1

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Profiling microRNA form brain by microarray in a transgenic mouse model of Alzheimer's diease

Authors: *L. WANG[1], R. LIU[1], H. JIANG[1], J. ZHANG[1], S. GUO[2], L. MIN[2], Q. GUO[2]
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Abstract: MicroRNAs (miRNAs) are small non-coding RNAs, which regulate numerous cell functions by targeting mRNA for cleavage or translational repression, and have been found to play an important role in Alzheimer’s disease (AD). Our study aimed to identify differentially expressed miRNAs in AD brain as a reference of potential therapeutic miRNAs or biomarkers for this disease. We used amyloid precursor protein (APP) and presenilin 1 (PS1) double transgenic mice and age-matched wide-type (WT) littermates to determine the expression of miRNAs in the brain. MiRNAs were profiled by microarray, and differentially expressed miRNAs underwent target prediction and enrichment analysis.
Microarray analysis revealed 58 differentially expressed miRNAs in AD mouse brain, which involved 39 miRNAs that were significantly up-regulated and 19 that were down-regulated at different ages. Among those miRNAs, a total of 11 miRNAs, including miR-342-3p, miR-342-5p, miR-376c-3p, and miR-301b-3p, was not only conserved in human, but also predicted to have targets and signaling pathways closely related to the pathology of AD.
To explore the potential functions of the 11 selected miRNAs, GO and KEGG pathway analyses were performed to elucidate the biological function. GO terms covered 3 domains: molecular function, biological process, and cellular component. Nervous system development was significantly enriched GO terms at molecular function domain. Moreover, the 10 most significantly enriched pathways mapped with KEGG pathway analysis including MAPK signaling pathway, endocytosis, TGF-beta signaling pathway, and the Wnt signaling pathway are closely connected with AD.
In conclusion, in this study, differentially expressed miRNAs were identified in AD brain, and proposed as biomarkers, which may have the potential to indicate AD progression. Although

preliminary, these results may aid in investigating pathological hallmarks and identify effective therapeutic targets.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

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Program #/Poster #: 466.25/G2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA grant R01AG054180
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UTHSC Neuroscience Institute

Title: Genetically diverse AD model identifies dipeptidyl peptidase 7 as a novel modifier of cognitive function

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Abstract: Recent studies of familial AD cases suggest genetic modifiers may delay the onset and progression of AD symptoms by decades. However, specific genetic modifiers and mechanisms involved in providing protection against high-risk AD mutations remain largely unknown. Unfortunately, resilience to AD has generally been difficult to study in human populations, as the number of patients with causal mutations is relatively small and unaffected individuals rarely enter the clinic. As genetic factors promoting resilience may provide key targets for prevention of AD, our lab has recently developed a novel panel of genetically diverse mice harboring five causal human FAD mutations in *APP* and *PSEN1* to address this significant question. We have evaluated cognitive function across this panel (termed the AD-BXDs), and corresponding non-transgenic littermate controls (Ntg-BXDs), throughout the lifespan using a battery of memory tests, and have found that the genetic background of each individual strain has a profound effect on the penetrance of FAD mutations. Using genetic mapping, a significant quantitative trait loci (QTL) containing gene variants that modify severity of contextual fear memory (CFM) deficits across both AD- and Ntg-BXD mice at 6 and 14 months of age was identified, using sex, age, and genotype as covariates in the model. Dipeptidyl peptidase 7 (*Dpp7*) was identified as the

most likely positional candidate involved in modifying cognitive function due to strong correlation with CFM ($r = -0.4$, $p < 0.001$), presence of local variants affecting expression (cis-eQTL, LOD = 7.7, $p < 0.05$), and upregulated expression in AD mice relative to Ntg mice ($log_2FC = 0.4$, adj. $p < 0.001$). To test the hypothesis that *Dpp7* is causally involved in regulating CFM, adeno-associated viral serotype 9 (AAV9) vectors encoding either cDNA for *Dpp7* or an eGFP control were delivered into the hippocampus of adult (4m) 5XFAD mice. Eight weeks later, mice were trained on contextual fear conditioning and we found that overexpression of *Dpp7* significantly enhanced CFM [$t(1,15) = 2.6$, $p = 0.02$, n = 7-10/grp], suggesting that *Dpp7* may promote cognitive resilience in AD. Ongoing work in the lab will investigate the mechanism of this enhancement, assess the utility of *Dpp7* as a therapeutic target to prevent or delay the cognitive decline typically observed in AD, and evaluate the effect of *Dpp7* overexpression in Ntg mice. Overall, work presented here demonstrates the utility of incorporating genetic diversity into animal models of disease in order to identify novel gene variants that are causally involved in modifying susceptibility to cognitive deficits.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 466.26/G3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Ressler/Gertz Foundation

Title: Cell-type specific transcriptomics using viral TRAP to identify neuron-glial relationships in neurodegeneration

Authors: *Y. KOMURO, M. MACHNICKI, S. CARMICHAEL, J. D. HINMAN
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Abstract: The inciting pathogenic events in Alzheimer’s disease remain unknown, and increasing evidence suggests that multicellular interactions may be antecedent to classic pathology. One possible approach for identifying relevant and novel pathways for multicellular interactions in Alzheimer’s disease is to study variance in spatial and temporal gene expression patterns within and between cell types. Transcriptomics allows increasing power to quantify and analyze these patterns and can provide an unbiased entry point for identifying disease-relevant genes and pathways. Single-cell and whole tissue post-hoc gene expression approaches are insightful but limit the sequencing depth or spatiotemporal accuracy of transcriptional profiling. In this study, we characterize novel viruses that utilize translating ribosome affinity purification

(TRAP) in a cell-type specific manner for rapid collection of cell-type specific RNA transcripts and subsequent sequencing. The engineered lentiviruses and adeno-associated viruses express an HA-tagged ribosomal protein (Rpl10a-HA) driven by a cell-type specific promoter (CamKII, GFAP, or PDGFRa). We demonstrate the utility of the viruses for targeting specific cell types under particular spatiotemporal conditions and the ability to sequence the transcripts at high depth. Following injection into an in vivo mouse model, RNA sequencing indicated that the viruses were expressed with high specificity in the target cell types. Furthermore, quality control measures showed that the rapidly-isolated RNA was robust in both quantity and quality, allowing for a high sequencing depth. These results establish viral TRAP as a promising tool for cell-type specific transcriptomics. In this manner, viral TRAP methodology may increase the utility of transcriptomics for novel pathway identification in multicellular transcriptional profiling of neurodegenerative processes.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA 1 R01 AG057914-01 to C.C.K.
NIA 1 R01 AG054180-01A1 to C.C.K

Title: Central nervous system-mediated sensorimotor decline in a novel transgenic mouse model of Alzheimer’s disease

Authors: *G. G. ACOSTA[1], S. M. NEUNER[1,2], A. R. OUELLETTE[1], N. BACHELDER[1], K. M. S. O’CONNELL[1], C. C. KACZOROWSKI[1]
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Abstract: Alzheimer’s disease (AD) often presents with multiple non-cognitive comorbidities including sensorimotor deficits, significantly impacting the quality of life for patients and caregivers. Mechanisms underlying these multifactorial symptoms are poorly understood, yet their identification will be critical to find and develop effective therapeutic targets. We recently developed a novel panel of genetically diverse mice harboring five causal human familial AD mutations (AD-BXDs) and have previously demonstrated differential susceptibility to cognitive symptoms of AD. Here, we assessed effects of aging and AD mutations on a battery of sensorimotor tasks. Both aging non-transgenic and AD mice showed overall sensorimotor impairment relative to young mice, suggesting aging alone worsens motor function. However,

AD-BXD mice showed an exacerbated decline in motor coordination tasks requiring CNS involvement (negative geotaxis, narrow beam), but not grip strength. Additionally, AD-BXD females showed worsened negative geotaxis compared to males. Interestingly, motor deficits did not correlate with cognitive deficits, suggesting that these deficits may be regulated by distinct mechanisms. This is the first study examining effects of aging and AD mutations on sensorimotor performance in a large panel of genetically diverse mice (n=25 strains, 833 mice) that better model human genetic diversity. Our results parallel motor deficits reported in human AD and in previous transgenic AD mouse models. Ongoing genetic mapping studies will identify modifiers of motor deficits in our mouse panel and evaluate their utility as potential therapeutic targets. Results here provide insight into mechanisms of non-cognitive deficits associated with AD and provide a more complete understanding of AD pathophysiology.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

Location: SDCC Halls B-H

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Program #/Poster #: 466.28/G5

Topic: C.02. Alzheimer's Disease and Other Dementias

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NIA R01 AG054180-01A1
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Title: Gene-by-diet interactions modify symptoms of Alzheimer's disease

Authors: *A. DUNN[1], A. R. OUELLETTE[1], S. M. NEUNER[2,1], K. M. S. O'CONNELL[1], C. C. KACZOROWSKI[1]
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Abstract: Alzheimer's disease (AD) is complex, with both genetic (G) and environmental (E) factors regulating disease progression. Identification of gene-by-environment interactions that modulate AD pathogenesis is critical to developing novel and personalized treatments. However, extracting GxE effects is challenging in humans due to human genome complexity and difficulty controlling environmental factors, such as diet. To overcome these barriers, we developed a panel of genetically diverse mice carrying the 5XFAD transgene which contains five human familial AD mutations (AD-BXDs). Because the AD-BXDs model some of the genetic heterogeneity of humans, they are ideally suited to investigate translationally-relevant GxE

interactions. Here, we used AD-BXDs to determine how genetics and diet interact to modify AD-related pathogenesis. To determine the effect of genetic background, diet, and gene-by-diet interactions in AD-related metabolic and cognitive traits, we fed a high fat diet (HFD; 45% fat by calorie) to 10 strains of AD-BXDs for eight weeks and monitored metabolic and cognitive function before and after HFD. Control groups included AD-BXDs on chow, and nontransgenic BXDs on chow and HFD. We observed accelerated working memory decline in AD-BXDs on HFD compared to controls after eight weeks on HFD. However, this was dependent on genetic background and genetic risk for AD, with some AD-BXD strains maintaining cognitive function on HFD. Subsequent analyses indicated gene-by-diet interactions accounted for 18% of individual variation in memory decline in transgenic AD-BXDs on 8 weeks of HFD. Higher body weight and adiposity were protective against working memory decline in nontransgenic BXDs, but not in AD-BXDs. Our results suggest that diet and genetic background interact to mediate vulnerability to AD pathogenesis, and that metabolic factors (e.g., obesity, body composition, glucose metabolism) may contribute to cognitive decline differentially in normal aging versus AD. Ongoing work is examining the effects of longer-term HFD on cognitive and metabolic function in the AD-BXDs, as well as differences in hippocampal gene expression that may contribute to differential cognitive effects of HFD. The sizable contribution of gene x diet effects on cognitive decline in the AD-BXDs suggests that the mechanisms underlying cognitive decline in response to HFD are ripe for discovery. Future analyses will build upon these data to identify genetic and molecular targets contributing to AD pathogenesis sensitized by a HFD that may be exploited to delay, prevent or treat AD.

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Poster

466. Alzheimer's Disease and Other Dementias: Genetic Analysis and Omics Approaches

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A2016397S

Title: Systems genetics reveals microglia involvement in resilience to Alzheimer’s disease

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Abstract: In Alzheimer's disease (AD), the age of symptom onset is highly variable, with some patients exhibiting cognitive symptoms several decades later than predicted based on family history and genetic status. This variability cannot be explained by simple clinical or environmental factors, suggesting that additional genetic factors modify disease onset. The identification of modifier genes that confer resilience in high-risk patient populations would reveal new mechanisms and thus therapeutic strategies to delay disease onset. Disease-relevant genetic variants are difficult to identify in human populations, primarily because asymptomatic individuals rarely enter the clinic. Mouse models represent an ideal complement to human studies, as they present many advantages, such as defined genotypes, early access to brain tissue, and precise environmental control. However, the traditional mouse models of AD have failed to translate into successful treatments that improve cognition in humans. Here, we employ a novel AD mouse genetic reference panel, designed to overcome some of the barriers presented by current AD models. Analyses of whole-genome RNA expression from the hippocampus using a variety of bioinformatics approaches including differential expression, gene set enrichment, principal component, and Pearson's correlations revealed a strong negative association between microglia transcriptional signatures and cognitive resilience to AD, when assessed using a variety of memory tasks. Overall, work here introduces a humanized mouse population as an innovative and reproducible resource for the study of AD and identifies a core set of microglial genes as novel therapeutic targets to promote cognitive resilience to AD.

Disclosures: S.E. Heuer: None. **S.M. Neuner:** None. **M.J. Huentelman:** None. **K.M.S. O'Connell:** None. **C.C. Kaczorowski:** None.

Poster

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Topic: C.02. Alzheimer's Disease and Other Dementias

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NIH Grant R01AG054180
NIH Grant R01AG057914
Brightfocus A2016397S
NIH Grant F31AG050357

Title: Hypothalamic dysfunction in the etiology of Alzheimer's disease

Authors: *K. O'CONNELL[1], T. MCMURPHY[1], A. DUNN[1], S. NEUNER[2], C. C. KACZOROWSKI[1]
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Abstract: For a patient diagnosed with Alzheimer's disease (AD), there exist no treatments to prevent, slow, or halt disease progression. Memory loss and cognitive decline are hallmarks of AD, thus current research is focused on CNS regions relevant to learning and memory, such as the hippocampus. However, one of the most consistently reported non-cognitive symptoms in AD patients is weight loss, which may precede the onset of dementia by up to 17 years. Thus, dysfunction in CNS regions regulating metabolism and energy balance, such as the hypothalamus, may represent some of the earliest causative changes associated with AD. Here, we used our novel mouse model of genetic diversity in AD (AD-BXDs), which combines high-risk familial AD mutations with a well-established background of genetic diversity, to investigate complex interactions between genetic background, age, and energy homeostasis. To determine the relationship between body weight and cognitive decline, we measured body weight and working memory in 25 strains of female AD-BXDs and their non-transgenic littermate controls (Ntg-BXDs) and 17 strains of male AD/Ntg-BXDs across the lifespan. Working memory was assessed using Y-maze task; the age at which performance dropped below 50% was designated the age of onset for cognitive decline. At 2 months of age, AD and Ntg-BXDs exhibit similar body weights, but by 6 months, the AD-BXD mice begin to significantly diverge from the Ntg-BXDs, preceding cognitive decline by 3 months. Further, in AD-BXDs (but not Ntg), body weight at 6 months was significantly correlated with long-term memory at 14 months, suggesting this is specific to AD and not a general feature of aging. We also found that there is amyloid deposition in the hypothalamus that is closely associated with Iba-1^{+}microglia, therefore on-going experiments are testing a specific role for the hypothalamus in AD pathogenesis using a mouse model that expresses Aβ exclusively in the hypothalamus to determine the impact of hypothalamic dysfunction in both cognitive and non-cognitive symptoms of AD. The hypothalamus is understudied in the context of AD; the present work is well-poised to directly test the causality of hypothalamic dysfunction in AD using well-controlled model systems with high translational relevance.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.01/G8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA U54 AG054345-01

Title: Novel models of late-onset Alzheimer's disease

Authors: *M. SASNER[1], H. WILLIAMS[1], A. OBLAK[2], C. PREUSS[1], B. LOGSDON[4], K. NHO[3], A. J. SAYKIN[3], S. J. SUKOFF RIZZO[1], P. R. TERRITO[3], B. T. LAMB[5], G. CARTER[1], G. HOWELL[1]
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Abstract: The Alzheimer's Disease (AD) patient population consists almost entirely (~98%) of the late-onset form of AD (LOAD); however, most animal models currently used to develop therapies for AD are based on familial AD (fAD) mutations in *APP*, *PSEN1* or *PSEN2*. This may contribute to the lack of translation to the clinic for therapeutic agents being evaluated in preclinical studies. The Model Organism Development and Evaluation for Late-onset AD (MODEL-AD) Center was created to develop, characterize, and distribute more precise preclinical models for LOAD. Our approach is to engineer mouse models to express combinations of genetic variants identified in human LOAD patient populations. This strategy integrates human and mouse data, with the purpose of creating new AD models with a high degree of preclinical translatability for novel therapeutic targets.
Since the *APOE4* allele and variants at the *TREM2* locus are among the strongest genetic risk factors for LOAD, we first created a homozygous model expressing humanized *APOE4* and the R47H allele of the *Trem2* gene. This model exhibits altered metabolic phenotypes and neurovascular deficits. We then generated a humanized *APP* model on this background by altering the three amino acids that differ between human and mouse Abeta42, as the human protein may be more prone to aggregate.
Additional genetic variants have been prioritized in loci previously identified by GWAS using data from the ADNI and ADSP projects. These variants have been engineered into the APOE4/Trem2*R47H model to increase the risk of developing AD-like phenotypes. We have created mouse models expressing SNPs corresponding to risk variants in *ABCA7, MTHFR and PLCG2*, knockouts of mouse *Il1rap* and *Ceacam1* and a knock-in model expressing human *CR1*. In addition, we have generated *APOE3* and *APOE2* variants to serve as controls.
The new models are aging for phenotypic studies. We will present validation data including transcriptomics, pathology, and functional assays, with new models being compared to both fAD models and clinical samples.
All new models will be made available for both academic and for-profit use from The Jackson Laboratory, and all validation data will be shared via the AMP-AD knowledge portal (www.synapse.org/alzheimers). We seek input and collaborations from the basic research and pharma/biotech communities. For more information see www.model-ad.org .

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

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Topic: C.02. Alzheimer's Disease and Other Dementias

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Alzheimer’s Association AARF-16-440760
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LLHF grant 2016-A-016-FEL

Title: hAb-KI: A knock-in mouse model for sporadic Alzheimer's disease

Authors: *S. FORNER[1], D. BAGLIETTO-VARGAS[1], L. TRUJILLO-ESTRADA[1], A. CADETE MARTINI[1], E. A. KRAMAR[2], S. JIANG[3], D. MATHEOS[2], C. DA CUNHA[1], K. C. GREEN[1], M. A. WOOD[2], A. MORTAZAVI[3], G. R. MACGREGOR[3], A. J. TENNER[1], F. M. LAFERLA[1]
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Abstract: The majority of Alzheimer’s disease (AD) cases are sporadic, which means that the disease originates spontaneously without any known cause. To date, no lab has succeeded in developing a model for sporadic AD, which represents one of the consequential hurdles remaining in the field. Thus, it is critical to study and elucidate factors and conditions that trigger the disease in the 98% of patients that lack the known mutations that cause familial AD (FAD). Here, we introduce a novel animal model of sporadic AD (hAß-KI), in which the mouse Aβ encoding DNA sequence was replaced with the human Aβ sequence (which is known to more readily aggregate than the mouse Aß). We used a combination of genetic, biochemical, histological and behavioral approaches to generate and characterize this innovative AD model. DNA sequence analysis demonstrated that hAβ-KI express humanized Aβ and that expression of amyloid precursor protein (APP) was similar between wild type and hAβ-KI mice. hAβ-KI present with diffuse Aβ aggregates from 18 months of age and no Congophilic or ThioS aggregates were observed. Cognitive deficits begin at 10 months in hAβ-KI and long-term potentiation (LTP) deficits is observed at 18 months of age. A highly innovative aspect of this study is that we generated the first Knock-in mouse that express human non-mutated Aβ in the fully natural context of the endogenous mouse App gene and without the addition of any FAD

mutations or overexpression of APP or its metabolites. This mouse model should enable a more physiologically relevant understanding of the underlying mechanisms driving AD pathology, by more closely recapitulating the pathological cascade of events that occurs in the majority of human AD patients.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA AG054345

Title: MODEL-AD: Late-onset Alzheimer’s disease models

Authors: *A. OBLAK, H. WILLIAMS[1], M. SASNER[1], D. BAGLIETTO-VARGAS[2], M. A. WOOD[3], S. A. MORTAZAVI[5], K. N. GREEN[6], S. FORNER[4], G. CARTER[1], S. RIZZO[1], P. R. TERRITO[7], G. MACGREGOR[5], G. R. HOWELL[9], A. J. TENNER[10], F. M. LAFERLA[11], B. LAMB[8]
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Abstract: Alzheimer’s disease (AD) is an irreversible, progressive brain disorder that slowly destroys memory and cognition, and eventually the ability to carry out the simplest tasks. In most people with Alzheimer’s, symptoms first appear in their mid-60s. Estimates vary, but data suggest that more than 5 million Americans may have AD. Most of diagnosed cases (>95%) are late-onset AD (LOAD). One of the obstacles to developing compounds to treat AD may be that models currently used for preclinical testing are based on familial mutations, which account for less than 5% of all AD cases. The Model Organism Development and Evaluation for Late-onset AD (MODEL-AD) Center has been established as a consortium consisting of Indiana University, The Jackson Laboratory, University of California-Irvine and Sage Bionetworks with the purpose

of creating animal models of LOAD that can be used to develop therapeutics to prevent AD. Therefore, MODEL-AD aims to: identify and prioritize novel genetic variants, genes and biomarkers from AD patient data; generate and validate new animal models based on LOAD variants; and utilize these novel models in a preclinical testing paradigm. The consortium consists of multiple cores at each site. The Bioinformatics and Data Management Core (BDMC) prioritize novel sequence variants, create analytical pipelines for human-mouse phenotype comparisons, and analyze phenotypic data. The Disease Modeling Project (DMP) creates new mouse models based on variants identified by the BDMC, and validates them by comparing to quantitative measures (e.g. transcriptomics) to clinical data. The Preclinical Testing Core (PTC) evaluates novel compounds in new models with an AD-like phenotype based on a tertiary screening pipeline with predetermined go/no go criteria. These criteria include exposure levels in target tissues, target engagement, disease modifying effect, and *in vivo* functional activity and therapeutic index. The *APOE4/Trem2* model as well as a humanized Aß mouse will serve as standard backgrounds as additional LOAD genetic variants are introduced at IU/JAX/ UCI. Data from these models include: functional assays, neuropathology, amyloid and tau pathology, transcriptional and metabolic profiling, and *in vivo* imaging. All data will be made available through the Sage-Synapse portal. Conclusions: All models, protocols, and data sets will be made widely available. For more information see www.model-ad.org.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

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Topic: C.02. Alzheimer's Disease and Other Dementias

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Title: Preclinical screening strategy of the MODEL-AD consortium: Evaluation of the pharmacokinetics and pharmacodynamics of treatment with levetiracetam

Authors: *S. J. SUKOFF RIZZO[1], K. D. ONOS[1], K. J. KEEZER[1], S. K. QUINNEY[2], D. R. JONES[2], A. R. MASTERS[2], I. METZGER[2], J. A. MEYER[3], J. PETERS[3], S. A. PERSOHN[3], B. P. MCCARTHY[3], A. A. BEDWELL[3], M. SASNER[1], H. WILLIAMS[1], G. R. HOWELL[1], A. OBLAK[4], B. T. LAMB[4], P. R. TERRITO[3]

[1]The Jackson Lab., Bar Harbor, ME; [3]Radiology and Imaging Sci., [2]Indiana Univ. Sch. of Med., Indianapolis, IN; [4]Stark Neurosciences Res. Inst., Indianapolis, IN

Abstract: The preclinical testing core (PTC) of the Model Organism Development for Late Onset Alzheimer's Disease (MODEL-AD) consortium has established a streamlined preclinical strategy with go/no-go decision points that allow critical and unbiased assessments of potential therapeutic agents. The PTC strategy includes a primary screen to determine: 1) drug formulation; 2) drug stability; and 3) in vivo pharmacokinetics and target tissue concentrations in models at disease-relevant ages. A secondary screen evaluates target engagement and disease modifying activity utilizing non-invasive PET/MRI as a pharmacodynamic (PD) readout matched to known disease pathology in the model. Compounds demonstrating positive PD effects in the secondary screen are further interrogated via a tertiary screen of functional assays that assess the compounds ability to normalize a disease-related phenotype in cognition and neurophysiological tests. For the present studies, we selected the anti-epileptic drug levetiracetam (LEV), a compound currently in clinical trials for the treatment of cognitive impairment associated with AD, for testing in the 5XFAD mouse model of early onset AD. Serial plasma and terminal brain tissue samples following acute oral administration (10, 30, and 100 mg/kg, n=3/sex/dose) revealed brain concentrations were linearly related with plasma concentrations over a broad range. Using a non-compartmental analysis (NCA), the terminal elimination half-life (T1/2, 2.7±0.56 hr), time to maximum concentration (Tmax, 0.86±29 h), volume of distribution (Vd/F, 2.54±0.68 L/kg), and plasma clearance (Cl/F, 0.59±0.33 L/h/kg) were independent of dose level. As expected there were dose-dependent changes in oral maximum plasma concentration (Cmax) and drug exposure (AUC0-inf). Interestingly Cmax revealed a statistically significant effect of sex ($p<0.05$). Using NCA rate constants and a one-compartment model, PK/PD simulations revealed a requirement of twice daily (BID) dosing for pharmacodynamic studies which enabled a 3 month prophylactic treatment trial of 5XFAD mice. In these studies, the effects of BID LEV (10, 30, and 56 mg/kg PO) dosing on 18F-FDG and 18F-AV45 PET/MRI, EEG, cognitive and locomotor effects are currently being evaluated.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

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Topic: C.02. Alzheimer's Disease and Other Dementias

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Title: Translational genetic and genomic analyses of new mouse models of alzheimer's disease

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Abstract: The abundance of genetic associations and genomic characterizations are motivating the creation and assessment of new animal models for late-onset Alzheimer's disease (LOAD). To complement existing models, the MODEL-AD consortium is creating new mouse models based on specific genetic variants prioritized from genome-wide association studies. Detailed phenotyping of these models will provide the necessary information for further basic research and preclinical use.
We have developed bioinformatics pipelines to: (1) identify key genetic variants that confer risk of AD from genome-wide association studies; (2) translate candidate variants into mouse models; (3) align human disease and animal model phenotypes to specify the optimal research use of each animal and characterize the effects of multiple genetic variants; and (4) broadly disseminate all data and preclinical research protocols for community use. Here we present our analysis to date and future plans.
Drawing from multiple large-scale genetic resources, including IGAP, ADNI, and ADSP, we have identified candidate variants in *APOE*, *TREM2*, *ABCA7*, *MTHFR*, and *PLGC2* for engineering in mouse models. We additionally identified *IL1RAP* and *CEACAM1* as candidate genes for deletion. Mouse models have been created to incorporate these variants, and we will present analysis of transcriptomic data from some of these models. Transcriptome clustering methods were used to identify sets of genes with differential expression driven by one or more

variants, and these sets were compared to human LOAD transcriptomes from the Accelerating Medicine's Partnership for Alzheimer's Disease (AMP-AD). This analysis identified specific molecular modules that are altered by the genetic variants in a similar manner as observed in the human postmortem brain tissues.
All data are broadly shared data via the AMP-AD Knowledge Portal hosted by Sage Bionetworks. Future work will expand all of these findings and resources, and additionally integrate data and protocols from preclinical studies that use the animal models. These resources will be part of a broad knowledgebase to serve the creation and study of multiple animal models to effectively model late-onset Alzheimer's disease *in vivo*.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.06/H1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: U54 AG054345-01

Title: Model-ad: Standardized characterization of familial Alzheimer's disease models (5xfad, 3xtg-ad, app/ps1, and htau)

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Abstract: To date, Alzheimer's disease (AD) is the most common form of dementia that has no effective treatment. Over the past 20 years researchers have used animal models to further understand the etiology of AD, and determine the pathways involved in this neurogenerative disease. While these animal models have proved fruitful in the understanding of some of the hallmark features associated with AD, they have not demonstrated predictive translatability for AD. The Model Organism Development and Evaluation of Late-onset Alzheimer's Disease

(MODEL-AD) Center was established to develop, validate, and distribute novel mouse models for LOAD, with the aim to aid in the development of novel therapeutics for AD. MODEL-AD is a consortium involving Indiana University, The Jackson Laboratory, University California-Irvine, and Sage Bionetworks. To validate our characterization paradigm and preclinical pipeline for new models, we have utilized familial AD (fAD) models. Our phenotyping pipeline includes functional assays, *in vivo* MRI and PET imaging, transcriptomics, biochemistry, and neuropathology. Mice were assessed using a battery of functional assays and *in vivo* imaging performed at a variety of ages ranging from 4 mos to 14 mos (the timeframe when the majority of reported phenotypes occur in these strains). Tissue was then harvested and transcriptional profiling and neuropathology of the brain assessed in both male and female mice as follows. One brain hemisphere was frozen, and the other hemisphere fixed. Transcriptional profiling was performed on the frozen portion, while biochemical and neuropathological analysis was carried out on the fixed hemisphere. To assess AD relevant changes, we used antibodies against the following proteins: 22C11 (APP); 6E10, 4G8 (Aβ); Tau-46 (pan-tau); CP13, PHF1 (phospho-tau); NeuN, NFL, MBP, SYN and PSD-95 (neurons); GFAP, COL4 (astrocytes); IBA1, CD68, TREM2 (microglia, monocytes); PDGFRB (pericytes); and Fibrin, Albumin (vascular integrity). Transcriptional profiling was used to stage the progression of AD in fAD models and to compare the differentially expressed genes/pathways to those observed in human AD. This allows us to directly determine human relevance in each of these models. MODEL-AD is making all mouse models, protocols, and data sets widely available through a variety of resources including JAX mice, clnical and research services and the AMP-AD knowledge portal (Synapse). We welcome input and collaboration from the scientific community. For more information see www.model-ad.org.

Disclosures: G.R. Howell: None. **H. Williams:** None. **M. Sasner:** None. **A. Oblak:** None. **G. Carter:** None. **S. Rizzo:** None. **P.R. Territo:** None. **S. Forner:** None. **M.A. Wood:** None. **A. Mortazavi:** None. **G. MacGregor:** None. **A.J. Tenner:** None. **K.N. Green:** None. **F.M. LaFerla:** None. **B.T. Lamb:** None.

Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.07/H2

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Comparative effects of ethanolic extracts of bacopa floribunda and angraecum eichlerianum on amyloid beta model of male wistar rats

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Abstract: This study investigated the effects of crude extracts obtained from *Bacopa floribunda* and *Angraecum eicherianum*. A total number of 48 (n=6) male wistar rats were used for this study. *Angraecum eichlerianum* (AE) and *Bacopa floribunda* (BF) extracts were given at a dose of 200mg/kg/day and Alzheimer's disease was induced by a single bi-lateral intra-cerebroventricular injection of Amyloid beta protein (4µg/µl/site) using a stereotaxic apparatus. A pre-treatment and post-treatment model with BF and AE was employed for 21 days. Rats were grouped as follows; Group 1 (Normal saline), Group 2 (Amyloid beta without treatment), Group 3 (BF alone), Group 4 (AE alone), Group 5 (group pre-treated with BF), Group 6 (group Pre-treated with AE), Group 7 (group post-treated with BF) and Group 8 (group Pre-treated with AE). Morris water maze task and Y maze was carried out on different days during the course of the study. Twenty-four hours after the last administration, rats were sacrificed and brain tissues excised. The hippocampus was removed and assayed for the levels of glutamate, acetylcholinesterase, Na^+ - k^+ ATPase activities and Amyloid beta deposition using ELISA kits. Data were analyzed using One-way ANOVA followed by a post-hoc test and expressed as Mean ± SEM.

A significant ($p < 0.05$) increase was observed in the activities of acetylcholinesterase in group 6 when compared with every other group, likewise, a significant ($p < 0.05$) decrease was observed between groups 5 and 7 when compared with groups 1, 2, 3, 4 and 8. Results also showed that group 3 alone had the highest level of significance ($p < 0.05$) of Na^+- k^+ ATPase activities when compared with every other group. Groups 6, 7 and 8 also showed some levels of significance when compared with groups 1, 2, 4 and 5. Neurobehavioural scores (Y maze and Morris Water maze) were observed to be better in BF and AE groups compared to untreated and normal saline groups.

In conclusion, BF elicited its protective action by increasing the levels of Na^+ - k^+ ATPase while the mechanism of action of AE was by reducing the activities of acetylcholinesterase in Amyloid beta induced Alzhiemer's disease.

KEYWORDS: Amyloid beta 1-42; Bacopa floribunda; Na^+- k^+ ATPase

Disclosures: M. Oyeleke Omotola: None. **O.L. Arokoyo:** None. **H.T. Oni:** None. **B.V. Owoyele:** None.

Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.08/H3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01MH109466-03

Title: Aav9 and crispr cas9 based epigenetic manipulations to study antipsychotic drugs induced side effects in aged mice

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Abstract: Alzheimer's disease (AD) is a progressive cognitive decline and over 90 % patients also develop behavioral and psychological symptoms of dementia (BPSD) that increase disease progression, causing great distress to caregivers, and lead to institutionalization. However, there is currently no FDA approved treatment for AD patients with BPSD. Antipsychotics are still common prescribed drug for BPSD at increased risk for developing side-effects. Previously, we have shown that the changes histone markers at gene promoters such as dopamine receptor 2 (Drd2) and serotonin receptor 2A (5HT-2A) leading to decreased receptor expression and functionality in aged mice, suggesting epigenetic mechanisms may regulate antipsychotic action during aging. In this study, we will further confirm our hypothesis that age-related histone modification is one of the key mechanisms underlying increased sensitivity to the side effects induced by antipsychotic in aged mice by using gene editing tools with AAV9 and CRISPR Cas9 system intervention.
Young C57BL/6 mice (3 months old) were microinjected bilaterally into the frontal cortex and striatum with AAV9-HDAC1-GFP (Vectorbio labs) containing hSYN1, a neuron-specific promotor. After 4-6 weeks of microinjection, haloperidol (HAL) induced drug response was measure by several behavioral tests. HDAC1 expression was confirmed by western blot and immunohistochemistry.
In the groups of the prefrontal injection with AAV9-HDAC1-GFP, the behavioral tests did not show any changes between vehicle and drug groups. However, in the striatum injected groups in Catalepsy behavioral tests, animals with AAV9-HDAC1-GFP microinjection show significant increase in duration of cataleptic episodes and in Rotor rod behavioral tests shorter latency to fall (Sec) as compared to vehicle control group , suggesting motor function impaired due to HDAC1 overexpression by AAV9-HDAC1-GFP virus injection. Currently we are looking at how AAV9-HDAC1-GFP in combination with HAL effect young animals in cataleptic and memory function behaviors. We will also determine whether decreasing HDAC1 by AAV9-CRISPR-Cas9-GFP (Applied Biological Material Inc) into brain regions similar to the regions in the AAV9-HDAC1-GFP overexpression experiments in aged mice can reverse D2R and 5-HTR repression and mitigate sensitivity to the side effects induced by HAL.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

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Program #/Poster #: 467.09/H4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant NS067078
NIH Grant NS034179

Title: Neuronal deletion of the mitochondrial protein prohibitin leads to neurodegeneration in mice

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Abstract: Prohibitin (PHB) is an inner mitochondrial membrane protein that is critical for normal mitochondrial function. PHB is also profoundly neuroprotective against several stress/injury paradigms including cerebral ischemia (J. Neurosci., 32:583, 2012, Stroke 45:1131, 2014, JCBFM 2017). However, it is unknown if PHB loss is in itself damaging to the brain. To answer this question, we utilized conditional deletion of neuronal PHB by crossing $PHB^{flox/flox}$ mice with mice expressing Cre under the control of the CamKIIα promoter ($PHB^{fl/fl/cre+}$) to achieve postnatal selective neuronal ablation of PHB. $PHB^{fl/fl/cre-}$ littermates were used as controls. $PHB^{fl/fl/cre+}$ mice were born and developed normally. Western blots of brain tissue lysates showed that PHB deletion starts at 14 weeks of age in the cortex, hippocampus, striatum, but not in cerebellum, as expected from the pattern of CamKIIα directed Cre expression. $PHB^{fl/fl/cre+}$ mice exhibited progressive brain atrophy, starting at 6 months of age (35% loss at 12 months of age, $p<0.05$, n=8-12/group), associated with synaptosome loss (48% at 10 months of age), indicative of neurodegeneration. The brain atrophy was also associated with a progressive body weight loss, starting also at 6 months of age. In brain, the most severe changes were observed in the cortex and hippocampus, while the cerebellum was unaffected. Histologically, we found evidence of neuronal and white matter damage with a significant decrease in the g-ratio (axon diameter/axon+myelin diameter) in the corpus callosum. There was neuronal and astrocytic accumulation of lysosomes, that was especially evident near cortical blood vessels. Biochemical analyses revealed accumulation of ubiquitinated protein aggregates in brains of $PHB^{fl/fl/cre+}$ mice starting at four months of age. These pathological changes resulted in abnormalities in behavior and memory. $PHB^{fl/fl/cre+}$ mice showed increased anxiety starting earlier in female than in male mice (4 vs. 6 months of age). Furthermore, Barnes maze testing

revealed deficits in spatial memory that affected $PHB^{fl/fl/cre+}$ female mice earlier than male mice (6 vs. 8 months of age). In summary, conditional deletion of PHB in neurons results in a progressive neurodegenerative phenotype and behavioral/cognitive changes reminiscent of alterations seen in neurodegenerative diseases, such as brain atrophy and memory loss in Alzheimer's disease. The data unveil an absolute requirement for PHB in neuronal health and in maintaining the structural and functional integrity of the brain. This mouse model may serve as a useful tool to understand neurodegenerative processes initiated by mitochondrial dysfunction.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

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Program #/Poster #: 467.10/H5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Funding from Srinakharinwirot University

Title: Aegle marmelos in Thai herb formula reduced amyloid-beta toxicity via daf-16-mediated signaling pathway in *Caenorhabditis elegans*

Authors: *R. KEOWKASE, S. POOMBORPLAB, C. SANTA-ARDHARNPREECHA, N. KIJMANKONGKUL, W. SANGTIAN, W. SITTHITHAWORN
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Abstract: Alzheimer's disease (AD) is the most common form of dementia found in elderly. AD is caused by the accumulation of toxic proteins including amyloid-β (Aβ). At the present, none of the approved medications for AD can stop the progression of the disease or reverse brain function. The purpose of this study was to investigate the effect of the extracts of *Jatropha multifida, Aegle marmelos, Nelumbo nucifera* and the mixture of three extracts against Aβ toxicity in *Caenorhabditis elegans* (*C. elegans*). The mixture of three extracts is a traditional Thai herb formula used in fatigue patients recovering from illness such as fever and diarrhea. We used a transgenic *C. elegans* strain CL4176 which expresses the human $A\beta_{42}$ to investigate the effects and the mechanisms of action of these extracts against Aβ toxicity *in vivo*. The extract of *A. marmelos, N. nucifera*, and the mixture extracts significantly delayed Aβ-induced paralysis. Using RNAi method, we found that *A. marmelos* lost the ability to delay Aβ-induced paralysis in worms fed with *daf-16* RNAi bacteria, but not in worms fed with *hsf-1* and *skin-1* RNAi bacteria. These results indicated that *daf-16* transcription factor was required for *A. marmelos*-mediated delayed paralysis. On the other hand, both *N. nucifera* and the mixture extracts did not require

daf-16, *hsf-1*, and *skin-1* in order to reduce Aβ toxicity. Using real-time PCR, we found that *A. marmelos* also enhanced the level of *daf-16* gene. Taken together, these results indicated that *A. marmelos* reduced Aβ toxicity via DAF-16-mediated cell signaling pathway. Furthermore, we also found that *A. marmelos* and the mixture extracts significantly extended lifespan and displayed anti-oxidative effect against paraquat-induced oxidative stress in wild type *C. elegans*.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.11/H6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: VA Grant BX003040

Title: Mechanisms of corticotropin-releasing factor receptor 1 mediated increases in Alzheimer's disease pathology

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Abstract: Stress is a risk factor for various neuropsychiatric disorders and neurodegenerative diseases. For example, individuals who develop post-traumatic stress disorder (PTSD) have an higher risk of Alzheimer’s disease (AD). Exposure to stress in rodent models confers increased AD-related neuropathology, as measured by increased production of amyloid-beta (Aβ) and hyperphosphorylated tau (p-tau). The stress-mediating peptide, corticotropin-releasing factor (CRF), has been demonstrated to be mechanistically linked to these pathological hallmarks through CRF receptor 1 (CRFR1) signaling, yet the mechanism(s) underlying the CRF-AD link is currently unknown. Elucidation of the signaling intermediates involved in this relationship could provide novel therapeutic targets, uncovering additional routes that could alleviate the burden of AD. Small molecule CRFR1 antagonists, such as R121919, are an underexplored class of potential therapeutic drugs that can may be efficacious in preventing and/or treating AD in Veteran populations. This study explored the therapeutic potential of R121919 on disease pathology and behavioral deficits at various endpoints in an AD mouse model (PSAPP). R121919 significantly reduces Aβ in the cortex and hippocampus of PSAPP mice. CRFR1 antagonism also impacted changes in the inflammatory tone, as evidenced by change in microglial activation patterns surrounding plaques. Additionally, treatment with R121919

prevented the onset of hippocampal dependent memory deficits normally seen in PSAPP mice. These data support the therapeutic potential of small molecule CRFR1 antagonists on AD pathogenesis.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

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Program #/Poster #: 467.12/H7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: National Natural Science Foundation of China (81671248)
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Title: Brain-specific estrogen improves cognitive functions

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Abstract: Estrogen decline has been implicated in a higher risk of Alzheimer’s disease (AD) for post - menopausal women, due to the role of estrogen in learning and memory. Although estrogen replacement therapy improves cognitive functions and delays the onset of AD, it may cause severe side effects, including breast, endometrial and ovarian cancer. Therefore, development of brain-specific estrogen reagents would be critical for potential therapies of neurological disorders. In the brain, both neurons and astrocytes produce estrogen. To investigate whether increasing estrogen specifically in neurons and in astrocytes would enhance learning and memory, we have generated Thy1-Ar and hGFAP-Ar mice in which aromatase, the estrogen synthetase, is specifically overexpressed in neurons and astrocytes, respectively. In the barns maze tests, which are commonly used to examine mouse spatial and reference memory, we found that Thy1-Ar and hGFAP-Ar mice of both sex spent significantly less time to find the target hole compared with the age- and sex-matched wild type mice, suggesting that brain-specific estrogen significantly improved cognitive functions. To investigate neural mechanisms underlying the cognitive enhancement, we recorded the electrophysiological properties of pyramidal neurons of the hippocampus in Thy1-Ar and hGFAP mice. In both female and male hGFAP-Ar mice, the amplitude of excitatory postsynaptic current (mEPSC) was significantly enhanced, whereas the inhibitory postsynaptic current (mIPSC) was unaltered compared to wild

type mice. In contrast, neither mEPSC nor mIPSC of Thy1-Ar mice changed, except for a significant increase of the frequency of mEPSC in male Thy1-Ar mice. These results suggest that the estrogen produced by both neurons and astrocytes could enhance learning and memory. Astrocyte-derived estrogen functions by enhancing the excitatory synaptic transmission, whereas, neuron-derived does probably in a different mechanisms. This observation demonstrates that brain-specific estrogen reagents could be an advanced intervention for cognitive impairment of post - menopausal women.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

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Program #/Poster #: 467.13/H8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NSERC Grant 2015-04537
Weston Brain Institute Grant

Title: 5alpha-reduced metabolites of testosterone offer protection against the development of AD neuropathology in 3xTg Alzheimer's disease male mice

Authors: *H. A. WILSON[1], A. L. MENDELL[1], S. D. CREIGHTON[2], B. D. WINTERS[2], N. J. MACLUSKY[1]
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Abstract: The gonadal steroid hormone, testosterone, may protect against the development of Alzheimer’s disease (AD). The gradual reduction of testosterone in aging males is linked to an increased risk of AD, while gonadectomy and testosterone replacement in male mice alter pathophysiological markers of AD, such as amyloid β (Aβ) deposition and hyperphosphorylation of tau. In the brain, testosterone is metabolized via 5α-reductase (5α-R) to other neuroactive steroids. Levels of these metabolites are also altered in male triple transgenic AD (3xTg) mice, and may contribute to the protection conferred by testosterone. In this study, we explored whether inhibition of 5α-R might impact pathophysiological markers of AD in male 3xTg mice. Male wild type (WT; C57bl/6/129S) and 3xTg mice were given daily injections of finasteride (5α-R inhibitor; 50mg/kg i.p) or vehicle (18% β-cyclodextrin) for 20 days. Female WT and 3xTg mice were included, receiving vehicle injections only, to evaluate potential sex differences. Western blots were conducted to characterize total tau expression, phosphorylation of tau at AD-related residues, and Aβ expression in the hippocampus (n=5-6/group). Results demonstrated increased tau hyperphosphorylation at Serine-202 in 3xTg females and finasteride-treated 3xTg

males, but not vehicle-treated 3xTg males. Changes in tau hyperphosphorylation at Serine-202 were not accompanied by any significant differences in total tau, or by changes in phosphorylation at Serine-396. Small oligomeric -Aβ expression was detected in the hippocampus in all 3xTg animals, with a trend toward higher expression in females. Immunohistochemistry (IHC) was then conducted to examine region-specific differences in Aβ (n=4-5/group). Female 3xTg mice had stronger Aβ staining compared to all 3xTg males in dorsal cornu ammonis (CA) 1, the dorsal subiculum in the anterior ventral hippocampus (VHC), CA1 of the anterior VHC, and layer V of the primary somatosensory cortex. No significant effects of finasteride treatment were observed for Aβ IHC. However, female 3xTg mice had stronger Aβ staining in CA3 of the posterior VHC compared to vehicle-treated, but not finasteride-treated 3xTg males. Strong positive staining for Aβ was also observed in the anterior basolateral amygdala, with no significant sex differences. Together, these results suggest that the relative protection of testosterone in the development of AD in males may be partially dependent on metabolites of testosterone, which reduce site-specific tau hyperphosphorylation in the hippocampus and may impact Aβ levels in a region-specific manner.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.14/H9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Inge und Fritz-Kleekamm-Preis - Alzheimer Stiftung Göttingen

Title: Effects of cannabidiol and tetrahydrocannabinol treatment on memory function, neuron loss and molecular signature in a mouse model of Alzheimer’s disease

Authors: M. E. SICHLER[1], J. WILTFANG[2], M. J. LÖW[1], C. BOUTER[3], T. A. BAYER[1], *Y. BOUTER[1]
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Abstract: Introduction: Limited therapeutic effects of current Alzheimer (AD) treatments highlight the need for new research approaches. Thereby drugs that target different aspects of AD pathology simultaneously could provide therapeutic benefits compared to more traditional interventions. Targeting the endocannabinoid system is such an approach. Endocannabinoid signaling has been demonstrated to be involved in numerous processes, including brain

development, memory formation, motor control, neuroinflammation, excitotoxicity and oxidative stress. Furthermore, several in vitro studies showed that cannabinoids reduce Aβ-induced neurotoxicity as well as cell death and facilitate neurogenesis. It could also be demonstrated that cannabinoids stimulate the removal of intraneuronal Aβ in vitro. The aim of the study was to investigate the multi-faceted therapeutic potential of Tetrahydrocannabinol (THC) and Cannabidiol in a mouse model for Alzheimer's disease.
Material & Methods: Tg4-42 mice express Abeta4-42 and develop severe hippocampal neuron loss as well as memory deficits starting at 4 months of age. Tg4-42 Alzheimer mice were treated daily with Cannabidiol and Tetrahydrocannabinol, respectively. Treatment started presymptomatically at 3 months and continued for six weeks. Behavior tests were performed to access motor and memory functions as well as anxiety. Design-based Stereology was used to analyze neuron loss in the hippocampus of Tg4-42. Deep sequencing will be performed to identify differentially expressed genes.
Results and Conclusion: THC- and Cannabidiol-treatment improved spatial reference memory in an dose-dependent manner. Treatment with cannabinoids did not alter the anxiety behavior or motor performance of Tg4-42 mice. In addition, the effects of THC and Cannabidiol on the molecular signature will be presented as well as the effects on neuron loss in the dentate gyrus and CA1 of the hippocampus. Cannabinoid-treatment in Tg4-42 mice show the potential of the endocannabinoid system as a therapeutic target in Alzheimer's disease influencing the molecular signature and improving memory deficits. Our findings reinforce a cannabis-based medicine as a potential AD therapy.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Canadian Consortium on Neurodegeneration and Aging
Fonds de recherche du Québec
Canadian Vascular Network
Alzheimer's disease Society
Healthy Brains for Healthy Lives

Title: Benefits of exercise on cognition and white matter pathology in a mouse model of vascular cognitive impairment and dementia

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Abstract: Rationale: White matter (WM) pathology is a clinically predictive feature of vascular cognitive impairment and dementia (VCID). Here, we investigated WM changes in a VCID mouse model and determined whether physical exercise (PE) could be protective based on evidence pointing to its ability to delay dementia onset. Transgenic mice overexpressing transforming growth factor-β1 (TGF mice) with an underlying cerebrovascular pathology were fed a high cholesterol diet (HCD) to trigger cognitive deficits. We investigated WM pathology and the mechanisms underlying the benefits of PE.
Methods: Six groups of equally distributed male and female mice (*n* = 20-24/group, 3-4 months old) were used and all *in vivo* experiments were performed blind to the identity of the mice. Groups consisted of wild-type (WT) and TGF mice fed standard lab chow, WT and TGF mice fed a 2% HCD, and WT and TGF mice fed the HCD and given access to running wheels. After 3 months of treatments, behavioural tests were performed: Morris water maze, novel objection recognition, and Y-maze. Fluorescent-activated cell sorting was used to investigate peripheral immune cell infiltration. Cerebral blood flow (CBF) responses evoked by whisker stimulation were measured by Laser Doppler flowmetry, whereas baseline CBF was measured in WM areas with [14C]-iodoantipyrine autoradiography. WM functionality was measured in micro-dissected corpus callosum using *in vitro* electrophysiology to record compound action potentials. Mice were intracardially perfused for immunohistochemistry analysis.
Results: The HCD had a significant effect in WT and TGF mice that was prevented by PE on the novel object recognition task, the same was observed but only in TGF mice for the Y-maze. Both baseline WM CBF and sensory-evoked CBF increases were reduced in VCID mice, deficits that were countered by PE. VCID mice displayed focal WM functional deficits characterized by lower compound action potential amplitude, which were not found in PE groups. In addition, markers of WM pathology in VCID mice such as increased number of collapsing capillaries, microglial activation associated with WM damage, and reduced number of oligodendrocytes, were all prevented by PE.
Conclusion: Our findings suggest that targeting WM pathology in VCID may be key to improving cognitive symptoms and that regular aerobic PE is an effective preventative treatment. It is possible that reduced CBF in conjunction with increased WM inflammation and reduced number of oligodendrocytes resulted in memory impairments. Increased CBF and oligodendrocyte maturation, and reduced WM-associated inflammation by PE may have helped overcome cognitive deficits induced by HCD.

Disclosures: L.J. Trigiani: None. **M. Lacalle-Aurioles:** None. **M. Bourourou:** None. **L. Li:** None. **A.D. Greenhalgh:** None. **J.G. Zarruk:** None. **S. David:** None. **M.G. Fehlings:** None. **E. Hamel:** None.

Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.16/H11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: K99/R00 AG044469
R01 AG055581
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A2017457S

Title: Memory impairments and synaptic failure in APP/PS1 AD model mice are alleviated by eEF2K inhibitor NH125

Authors: *N. KASICA, W. YANG, X. ZHOU, T. MA
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Abstract: Mounting evidence indicates synaptic failure as an early and key event in Alzheimer's Disease (AD) pathophysiology. Maintenance of long-term memory and synaptic plasticity requires *de novo* protein synthesis. Phosphorylation of mRNA translation factor eukaryotic elongation factor 2 (eEF2) by its kinase eEF2K results in inhibition of general protein synthesis. Previous studies have shown elevated levels of eEF2 phosphorylation in *post mortem* AD human brain tissue and in AD mouse models. Here we investigated whether suppression of eEF2 phosphorylation via eEF2K inhibitor NH125 can alleviated AD-associated synaptic failure and memory impairments. Aged APP/PS1 mice (12-16 months) and age-matched controls were injected intraperitoneally with NH125 or vehicle following a previously established dosing protocol over two weeks. The mice then underwent cognitive assessment via the Novel Object Recognition (NOR) and Morris Water Maze (MWM) tasks. We found that cognitive impairments displayed in aged APP/PS1 mice were alleviated with treatment of NH125. Furthermore, electrophysiology experiments demonstrated that AD-associated defects in hippocampal long-term potentiation (LTP) were rescued by NH125. Additionally, results from Surface sensing of translation (SUnSET) assay revealed that impaired *de novo* protein synthesis in hippocampus of AD model mice was improved by NH125. Taken together, our results suggest that treatment with a eEF2K inhibitor, NH125, alleviates cognitive impairments and restores translational capacity in a mouse model of AD.

Disclosures: N. Kasica: None. **W. Yang:** None. **X. Zhou:** None. **T. Ma:** None.

Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.17/H12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG023084
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Cure Alzheimer's Fund

Title: Upregulation of endothelial Picalm using an FDA approved drug enhances amyloid-β clearance from murine brain

Authors: *K. KISLER, A. P. SAGARE, S. BAZZI, C.-J. HSU, D. LAZIC, E. J. LAWSON, A. R. NELSON, Z. ZHAO, B. V. ZLOKOVIC
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Abstract: PICALM, phosphatidylinositol binding clathrin assembly protein, is a known genetic risk factor for Alzheimer's disease (AD). In healthy mice and humans, PICALM is highly expressed in brain endothelial cells, involved in clathrin-mediated endocytosis and trafficking, and clearance of amyloid-β (Aβ) from the brain across the blood-brain barrier. However, in AD PICALM brain endothelial levels are reduced. We have previously shown that PICALM reduction leads to reduced Aβ clearance from brain and exacerbation of Aβ pathology, which could be reversed by increased endothelial-specific expression of PICALM after viral transfection. Thus, therapeutic strategies that upregulate *Picalm* expression in the vasculature could lead to novel advancements in AD treatment. Using a drug screening approach, we have identified an FDA-approved drug capable of upregulating endothelial *Picalm in vivo*. To mimic features of AD, we used 5XFAD mice carrying a single copy of the *Picalm* gene ($Picalm^{+/-}$; 5XFAD) and treated them with the drug for two months, beginning at 3 months of age. Drug-induced *Picalm* upregulation in these animals reduced brain Aβ load by 40-60% in the cortex and hippocampus, significantly improved performance in hippocampal-dependent behavioral tests, and improved cerebral blood flow response to stimulus, indicating cognitive and cerebrovascular improvements compared to vehicle treated animals. Together this data indicates that *Picalm* upregulation could be a promising new therapeutic target for AD.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.18/H13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: National Health and Medical Research Council (NHMRC) Australian Research Council (ARC) Dementia Research Development Fellowship

Title: Comprehensive touchscreen cognitive characterisation of APP/PS1 mouse model of Alzheimer's disease reveals subtle and progressive impairments

Authors: *A. SHEPHERD[1], T. ZHANG[1], J. K. H. LIM[2], V. H. Y. WONG[2], C. T. O. NGUYEN[2], B. V. BUI[2], A. J. HANNAN[1], E. L. BURROWS[1]
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Abstract: Mouse models expressing human gene mutations provide powerful tools to investigate mechanisms underlying cognitive decline in Alzheimer's disease (AD). Touchscreen technology facilitates the assessment of cognitive domains directly relevant to impairments described in AD patients. We examined cognition in male mice expressing familial AD mutations in amyloid precursor protein (APPswe) and presenilin-1 (PS1ΔE9) and littermate controls using touchscreen technology, as well as vision using electroretinography and ocular coherence tomography (n=8-12, 4 cohorts), with researchers blinded to genotype. Mice were initially trained to nose-poke a visual stimulus on a touch-sensitive computer screen for a reward. Mice were food restricted to 75% throughout the testing period to facilitate motivation and tested for 1 hour, 6-7 days a week. Tasks were scaled in complexity to test cognitive domains relevant to those impaired in human AD and analysed using regression models, analogous to clinical methods. APP/PS1 mice show subtle behavioural inflexibility impairments at 12 months of age, that progressively worsen to severe at 24 months of age. Working and associative memory were assessed in APP/PS1 mice at 8-15 months and, unexpectedly, showed no impairments. Mice were assessed in two equivalent maze-based tests at comparable time-points for bench-marking with published findings. Conflicting with published results, neither cognitive impairments nor retinal changes were uncovered in these mice. The absence of impairment is speculated to be due to several experimental factors known to improve memory, including daily cognitive stimulation, increased physical exercise and chronic food restriction. This is the first exploratory cognitive characterisation of APP/PS1 mice using touchscreens, and informs the validity of this mouse model of AD. Furthermore, our findings validate this approach of utilising clinically relevant modes of assessment to facilitate translation from pre-clinical models to the clinic.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.19/H14

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Eli Lilly-Stark Postdoctoral Research Fellowship in Neurodegeneration

Title: Potential therapeutic role of niacin in Alzheimer's disease

Authors: M. MOUTINHO, V. E. VON SAUCKEN, *G. E. LANDRETH
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Abstract: The niacin receptor (HCAR2 or GPR109A) is expressed in immune cells, and its activation by specific agonists results in decreased inflammation. The expression of HCAR2 is stimulated by an inflammatory environment, suggesting that this receptor is part of a natural compensatory response to control inflammation. Alzheimer’s disease (AD) has a prominent inflammatory component, however it remains unknown if HCAR2 plays a direct role in AD pathology. Interestingly, dietary intake of niacin, a HCAR2 agonist, has been suggested to be protective against AD and age related cognitive decline. Therefore, we hypothesized that HCAR2 activation by niacin could have a therapeutic role in AD. Our results indicate that HCAR2 expression increases with disease progression in the brains of the 5xFAD mouse model of AD. These findings suggest that this pathway is already primed in the AD brain due to the robust inflammatory environment, which supports the idea of HCAR2 as a promising therapeutic target for disease modification. We treated a cohort of 5-month old 5xFAD mice with a commercially available formulation of niacin (Niaspan®) daily by oral gavage for 30 days, with the dosages of 0, 50 and 100 mg niacin/kg. The 5xFAD mice treated with 50 and 100 mg/kg of niacin exhibited a significant reduction in amyloid-β burden as assessed by 6E10 staining. Immunohistochemical analysis revealed a small reduction in the number of compact, thioflavin S-positive plaques in the subiculum of mice treated with niacin 100 mg/kg. Importantly, niacin exerts a neuroprotective effect as evidenced by reduced neuronal loss in the subiculum of Niaspan® treated mice. These preliminary data suggest that niacin treatment could have beneficial effects in AD, including neuroprotection, even after the onset of severe amyloid pathology. Niaspan® is a FDA approved drug, thus there is translational potential of this strategy into clinical practice, supporting further study of this therapeutic approach.

Disclosures: M. Moutinho: None. **V.E. von Saucken:** None. **G.E. Landreth:** None.

Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.20/H15

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant NS069375
NIH Grant NS097945

Title: G protein-biased beta1-adrenergic receptor partial agonists for the treatment of Alzheimer's disease

Authors: *B. YI, A. JAHANGIR, A. K. EVANS, J. ERNEST, M. GREEN, M. SHAMLOO
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Abstract: Beta1-adrenergic receptor (ADRB1) is a therapeutically attractive target for Alzheimer's disease that can provide symptomatic relief and disease-modifying effects. Here, we report our effort to develop novel ADRB1 agonists with high CNS penetration. Xamoterol is a partial agonist of ADRB1 that selectively activates the cAMP cascade. In two independent mouse models of Alzheimer's disease, xamoterol was shown to be effective in rescuing memory deficits and attenuating pathology associated with the disease, suggesting that this class of compounds may have the unique potential to provide comprehensive therapeutic benefits for the treatment of Alzheimer's disease. While xamoterol is the best tool compound available, use of xamoterol for CNS indications is limited by its poor oral bioavailability and low CNS penetration. Based on these findings, we sought to develop a novel ADRB1 partial agonist with pharmacological properties similar to xamoterol, but with improved bioavailability and enhanced CNS penetration. Our medicinal chemistry effort exploring the structure-activity relationship of xamoterol derivatives led to the discovery of a series of compounds. These compounds produce partial agonistic activity on G-protein signaling with EC_{50} values in the low nanomolar range. Similar to xamoterol, these compounds are functionally biased and selectively activate G-protein coupled signaling with very little activity on the beta-arrestin pathway compared to the unbiased agonist isoproterenol. The compounds also produce strong anti-inflammatory effects both *in vitro* and *in vivo*, and show high brain penetration. The newly identified, functionally selective partial agonists of ADRB1 are invaluable research tools to investigate the adrenergic system in Alzheimer's disease pathology and potential novel lead compounds for restoring cognitive deficits and altering the progression of Alzheimer's disease.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.21/H16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NSERC Grant 2015-04537
Weston Brain Institute Grant

Title: Finasteride differentially impacts dendritic morphology of hippocampal neurons and impairs object recognition memory in male 3xTg-AD mice

Authors: *A. L. MENDELL[1], S. D. CREIGHTON[2], H. WILSON[1], L. ISAACS[1], B. D. WINTERS[2], N. J. MACLUSKY[1]
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Abstract: Alzheimer's disease (AD) is characterized by amyloid beta deposition and neurofibrillary tangle formation. Development of pathophysiology in AD has been shown to lead to alterations in neuronal structure, which have been proposed to contribute to functional memory impairments. The incidence of AD is higher in women compared to men, and several studies have demonstrated that the severity of neuronal dysfunction and cognitive decline are worse in females. These sex differences may be associated with loss of protection due to the menopausal decline of circulating ovarian steroids, while the age-related decline in testosterone levels in men is more gradual. Work by our group and others has shown that 3alpha-hydroxy, 5alpha-reduced metabolites of testosterone may contribute to neuroprotection conferred by androgens, as well as to sex differences in the incidence of AD. In this study, we explored the impact of inhibiting synthesis of testosterone-derived neurosteroids on object recognition memory (ORM; n=9-11/group) and dendritic morphology (n=5-6/group) in the CA1 and CA3 hippocampal subfields in male triple transgenic AD mice (3xTg-AD), with females included to evaluate sex differences. Male 6-month old wild-type (WT) and 3xTg-AD mice received daily injections of finasteride (5alpha-reductase inhibitor; 50mg/kg i.p) or vehicle (18% beta-cyclodextrin, 1% v/b.w.) for 20 days. Female WT and 3xTg-AD mice only received vehicle injections. Finasteride treatment in males differentially impaired ORM after short-term (5min; 3xTg-AD only) or long-term (3h; 3xTg-AD and WT) retention delays, while vehicle-treated 3xTg-AD males and females were only impaired after the long-term delay. Dendritic spine density (DSD), dendritic branching, and total dendritic length of pyramidal neurons in the CA3 subfield were reduced in 3xTg-AD females, but not males. Both DSD and dendritic branching were significantly reduced by finasteride in 3xTg-AD males, abolishing the sex difference in CA3. In the CA1 subfield, DSD and dendritic branching were reduced in all 3xTg-AD mice,

with no significant effects of finasteride. These results highlight subfield-specific sex differences in dendritic structure of hippocampal neurons in 3xTg-AD mice, and suggest that these differences are at least partially attributable to 5alpha-reduced neurosteroids. Memory impairments were exacerbated by finasteride in 3xTg-AD males, indicating that the changes in neuronal structure were associated with altered cognitive function. Overall, these findings suggest that 5alpha-reduced neurosteroids may contribute to sex differences in the development and severity of AD.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.22/H17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: UKK Investitionsfond Lehre und Forschung 2016

Title: Cognitive effects of intermittent deep brain stimulation of the Nucleus basalis of Meynert in a transgenic rat model for Alzheimer’s disease

Authors: P. KOULOUSAKIS, V. VISSER-VANDEWALLE, *T. SESIA
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Abstract: Alzheimer’s disease (AD) is a fatal progressive neurodegenerative disease and the most prevalent form of dementia. Degeneration of cholinergic neurons in the basal forebrain has been shown to be one of the earlier hallmarks of the disorder. Associated acetylcholine deficiency has been positively correlated with cognitive impairment in AD. The nucleus basalis of Meynert (NBM) has a high density of cholinergic efferent neurons projecting to the entire cortical mantle. Deep brain stimulation (DBS) is a neurosurgical procedure in which electrodes are implanted into specific areas to be electrically stimulated. Lately, NBM DBS has been proven safe and successful in AD patients, who are stimulated continuously. A recent study in healthy aged monkey suggests that an intermittent pattern of stimulation (20 s ON/ 40 s OFF) boost performance in a cognitive test. We aim at testing this new pattern of electric stimulation in an animal rat model for AD. For this study, we use the transgenic rat line Tgf344-AD due to its robust validity in modeling AD. We use three behavioral tests adapted from the characterization study of the Tgf344-AD rat line in combination with three patterns of stimulation. Tests include open field maze (OFM), object recognition task (ORT), and modified Barnes maze (BM). Rats were stimulated at 200 µA either intermittently at 20 Hz (new

paradigm) or continuously at 60 Hz (current clinical standard). Post-mortem tissue analysis confirms electrode localization. Performances under stimulation conditions are compared to baseline performances acquired prior any stimulation. We use one group of 8 rats from 12-18 months old of age and another group of 8 rats of 18-26 months old of age. Older rats retrieved the escape hole faster, even under the longest retention period condition, when stimulated intermittently. Under this new pattern of stimulation, their performances also exceeded those of the younger group. Intermittent bilateral stimulation of the NBM shows the best improvement cognitive performance in older (18 months) rats. These preliminary results suggest that intermittent stimulation is a promising new pattern of stimulation to be tested in the clinic to further optimize NBM DBS in AD patients.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.23/H18

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 2018 NRF 2018R1A2B6002804
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2018 GIST Research Institute (GRI) Grant (Silver Health)

Title: Repeated acoustic stimulation improved sleep-wake behavior and electroencephalographic markers in a mouse model of Alzheimer's disease

Authors: *V. J. DREW, M. PARK, J. LEE, S. RYU, T. KIM
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Abstract: Background: Alzheimer’s disease (AD), a neurodegenerative disease associated with memory loss, accounts for the majority of dementia patients. Pathophysiology of AD is not fully understood, but amyloid beta (Aβ) accumulation and tauopathy have been implicated as the major biomarkers and, possibly, pathogenic factors. Recently it has been known that gamma frequency entrainment reduced Aβ in the brain (Iaccarino, et al., 2016) and a growing body of evidence supports the relationship between sleep and dementia. However, careful investigation of sleep-wake behavior in the animal model of AD is still lacking. Therefore, we sought to examine the characteristics of sleep-wake control in an AD model and their changes caused by acoustic stimulation at 40 Hz. Methods: We used 5XFAD transgenic mice as an AD models of Aβ overproduction. At the age of six months, two-hour daily acoustic stimulation of click sound at 40 Hz were given for 14 days at the beginning of dark period. We also performed the 24-hour

electroencephalographic (EEG) recordings for the sleep-wake analyses at the stimulations days 1, 7 and 14. Aβ load was measured with immunohistochemistry and ELISA of the pre- and infra-limbic cortices and hippocampus and EEG data were analyzed for the gamma oscillations and brain connectivity. We analyzed the 24-hour sleep-wake profiles, bout length and frequency, and the power spectrums. The sleep data were analyzed using Sirenia Sleep software. Results: We found that the number of Aβ plaque, as well as Aβ40 and Aβ 42, decreased in the brain after 14-day acoustic stimulation. Sleep analysis revealed that the amounts of sleep and wake were not different among the three consecutive EEG recordings. However, there were trends toward shortened and less frequent sleep and wake bouts over the stimulation period. Power spectrum of wake epochs showed abnormally increased delta power and reduced stepwise at days 7 and 14. Conclusion: Repeated acoustic stimulation resulted in decrease levels of amyloid beta and wake delta power in EEG and more consolidated sleep and wake stages. These changes may reflect improved amyloid pathology could also ameliorate the continuity of wakefulness and sleep. We speculate that a better quality of wakefulness and cognition might be heralded by decreased wake delta power, but this should be confirmed with behavioral tests. Consequently, we suggest that non-invasive acoustic stimulations at 40 Hz might have therapeutic effect on a mouse model of Alzheimer's disease.

Disclosures: V.J. Drew: None. **M. Park:** None. **J. Lee:** None. **S. Ryu:** None. **T. Kim:** None.

Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.24/I1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NRF-2017M3C7A 1026959
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BK21plus education program

Title: Pharmacological PKR inhibition rescues deficits in synaptic plasticity and memory in Alzheimer's disease mouse models

Authors: K.-D. HWANG, M. BAK, S. KIM, *Y.-S. LEE
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder associated with memory loss and deficits in synaptic plasticity. Although amyloid β (Aβ) and hyper-phosphorylation of tau are considered as major causes, AD can be caused by a large number of different genetic mutations and other unknown factors. Considering such a heterogeneous nature of AD, it would

be desirable to develop treatment strategies that can improve memory irrespective of the individual causes. In this study, as a proof-of-concept, we targeted the phosphorylation of eukaryotic translation initiation factor 2α (eIF2α) as a memory-enhancing strategy. Previously, reducing the phosphorylation of eIF2α was reported to enhance long-term memory and synaptic plasticity in mice. Moreover, hyper-phosphorylation of eIF2α is observed in the brains of postmortem AD patients. In this study, we examined whether PKR inhibition can rescue synaptic and learning deficits in two different AD mouse models; 5XFAD transgenic and $A\beta_{1-42}$-injected mice. We found that the acute treatment of PKR inhibitor (PKRi) can restore the deficits in long-term memory and long-term potentiation (LTP) in both mouse models without affecting the Aβ load in the hippocampus. Our results prove the principle that targeting memory enhancing mechanisms can be a valid strategy for developing treatments for memory deficit associated with AD.

Disclosures: K. Hwang: None. **M. Bak:** None. **S. Kim:** None. **Y. Lee:** None.

Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

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Topic: C.02. Alzheimer's Disease and Other Dementias

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Title: Neurochemical and behavioral effects of intranasal insulin administration in young and aged rats

Authors: *J. M. ERICHSEN[1], C. B. CALVA[1], C. A. GRILLO[1,2], L. P. REAGAN[1,2], J. R. FADEL[1]
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Abstract: Alzheimer’s Disease (AD) is the most common form of dementia that affects ~10% of individuals over 65. Recently, insulin administration has been suggested as a potential therapy for AD patients, as individuals with insulin resistance and type 2 diabetes have demonstrated impaired memory and cognitive function. Peripheral administration of insulin can induce side

effects like hypoglycemia, but intranasal (IN) administration allows direct access to the brain without affecting systemic insulin or glucose levels, is non-invasive, and easy to administer. Additionally, IN insulin enhances memory in rodents, healthy individuals, and those with AD, although the mechanistic basis for these pro-cognitive changes has yet to be elucidated. To address these questions, a subset of young (3 months) F344xBN F1 rats were administered 250 ug biotin-labeled IN insulin and brain sections were prepared to examine the neuroanatomical pattern of IN insulin distribution and binding. Staining appeared in the medial septum, diagonal band of Broca, medial forebrain bundles, islands of Calleja, piriform cortex, and spinal trigeminal tract, indicating that the IN method effectively delivers insulin to the brain. Additional young and aged (26-28 months) rats were administered IN insulin or IN saline to examine effects on feeding behavior and neurochemistry. Food intake was assessed for 18 hours after IN administration of 250 ug insulin or saline in both young and aged rats. IN insulin significantly suppressed food intake in both groups but the effect in aged rats was delayed relative to young animals, suggestive of insulin resistance in the aged cohort. Finally, brain neurochemistry was assessed with *in vivo* microdialysis. Differences in acetylcholine and glutamate levels in the six hours after IN administration of insulin vs. saline were observed, indicating that changes occur at the neurotransmitter level. More studies are needed to fully understand the molecular and behavioral changes following IN insulin administration, but these data demonstrate the capacity for IN insulin to rapidly target the brain and influence neurotransmission and feeding behavior.

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Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

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Topic: C.02. Alzheimer's Disease and Other Dementias

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Brain Institute, University of Pittsburgh

Title: Cortical control of the stomach and its potential relevance to Alzheimer’s disease

Authors: *D. J. LEVINTHAL, R. P. DUM[1], P. L. STRICK[2]
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Pittsburgh, PA; [2]Neurobiology, Systems Neurosci. Ctr., Brain Inst., Univ. Pittsburgh Sch. Med., Pittsburgh, PA

Abstract: We injected rabies virus (RV) into the stomach wall of several macaques. The site we injected was innervated solely by the vagus nerve, a major output of the parasympathetic nervous system. The injections of RV resulted in retrograde transport to first-order neurons in the dorsal motor nucleus of the vagus and the ambiguus complex, followed by retrograde transneuronal transport to second-order neurons in the medulla, and then third-order neurons in the rostral insula. These results suggest that the insula functions as a "parasympathetic motor cortex" for central command signals that influence stomach function. The rostral insula has been regarded as a cortical site for monitoring our internal state (for references and review see Craig, '09). Our results indicate that descending command signals from the rostral insula have the potential to create or at least influence our internal state.

We next allowed virus transport to proceed beyond the rostral insula. This led to the surprising result of dense labeling in the entorhinal cortex (EC). This observation is especially noteworthy because EC is known to be one of the first sites of tau accumulation in Alzheimer's disease. Indeed, Braak and Braak ('91) designated tau accumulation in EC as Stage 1 of the disease. Our results raise the possibility of a link between the stomach's microbiome and tau deposition in EC. For example, a toxic substance could originate in the stomach and use retrograde transneuronal transport through the vagus nerve and a chain of as few as five interconnected neurons to gain access to EC. The presence of this material in EC neurons could then trigger a pathological process that results in the abnormal deposition of tau, and thus, the onset of the earliest stages of Alzheimer's disease.

In another animal, we allowed transport to proceed to one stage beyond EC and observed dense labeling in the hippocampus. Tau accumulation at this site is considered to be Stage 2 of Alzheimer's. There has been a growing awareness in the Alzheimer's field that the orderly progression of tau from its initial site in EC to other sites may be mediated by neural connections. If our results can be confirmed and extended, they indicate that retrograde transneuronal transport through specific neural connections may mediate the progression of tau in Alzheimer's disease. If these conclusions are correct, then one potential approach to impede the progression of Alzheimer's, and prevent cognitive impairment and memory dysfunction, would be to inhibit retrograde transport in these circuits.

Disclosures: D.J. Levinthal: None. **R.P. Dum:** None. **P.L. Strick:** None.

Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.27/I4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH grant NS069375
NIH grant NS097945

Title: G protein-biased beta1-adrenergic receptor partial agonists for the treatment of Alzheimer's disease

Authors: *P. MEMAR ARDESTANI, B. YI, A. K. EVANS, M. SHAMLOO
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Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disease, directly affecting about 24 million people worldwide. Currently, there is no effective treatment for AD to prevent, cure, or slow its progression, emphasizing the need for a novel therapeutic strategy. The lack of effective AD therapies can be attributed to the complex array of factors involved in its development and progression. Given the complex nature of AD, therapeutic agents that simultaneously modulate different key target points of AD pathology would represent the most ideal and comprehensive therapy. Beta1-adrenergic receptor (ADRB1), which is involved in multiple key aspects of AD, is a unique and therapeutically attractive target for AD that could enable a comprehensive strategy for the treatment and management of the disease. Here, we demonstrate that specific activation of G-protein signaling of ADRB1 leads to beneficial effects on impaired cognitive function and pathology associated with the disease in two independent mouse models of AD. In 2 different transgenic models in which mice either express 5 mutations related to Familial Alzheimer's Disease, [5XFAD; 3 mutations in the amyloid precursor protein and 2 in presenilin 1] or 2 mutations in amyloid precursor protein (T41B), transgenic and wildtype male mice were chronically dosed with vehicle or with the G-protein biased ADRB1 partial agonist, xamoterol (5XFAD, 6 mg/kg daily oral gavage or 3 mg/kg subcutaneous pump; T41B, 0.3-1.0 mg/kg daily subcutaneous injection). When chronically dosed, the G-protein biased ADRB1 partial agonist improved novel object recognition and spatial learning in 5XFAD mice, and reduced hyperactivity and improved contextual fear conditioning in T41B mice. Chronic dosing with xamoterol also decreased amyloid beta and modulated indices of neuroimmune activation in both models. Reduction in tau pathology was also observed with chronic dosing with xamoterol in 5XFDA mice. Together, our findings suggest that activation of the ADRB1 G-protein signaling pathway may be a therapeutic approach for AD.

Disclosures: P. Memar Ardestani: None. **B. Yi:** None. **A.K. Evans:** None. **M. Shamloo:** None.

Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.28/I5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Grant Agency of the Czech Republic No. 16-08554S

Title: Combination of memantine and 6-chlortacrine leads to promising dual inhibitor of acetylcholinesterase and NMDA receptor; a novel multi-target compound against Alzheimer’s disease

Authors: *O. SOUKUP[1], J. KORABECNY[2], E. NEPOVIMOVA[1], K. VALES[3], K. SKRENKOVA[4], L. KLETECKOVA[3], M. HORAK[5]
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Abstract: Alzheimer’s disease (AD) is the most common form of dementia in elderly. Current treatment is based on these cholinergic and glutamatergic, theory. It involves acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine, and NMDAR antagonist memantine. However, treatment is only symptomatological and temporary and it seems that cure needs to be complex due to a multifactorial nature of the disease. In this context, so called “multi-targeting approach” has been established almost two decade ago in order to successfully address not only the disease symptoms but also disease progression. This work provides design, synthesis in vitro and in vivo characterization of novel drug candidate amalgamating tacrine scaffold, namely 6-chlortacrine with memantine into one molecule. By using patch clamp, we have shown that novel hybrid is a potent open channel blocker of the NMDARs which acts by “trapping“ mechanism. Fuerthermore, the affinity to AChE (IC50=9nM) investigated by Ellman´s method is similar to donepezil and therefore the compounds possesses both requested properties, i.e. it is an anticholinesterase and anti-NMDA agent. We have also investigated the effect of the compound in vivo using NMDA-induced lession of the hippocompus and we have observed significant reduction of the lession, in comparison to both control and memantine treatment. Thus, the novel hybrid compound effectivelly combines both currently established approaches in the treatment of AD, capable to prevent from excitotoxicity in vivo.

Disclosures: J. Korabecny: None. **E. Nepovimova:** None. **K. Vales:** None. **K. Skrenkova:** None. **L. Kleteckova:** None. **M. Horak:** None.

Poster

467. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 467.29/I6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Inge und Fritz-Kleekamm-Preis of the Alzheimer Stiftung Goettingen

Title: Effects of tetrahydrocannabinol treatment on brain metabolism and inflammation in a mouse model of sporadic Alzheimer’s disease

Authors: *C. BOUTER[1], M. E. SICHLER[2], I. KOSTUL[2], T. A. BAYER[2], Y. BOUTER[2]
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Abstract: Limited therapeutic effects of current Alzheimer treatments highlight the need for new research approaches. The endocannabinoid system plays a role in neuroinflammation and memory formation and therefore addresses major pathological hallmarks of Alzheimer’s disease. The aim of this study was the evaluation of the therapeutic potential of Tetrahydrocannabinol (THC) on neuron loss and neuroinflammation in a mouse model of sporadic Alzheimer’s disease. Tg4-42 mice develop severe neuron loss in the hippocampus in correlation to intra-neuronal Aβ expression starting at 4 months of age. Furthermore, Tg4-42 mice display increased astrogliosis in the hippocampus. Tg4-42 mice were treated with high dose THC daily for 6 weeks starting at 5 months. GFAP and IBA1 markers were used to examine the impacts of THC treatment on inflammation in Tg4-42 mice. Unbiased stereology was applied in order to quantify neurons in the dentate gyrus and CA1 region of the hippocampus. Tg4-42 mice were characterized by autoradiography using the TSPO ligand ^{18}F-GE180. Furthermore, ^{18}F-FDG-PET/CT was used to study therapeutic effects in vivo at 3 and 6 months. While GFAP staining of reactive astrocytes did not show a significant difference between THC-treated mice and untreated controls, IBA1 detected significantly reduced microgliosis in the dentate gyrus of THC-treated Tg4-42 mice. Stereological analysis revealed that THC-treated animals displayed a significant increase in the number of neurons in comparison to controls. Autoradiography and ^{18}F-FDG-PET/CT results will be also presented.
First results on THC-treatment in Tg4-42 mice show the potential of the endocannabinoid system as a therapeutic target in Alzheimer’s disease influencing neuroinflammation and neuron loss.

Disclosures: M.E. Sichler: None. **I. Kostul:** None. **T.A. Bayer:** None. **Y. Bouter:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.01/I7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Merit Award BX001875 to A. Dedeoglu
NIH RF1 AG056032 to A. Dedeoglu
NIH R01 AG045031 to J.K. Blusztajn

Title: Long-term treatment of 7,8-dihydroxyflavone protects against cortical amyloid-beta accumulation and activates hippocampal BDNF-TrkB signaling in a mouse model of Alzheimer’s disease

Authors: *C. M. TOGNONI[1,2], A. R. SCIAUDONE[1,3], I. CARRERAS[1,3], J. K. BLUSZTAJN[2], A. DEDEOGLU[1,3]
[1]VA Boston Healthcare Syst., Boston, MA; [2]Pathology & Lab. Med., [3]Neurol., Boston Univ. Sch. of Med., Boston, MA

Abstract: Brain-derived neurotrophic factor (BDNF) signaling through the tropomyosin receptor kinase B (TrkB) is a candidate for targeted therapies to treat Alzheimer’s disease (AD). Recently, our lab demonstrated early protective effects of the TrkB agonist, 7,8-dihydroxyflavone (DHF), on AD-related pathology and dendritic arborization in the 5xFAD mouse model of AD when treated (5 mg/kg i.p., 3 days/week) from 1 to 3 months of age (Aytan et al. Eur J Pharmacol. 2018 Jun 5;828:9-17). In this study, we examined the effects of a longer-term and late-stage treatment with DHF in 5xFAD female mice from 1 to 8 months of age. Concentrations of Aβ proteins were measured via enzyme-linked immunosorbent assay (ELISA), which revealed that DHF treatment had significantly decreased soluble Aβ42 protein levels in the frontal cortex. We did not detect differences between untreated and treated mice in the densitometry of Aβ plaques in the hippocampus by immunohistochemistry (IHC) of Aβ42. By IHC with anti-phospho-TrkB (Tyr816) antibody, we found increased phosphorylated TrkB in the hippocampus and amygdala of DHF-treated compared to untreated 5xFAD mice, suggesting DHF enhanced activation of the receptor and its downstream signaling cascades that mediate synaptic plasticity and the maintenance and growth of dendrites and dendritic spines. Together, these preclinical results indicate that long-term treatment of DHF in the 5xFAD mouse model of AD protects against cortical Aβ accumulation and activates hippocampal BDNF-TrkB signaling, which is known to have protective effects on neuroplasticity and memory.

Disclosures: C.M. Tognoni: None. **A.R. Sciaudone:** None. **I. Carreras:** None. **J.K. Blusztajn:** None. **A. Dedeoglu:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.02/I8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: SAN/SfN 2018 slots: ABS18344

Title: Intravenous mesenchymal stem cells administration as a neuroprotective therapy in a rat model of sporadic alzheimer's disease

Authors: *M. ZAPPA VILLAR[1], J. LOPEZ HANOTTE[1], J. PARDO[1], G. MOREL[1], M. GARCÍA[2], P. REGGIANI[1]
[1]INIBIOLP, Sch. of Medicine, Natl. Univ. La Plata, La Plata, Argentina; [2]Gene Therapy Lab, Sch. of Biomed. Sciences, Austral Univ., Pilar, Buenos Aires, Argentina

Abstract: Alzheimer's disease (AD) is the most prevalent neurodegenerative pathology with no efficient therapy. The signaling pathways that become defective, altering the normal protein homoeostasis of amyloid β-peptide (Aβ) and tau protein, and thus initiating a series of pathophysiological responses ultimately causing synaptic loss and cognitive decline, are unclear and much sought after.
Our objective is to develop therapeutic strategies that allow preventing and/or overcoming the degenerative changes in the brain with experimental AD. In this context, cell therapy emerges as a promising therapeutic approach. We set up a model of sporadic AD by the intracerebroventricular (icv) injection of streptozotocin (STZ) in rats.
In a first study, we evaluated behavior and gliosis in the dorsal hippocampus of STZ-injected rats after 24 days. We assessed learning and spatial memory by the Barnes Maze (BM) and anxiety-related behavior by the Marble Burying (MB) test. STZ-treated rats exhibited impairments in these tests as compared with control counterparts. Furthermore, STZ rats displayed Stratum Radiatum (SR) volume reduction and a decreased NeuN immunoreactivity (neuron loss) in the hippocampal CA1 region, together with an increased immunoreactivity for the microglial (Iba1) and astroglial (GFAP) markers (neuroinflammation).
In another experimental approach, we assessed the effect of intravenous administration (as a non-invasive route) of Human Umbilical Cord Mesenchymal Stem Cells (HUC-MSC) on cognitive performance in the AD rat model. Three experimental groups were used: Sham, STZ, and STZ+MSC. After 24-day STZ injection, when the damage was already established, animals received every 18 days, a suspension of $1x10^6$ HUC-MSC in a tail vein. During the last two weeks until the end of the study we performed Open Field, BM, and MB tests to estimate memory, depression-like, and anxiety-like behaviors. STZ treated rats were deficient in all

behavioral tests and morphological assessment. STZ+MSC group increased exploratory frequency in the Open Field test. Moreover, these animals showed an improvement in their spatial memory performance in the BM. Anxiety-like behavior in the MB test was also attenuated by exposure to MSC. Interestingly, MSC therapy restored hippocampal atrophy in the SR region and ameliorated neuron loss. Additionally, decreased microgliosis and astrogliosis was observed in the MSC-treated rats.
We conclude that MSCs therapy is a suitable biological tool in neurodegenerative disorders, restoring the progression of cognitive impairment and neuroinflammation when systemically administered for more than two months.

Disclosures: M. Zappa Villar: None. **J. Lopez Hanotte:** None. **J. Pardo:** None. **G. Morel:** None. **M. García:** None. **P. Reggiani:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.03/I9

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Activation of endogenous neurogenesis is a potential therapeutic approach for Alzheimer's disease

Authors: *M.-Y. KIM, S. HAN
Shinebiopharma Inc., Seoul, Korea, Republic of

Abstract: Alzheimer’s disease(AD) is thought to be caused by damage of neural networks due to damage or loss of neurons in the hippocampus and cerebral cortex through the deposition of amyloid-beta plaques. Even though amyloid-beta was thought to be the target for AD treatment, no successful drug treatment has yet been established. This is because although the amyloid-beta aggregates were removed, it was not possible to induce the repair of the damaged neurons or nervous tissue. In this study, we evaluated whether the induction of endogenous neurogenesis could be a potential therapeutic approach in Alzheimer’s disease.
First, we established an assay system for screening drug candidates which simultaneously induce neuronal differentiation of neural stem cells (NSCs) and provide protection against cell death from Aβ oligomers. We identified SNR1611 which induced neuronal differentiation of NSCs and provided cell death protection to neurons in the presence of Aβ oligomers *in vitro*. SNR1611 also induced neurogenesis in the dentate gyrus of the hippocampus of 12-month old 5XFAD mice, an Alzheimer’s disease mouse model, when observed one month after its oral administration. SNR1611 not only activated neurogenesis in the dentate gyrus but also increased the number of neuronal cells in the cortex of 12-month old 5XFAD mice, characterized by the

many plaques and damaged neurons in the cortex. In addition, SNR1611 treated 5XFAD mice showed a tendency of recovery in recognition memory.
These results suggest that SNR1611 can be a potential drug for Alzheimer's disease by inducing endogenous neurogenesis and the strategy of inducing endogenous neurogenesis can be a novel target for treatment of Alzheimer's disease.

Disclosures: **M. Kim:** A. Employment/Salary (full or part-time):; Shine Biopharma Inc. **S. Han:** A. Employment/Salary (full or part-time):; Shine Biopharma Inc..

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.04/I10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: the National Natural Science Foundation of China (Grant nos. 81774129)
Hunan Administration of traditional Chinese medicine Science Foundation (Grant nos.201609)

Title: Effects of Danggui-Shaoyao-San decoction on hippocampal expression profiles of non-coding RNAs in a mouse model of Alzheimer's disease

Authors: ***S. CHENG**, Z. SONG, F. YIN, F. LI
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Abstract: Danggui-Shaoyao-San (DSS) is a well-known herbal formula that has been clinically applicable for treating neurological disorders. It is reported that it could improve the function of the dopaminergic, adrenergic, and serotonergic nervous systems. Interestingly, DSS can alleviate cognitive dysfunction of Alzheimer's disease (AD) patients. Accumulating evidence indicates that non-coding RNAs are strongly implicated in AD-associated pathophysiology. Whether the ameliorative functions of DSS is associated with ncRNAs remains largely unknown. In the present study, we used microarray analysis technology to characterize the expression patterns of circular RNAs (circRNAs), long-non-code RNA (lncRNA), microRNAs (miRNAs), and mRNAs in hippocampal tissue from APPswe/PS1ΔE9 (APP/PS1) mice treated with DSS, to integrate interaction data and thus provide novel insights into the mechanisms of DSS. A total of 287 circRNAs, 118 lncRNA, 156 miRNAs and 382 mRNAs were identified to be significantly dysregulated (fold-change ≥ 2.0 and p-value < 0.05) in the hippocampus of DSS treated AD mice. Quantitative real-time polymerase chain reaction (qRT-PCR) was then used to validate the expression of randomly-selected circRNAs, lncRNA, miRNAs and mRNAs. Next, GO and

KEGG pathway analyses were performed to further investigate ncRNAs biological functions and potential mechanisms. Our results suggest the ncRNA regulated by DSS involves in the neurodevelopment, intercellular communication, action potential regulation of neurons, development and differentiation of oligodendrocytes, neurotransmitters and regeneration of neurons in APP/PS1 mice

Disclosures: S. Cheng: None. **Z. Song:** None. **F. Yin:** None. **F. Li:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.05/I11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 2016R1A2B1009647
2016R1A6A1A03011325

Title: Amelioration of learning and memory deficits in aged and 3xtg-ad mice by mild level of stress

Authors: L. CHAN[1], G. PARK[2], *J.-H. JANG[1]
[1]Dept. of Pharmacol., Sch. of Medicine, Keimyung Univ., Daegu, Korea, Republic of; [2]Col. of Pharm., Kyungpook Natl. Univ., Daegu, Korea, Republic of

Abstract: Stress is regarded as one of the critical risk factors for neurodegeneration leading to learning and memory deficits. Although several researchers have reported that mild level of stress could enhance cognitive functions, its underlying molecular mechanisms are not clearly verified. In this study we have investigated the effect of mild restraint stress (MRS) against the learning and memory dysfunction in aged mice as well as triple transgenic mice of Alzheimer's disease (3xTg-AD) by conducting diverse behavior tests and molecular analyses. MRS improved mean escape latency, the time taken to find the platform during training trials in Morris water-maze test. In addition, the neuropathological markers for AD such as accumulation of beta-amyloid peptide and hyperphosphorylation of tau protein were mitigated by MRS. MRS effectively decreased ratio of pro-apoptotic Bax to anti-apoptotic Bcl-2, the representative proteins involved in apoptosis. To elucidate the neuroprotective mechanism of MRS, we have examined the molecules involved in the oxidative stress and inflammation. MRS attenuated the lipid peroxidation and protein oxidation through up-regulation of antioxidant enzymes via modulating redox-sensitive proteins such as NF-E2-related factor 2. MRS also attenuated the pro-inflammatory responses by suppressing expression of cytokines in aged mice. Moreover, MRS increased the levels of brain-derived neurotrophic factor by phosphorylation of cAMP

response element-binding protein in 3xTg-AD mice. Taken together, these findings suggest that MRS may have beneficial effects for the learning and memory impairments during neurodegenerative process by decreasing neuropathological markers of AD and oxidative stress as well as inflammatory responses, and increasing neurotrophic factors involved in neuroregeneration.

Disclosures: L. Chan: None. **G. Park:** None. **J. Jang:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

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Program #/Poster #: 468.06/I12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R37AG008796
NIH Grant RO1NS059879
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Eleanor Wood Prince Foundation of Northwestern Memorial Hospital
Alzheimer’s Research Gift Fund

Title: Risk-Factor induced memory dysfunction and Aβ oligomer pathology in a non-transgenic model of sporadic Alzheimer’s disease

Authors: *C. WEISS[1], K. L. VIOLA[2], M. A. BICCA[2], W. L. KLEIN[2], J. F. DISTERHOFT[1]
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Abstract: The purpose of this study is to develop a non-transgenic animal model of sporadic Alzheimer’s Disease (AD) in rabbit because its amino acid sequence for amyloid is nearly identical to the human sequence, and its lipid metabolism is very similar to human lipid metabolism. This suggests that the rabbit is a good species to examine diabetes and high cholesterol as risk factors for sporadic AD. We used aging female rabbits to compare the effects of diets enriched with either 2% cholesterol or 10% sucrose (vs standard chow) on cognition and neuronal pathology. Cognition was assessed with the novel object and novel location recognition tests to assess cortical and hippocampal function, respectively. A discrimination index was calculated based on the time investigating novel or familiar objects or locations. Scores ranged between 0 and 1.0 with 1.0 representing exclusive investigation of the novel object/place, and 0 representing equal exploration. Pathology was assessed by staining brain sections containing hippocampus and frontal cortex with NU4, an antibody specific for amyloid oligomers. Diabetes was assessed by an iv glucose tolerance test. Cognition was tested after 20 weeks of the

designated diet. High cholesterol diet impaired both object location and object recognition tests (mean scores of 0.06 and 0.10, respectively) relative to rabbits on standard diet (mean score of 0.70). High sucrose diet impaired object recognition (0.19 vs 0.44 control diet), but not the object location test (0.72 vs 0.70). Blood glucose levels (BGL) and insulin levels revealed a large spike in insulin release for rabbits on sucrose diet, and those rabbits exhibited BGL that returned to baseline more quickly than the BGL of the other two groups. This suggests a state of prediabetes and maybe insulin resistance in the brain, i.e., Type 3 diabetes (de la Monte and Wands, 2008). Analysis of immunoreactivity to amyloid oligomers with the NU4 antibody revealed a 20- and 35- fold increase respectively in hippocampus and frontal cortex relative to sections from control rabbits. Experiments are in progress to determine the basis for the differential impact of the diets on hippocampal-dependent memory dysfunction. **Conclusions:** Diets that promote high cholesterol or diabetes impair neuronal metabolism, increase AD-like pathology, and decrease cognitive functions. These diets in the rabbit provide model systems to understand mechanisms related to the onset and progression of sporadic AD.

Disclosures: C. Weiss: None. **K.L. Viola:** None. **M.A. Bicca:** None. **W.L. Klein:** None. **J.F. Disterhoft:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.07/I13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 AG050518
USC SPARC Graduate Research Grant

Title: Neurochemical effects of intranasal orexin-A and [Ala^{11},D-Leu^{15}]-orexin-B administration in rats

Authors: *C. B. CALVA, J. R. FADEL
Pharmacology, Physiology, Neurosci., Univ. of South Carolina Sch. of Med., Columbia, SC

Abstract: Cognitive dysfunction is well described in numerous psychiatric and neurological disorders. The hypothalamic orexin (hypocretin) system, a central integrator of physiological function, also plays an important role in coordinating proper cognition. Prior work from our lab has shown an age-related reduction of orexin (OX) neurons in rats, suggesting that orexins play a role in the cognitive and homeostatic dysfunctions observed during aging. While clinical investigations of OX antagonist-based pharmacotherapies are ongoing, the paucity of OX agonists has limited the ability to research their therapeutic potential. To circumvent this hurdle,

intranasal OX administration has been suggested as a means of directly targeting the brain while avoiding the side effects or limited brain penetration that occur with systemic administration. Preliminary behavioral evidence suggests that intranasal orexin-A (OxA) may enhance cognition and wakefulness; however, the receptor activation mechanisms underlying these effects remain largely unknown. We have previously demonstrated that intranasal OxA activates cortical and basal forebrain regions involved in attention and learning, and increases cortical acetylcholine release in both young and aged rats. Because OxA binds the orexin-1 and orexin-2 receptor with equal affinity, our observations could not be attributed to a specific receptor. Accordingly, we utilized intranasal administration of the selective orexin-2 receptor agonist, [Ala^{11},D-Leu^{15}]-orexin-B (OxB), to compare the patterns of neuronal activation in young and aged animals that result from intranasal administration of OxA or [Ala^{11},D-Leu^{15}]-OxB. Here, young (3-4 months) and aged (26-28 months) male Fisher344/Brown Norway rats received intranasal administration of saline, OxA, or [Ala^{11},D-Leu^{15}]-OxB (25 μL of a 100 μM solution) into each naris after 7 days of habituation to vehicle administration. Two hours post-treatment, animals were sacrificed and their brains were processed for immunohistochemical detection of the neuronal activity marker, c-Fos, and phenotypic markers of specific neuronal populations. In young rats, intranasal OxA significantly increased c-Fos expression in a larger number of cortical and basal forebrain regions compared to intranasal [Ala^{11},D-Leu^{15}]-OxB. Additionally, intranasal OxA administration resulted in significantly higher c-Fos expression in basal forebrain cholinergic neurons of aged animals versus young animals. In total, these data indicate that intranasal OX administration, largely via the orexin-1 receptor, activates brain regions and neurotransmitter systems that decline with age.

Disclosures: C.B. Calva: None. **J.R. Fadel:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.08/I14

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH SBIR 2 R44 AG043203-03.

Title: TgF344-AD rats exhibit alterations in locomotion and acoustic startle response prior to cognitive function impairment

Authors: *B. ZOU[1], K. XIAO[1], C. PASCUAL[1], W. S. CAO[1], F. MA[2], D. HUA[2], I. MAEZAWA[3], L. W. JIN[3], X. X. XIE[1]
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Abstract: Alzheimer's disease (AD) is becoming an increasingly widespread detriment in society with the growing aged population and lack of effective treatments. Establishing novel animal models that objectively identify early phenotypes, monitor disease progress, and evaluate responses can provide a powerful approach to the discovery of new interventions. To this end, we characterized the neurobehavior of a transgenic rat model (TgF344-AD) expressing mutant human amyloid precursor protein (APPsw) and presenilin 1 (PS1ΔE9) genes; each independently cause early-onset familial AD. The memory phenotype of TgF344-AD rats (10 - 11 months old) was evaluated using contextual and tone-fear condition (automated assessment by the SmartCage system) and novel object recognition tests. TgF344-AD rats exhibited memory similar to age-matched non-transgenic (nonTg) rats, but displayed increases in homecage spontaneous activity (active time and total infrared beam break counts), locomotion (travel distance, but not speed) and rearing compared to non-Tg rats monitored by the SmartCage for 8 days under a normal light/dark condition. Furthermore, evaluation of startle response and pre-pulse inhibition (PPI) with acoustic stimulation revealed that the PPI was significantly impaired at 80 and 90db of pre-pulse stimulation, while there was a trend of enhancement in startle response of TgF344-AD compared to nonTg rats. These preliminary results indicate that homecage activity, particularly locomotion and startle PPI assessments, along with learning and memory tests can be used to evaluate TgF344-AD rat behavioral phenotypes and treatment responses. Our novel tricyclic pyrone compounds (especially CP2), which have been shown to reduce Aβ accumulation, Aβ plaque formation, and *Tau* pathology, are currently under evaluation via chronic treatment using this rat AD model and behavioral phenotypic analysis.
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Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.09/I15

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Extra support from the federation to the BUAP

Title: The recombinant C-terminal fragment of the tetanus toxin protects the acetylcholinesterase activity and spatial memory by intraseptal injection of amyloid-β peptide (25-35)

Authors: *I. LIMON PEREZ DE LEON[1], A. PATRICIO-MARTÍNEZ[2], L. SÁNCHEZ-ABDÓN[3], F. LUNA-MORALES[4], J. AGUILERA[5], G. MORALES-FLORES[3]
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Abstract: The C-terminal fragment of tetanus toxin (Hc-TeTx) is a non-toxic peptide of tetanus toxin with neuroprotective effects. Hc-TeTx has the ability to bind to nerve cells and be retrogradely transported through synapse. It has been shown that the administration of the peptide Amyloid-β (25-35) ($A\beta_{25-35}$) in the *Septum Medial* (SM) decreases the expression of (AChE, an enzyme that degrades acetylcholine). The administration of Hc-TeTx in SM protects the expresion of AChE of cholinotoxic effect of $A\beta_{25-35}$, however there is no evidence of the protective effect of Hc-TeTx administered peripherally. The aim of this work was to evaluate the effect of intramuscular administration of the Hc-TeTx fragment on the activity of AChE and spatial memory by intraseptal injection of $A\beta_{25-35}$ in rats. Male Wistar rats were used approximately 250-350g, Hc-TeTx or SSI was administered intramuscularly, Twenty four hours later SSI, $A\beta_{35-25}$ and $A\beta_{25-35}$ were administered by stereotactic surgery in SM (AP: +0.6, L: 0.0, P: -5.2, according to Paxinos). The experimental groups were: Intact, SS+SSI (2μL), SSI+$A\beta_{35-25}$ (2μg/2μL), Hc-TeTx+SSI (20μg/kg), SSI+$A\beta_{25-35}$ (2μg/2μL) and Hc-TeTx+$A\beta_{25-35}$. Fifteen days post-injury the spatial learning was evaluated and twenty nine days post-injury the memory was evaluated in the Morris water maze (MWM). The next day, the groups were euthanized for the dissection and extraction of the SM and dorsal hippocampus to evaluate the activity of the AChE by the Ellman test. The experimental groups showed no impair the spatial learning, but the SSI+$A\beta_{25-35}$ group significant decrease of 50% the memory compared to the intact group. The Hc-TeTx+$A\beta_{25-35}$ group performance in 73% of the animals in the memory compared with the SSI+$A\beta_{25-35}$ group. The experimental groups did not exhibit changes in the activity of the AChE in the hippocampus, while the peptide $A\beta_{25-35}$ group decreased about 43% the activity of AChE in SM compared with the intact group, the other experimental groups did not present a statistically significant difference. On the other hand, the group Hc-TeTx+$A\beta_{25-35}$ maintained the activity of the AChE in SM by 43% compared with the intact group; the findings of this study suggest that Hc-TeTx has a protective effect on the cholinergic system. In conclusion, the intramuscular administration of Hc-TeTx in injured rats causes the survival of SM neurons and prevents damage to memory by improving septo-hippocampal communication.

Disclosures: I. Limon Perez De Leon: None. **A. Patricio-Martínez:** None. **L. Sánchez-Abdón:** None. **F. Luna-Morales:** None. **J. Aguilera:** None. **G. Morales-Flores:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.10/I16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Spanish Ministerio de Ciencia e Innovación
PIUNA (Universidad de Navarra).

Title: Sirtuin 2 inhibition: A new therapeutic approach for age-related cognitive decline

Authors: *T. DÍAZ PERDIGÓN[1], B. BELLOCH PEREZ[2], R. TORDERA BAVIERA[2], E. PUERTA RUIZ DE AZUA[2]
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Abstract: Background: Aging is considered to be a major risk factor for neurodegenerative diseases including Alzheimer Disease (AD). Epigenetic changes are currently recognized as part of the aging process and have been implicated in many age-related diseases. In agreement with this hypothesis, a recent study has shown an age-dependent accumulation of SIRT2 in the mouse brain and spinal cord. Since excess SIRT2 might be deleterious to neurons, SIRT2 inhibition has been proposed as a novel therapeutic strategy for age-related cognitive decline.
Methods: A novel and potent SIRT2-selective inhibitor, the compound 33i (5mg/kg i.p., 4 weeks) or vehicle was administered to 5-month-old (preventive treatment) and 8-month-old SAMP8 (therapeutic treatment) and aged matched control SAMR1 mice. The SAMP8 mouse model, based on aging, has been considered to represent more closely the multifactorial nature of AD. Behavioral and biochemical tests were performed to study the effects of SIRT2 inhibition.
Results and conclusions: 33i significantly reversed the learning and memory impairments shown by 6 month-old SAMP8 mice in the Morris Water Maze. Although 33i did not reverse tau-hyperphosphorylation or Aβ accumulation, its beneficial effects as a preventive treatment could be due to an increase in GluN2A, GluN2B and GluA1 protein expression seen in both SAMR1 and SAMP8 mice treated with 33i. Furthermore, a decrease in neuroinflammation was seen in 6-month-old SAMP8 mice treated with 33i evidenced by a reduction of GFAP, IL1, IL6 and TNFα expression.
As a therapeutic treatment, SIRT2 inhibition slightly improved the performance of the 9 month-old SAMP8 in the MWM. GluN2A, GluN2B and GluA1 protein expression were also increased in both 9-month-old SAMR1 and SAMP8 treated with 33i. However, this compound didn't decrease the neuroinflammation shown by the SAMP8 at this age, suggesting that, once the pathology is established, SIRT2 inhibition could be proposed as an adjuvant treatment to improve memory in combination with other drugs.
Altogether, the results of this study indicate that SIRT2 inhibitors may be an ideal novel target to prevent or treat age-related cognitive decline, AD and other neurodegenerative diseases.

Disclosures: T. Díaz Perdigón: None. **B. Belloch Perez:** None. **R. Tordera Baviera:** None. **E. Puerta Ruiz de Azua:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.11/I17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant P30 MH075673 (BSS)
NIH Grant RO1 MH107659 (CR)

Title: Inhibition of neutral sphingomyelinase 2 with MS882 for the treatment of Alzheimer's disease

Authors: *K. RAHN[1,2], M. SALA[3], A. THOMAS[2], R. P. DASH[2], C. TALLON[2], L. LOVELL[2], Y. WU[2], R. RAIS[2], R. NENCKA[3], C. ROJAS[2], B. SLUSHER[2]
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Abstract: The enzyme neutral sphingomyelinase 2 (nSMase2) catalyzes the hydrolysis of sphingomyelin to phosphorylcholine and ceramide. This reaction is a major source of ceramide, a bioactive lipid critical for the cellular secretion of exosomes. Exosomes are lipid vesicles that play a critical role in standard intercellular cargo transport and communication. Over the last decade, it has become apparent that toxic intracellular tau aggregations travel within the brain in a manner reminiscent of a "prion-like" disease, potentially via exosomes. Recent studies have demonstrated that blocking nSMase2 activity, either genetically or pharmacologically using the prototype nSMase inhibitor GW4869, improves cognition, reduces histopathological signs of disease including tau propagation, and decreases brain exosome and ceramide levels in rodent models of AD. The current armamentarium of nSMase2 inhibitors, however, are not clinically viable, as they have low potency (uM IC_{50}s), poor solubility, and limited brain penetration. Our laboratory recently carried out a human nSMase2 inhibitor high throughput screening (HTS) campaign of over 350,000 compounds. Our chemistry hit optimization efforts led to a nanomolar potent, orally available, brain-penetrant (AUC_{brain}/AUC_{plasma}=0.6) inhibitor termed MS882, that was found to dose-dependently inhibit exosome release from glial cells both *in vitro* and *in vivo*, while a structurally similar but inactive analog had no effect. Using this compound, we performed efficacy studies using the 5XFAD mouse model of AD. Male and female wild type (WT) and 5XFAD mice were administered daily intraperitoneal injections of vehicle or 10mg/kg MS882 from 12 - 35 weeks of age (n=13-16/group). This dose was determined to provide MS882 levels in the brain sufficient to inhibit nSMase enzymatic activity for >10 hours post dose. Fear conditioning tests conducted at 34 weeks revealed a significant deficit in contextual memory in 5XFAD+Vehicle mice versus WT+Vehicle mice ($P<0.001$). This deficit was

significantly restored in 5XFAD mice treated with daily MS882 (P<0.01 vs 5XFAD+Vehicle). Post-mortem analyses including exosome, ceramide, and nSMase levels as well as histological endpoints are underway. Taken together, these data support the regulation of exosome release via nSMase2 inhibition as a novel treatment for AD.

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Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.12/J1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Beta Beta Beta National Biological Honor Society
Independent College Fund of New Jersey
Drew University
Sentience Foundation

Title: Effects ofDCP-LA on learning and memory in an *in vivo* Alzheimer's disease model with ovariectomized rats

Authors: P. A. SUTTER, R. B. KNOWLES, *C. R. MCKITTRICK
Biol., Drew Univ., Madison, NJ

Abstract: Alzheimer disease (AD) is the sixth leading cause of death in the United States and affects females disproportionately more than males for reasons unknown. Several promising studies have shown that the PKC-epsilon activator 8-[2-(2-pentyl-cyclopropylmethyl)-cyclopropyl]-octanoic acid (DCP-LA) reverses the effects of AD in *in vivo* models. Because these studies have been limited to either male transgenic mice or male rats, this study explores the effects of DCP-LA in a pharmacological AD model in female rats. The ferrous-amyloid-buthionine (FAB) model was used to induce AD pathologies. This model infuses a combination of ferrous sulfate, amyloid beta fragments, and buthionine sulfoximine into the lateral ventricle of rats over a four-week period. The FAB model mirrors both behavioral and molecular pathologies of AD and models the role of oxidative stress in AD. In the present study, half of the females also received ovariectomies (OVX) to model postmenopausal conditions, since the female population over 65 is the most susceptible to AD. Osmotic minipumps containing either FAB or saline were implanted into 48 three-month-old female Sprague-Dawley rats with infusion cannulae targeted to the cerebral ventricle; at the same time, animals received either

OVX or sham surgery. Four weeks postsurgery, the rats received a single intraperitoneal injection of DCP-LA (1 mg/kg in 5% DMSO) or vehicle 24h prior to exposure to the Morris Water Maze (MWM). Spatial learning was assessed over 5 days of training, and memory was assessed 48 h after the last training session. Immunohistochemistry for NeuN and synaptophysin is currently being conducted to determine neuronal and synaptic density differences between treatment groups.FAB-treated animals showed significant deficits in both learning and memory as compared to controls. OVX did not affect learning but did lead to memory deficits as compared to controls, with FAB + OVX rats performing worse than all other treatment groups in the memory task. DCP-LA administration effectively restored learning and memory performance back to control levels in the FAB-treated animals but did not fully restore memory deficits in OVX animals, suggesting that FAB and OVX impair memory through different mechanisms.These data suggest that the loss of sex hormones in females may lead to cognitive deficits and these deficits can be exacerbated by oxidative stress conditions similar to those implicated in AD. Furthermore, these results suggest that DCP-LA may have therapeutic potential for treatment of AD, as it has now been shown to reverse the of FAB in both male and femalerats.

Disclosures: P.A. Sutter: None. **R.B. Knowles:** None. **C.R. McKittrick:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.13/J2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 1RF1AG057884-01

Title: Plasminogen Activator Inhibitor-1 Antagonist TM5A15 reduce neuropathology and memory deficits in APP/PS1 mice

Authors: *G. RODRIGUEZ[1], S. DOMINGUEZ[1], D. E. VAUGHAN[2], T. MIYATA[3], H. DONG[4]
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Abstract: The pathological hallmark of Alzheimer’s disease (AD) is the aggregation of amyloid beta peptides in the brain which causes a varying degree of cognitive deficits. Amyloid beta peptides are metabolized through biosynthesis and degradation and it is a crucial equilibrium that is needed in order to prevent neuropathologies of AD. Plasmin, a serine protease, plays an

important role in the degradation of Aβ. Several previous studies have shown that there is an increase level of plasminogen activator inhibitors present in the plasma of AD mice models as well as in AD patients. However, whether reversing the increased plasminogen activator inhibitor could prevent neuropathgenesis of AD has not been well investigated. In this study, we test whether a novel plasminogen activator inhibitor-1 (PAI-1) antagonist, TM5A15, can ameliorate cognitive deficits and decrease the Aβ plaques deposition in APP/PS1 mice, an animal model of Alzheimer's disease. We administered 3 month old APP/PS1 mice with TM5A15 for up 6 months via chow diet. Mice underwent behavior testing of locomotor activity, novel object recognition, Morris water maze, and spontaneous alternation after 3 months of treatment and 6 months of treatment to assess the mice learning and memory performance. Blood serum was collected from all groups and mice were then sacrificed to collect brain tissue for biochemical and immunohistochemistry analysis. Behavioral tests showed there was no significant affect after 3 months treatment with TM5A15, when APP/PS1 mice were 6 months. However, after 6 months of treatment, the APP/PS1 mice displayed significant improvement in spontaneous alteration ($p<0.01$), novel object recognition ($p<0.01$), and Morris water maze ($p<0.05$) when they were 9 months of age. Biochemical results indicated a decrease of amyloid plaque deposition in the whole brain for APP/PS1 treated animal samples compared to those APP/PS1 mice that did not receive treatment. In addition, western blot analysis showed higher protein expression of BDNF ($p<0.05$) in APP/PS1 animals that were treated compared to those that were not. These data suggests that increased PAI-1 activity contributes to Aβ aggregation and TM5A15 could prevent the formation of Aβ plaques in APP/PS1 mice.

Disclosures: G. Rodriguez: None. **S. Dominguez:** None. **D.E. Vaughan:** None. **T. Miyata:** None. **H. Dong:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.14/J3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R21 AG051233

Title: ABCA1 activation in the CNS as a therapeutic target for APOE4-induced Alzheimer's disease risk

Authors: *A. C. VALENCIA[1], T. MCNALLY[1], D. BALU[1], N. FAULK[1], Y. SALEH[1], A. HANSEN[1], D. PHAM[1], N. ALLABABIDI[1], J. YORK[1], J. JOHANSSON[2], J. BIELICKI[3], M. LADU[1]

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Abstract: *APOE4,* which encodes the apolipoprotein E4, (apoE) is the greatest genetic risk factor for Alzheimer's disease (AD), increasing risk up to 15-fold compared to *APOE3*. However, there is a critical lack of therapeutics targeting mechanistic pathways for this *APOE4*-induced AD risk. While the mechanism underlying *APOE*-modulated AD risk remains unclear, *APOE4* is associated with accelerated amyloid-beta (Aβ) accumulation, both as amyloid plaque and soluble oligomeric forms of Aβ (oAβ), the latter considered a proximal neurotoxin. In addition, apoE4 levels in the brains of humans, and transgenic mice (Tg) expressing human *APOE,* are lower than apoE3. Thus, our therapeutic target for *APOE4* carriers is increasing apoE levels and decreasing Aβ levels. We used the EFAD-Tg mice, which specifically overexpress Aβ42 and express human *APOE4* (E4FAD) or human *APOE3* (E3FAD). ABCA1 is the major transporter of lipid to apoE-containing lipoproteins in the CNS. Thus, ABCA1 is a promising therapeutic target for increasing apoE levels by increasing its stability via an increase in lipidation. Artery Therapeutics, Inc. developed novel ABCA1 agonists, including CS6253 (Cs), for the treatment of peripheral cardiovascular disease. Cs demonstrates high selectivity and potency for ABCA1-mediated cholesterol efflux in a process where ABCA1 protein is stabilized. Both male and female E4FAD and E3FAD mice were treated with Cs using a prevention (4-8 months) paradigm. To establish dose, an *in-vitro* screen and PK analysis was done. In vitro, Cs increased apoE levels by 10-20-fold and the lipoprotein cholesterol efflux capacity in primary astrocytes expressing apoE3 or apoE4. *In-vivo,* Cs is brain penetrant, reaching higher concentrations than that needed for *in vitro* efficacy. Cs increased ABCA1 levels and reduced both soluble and insoluble Aβ as well as amyloid deposition in brains of male E3FAD and E4FAD mice. In male E3FAD mice, Cs increased learning in Morris Water Maze, synaptic viability, and reduced Aβ deposition and astrogliosis. There were no significant effects in female E3FAD or E4FAD mice except for an increase in ABCA1 levels. In summary, activation of ABCA1 by Cs was effective in male EFAD mice (E3FAD > E4FAD) in preventing synaptic loss, neuroinflammation, Aβ deposition, and reduction in soluble Aβ levels. Further investigation is needed to understand the mechanisms underlying sex differences with regard to ABCA1 activators, and to design optimal treatment paradigms for Cs-based ABCA1 agonism as a therapeutic for AD.

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Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.15/J4

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Modulation of circadian activity in pathological and non pathological aging

Authors: S. SUNDARAM, *D. GULICK
Univ. of South Florida, Tampa, FL

Abstract: Patients with Alzheimer's disease (AD) often suffer a disruption of circadian clock function, resulting in a constellation of abnormal behavior patterns in the evening hours, termed Sundown Syndrome (SS). Recent studies suggest modulators of the endogenous clock, particularly casein kinase 1 (CK1) isoforms ε and δ, as possible therapeutic targets for the alleviation of SS-related symptoms. CK1 is a serine/threonine kinase responsible for the phosphorylation and subsequent turnover of the Period (PER) protein, which is an essential component of the negative arm of the molecular circadian clock. We have hypothesized that PF-670462, a selective inhibitor of the CK1 ε/δ isoforms, will reduce SS-like behaviors in models of both pathological (AD) and non pathological aging. We have studied this in 7-10 month-old APP/PS1 transgenic mice as a model of β amyloid neuropathology commonly seen in AD, and in 18 22 month-old C57BL/6J mice as a model of normal aging. Changes in cognitive capacity and histopathology were studied among the following cohorts: 1) APP/PS1 + PF-670462, 2) APP/PS1 + vehicle (VEH), 3) C57BL/6J + PF-670462, and 4) C57BL/6J + VEH. We assessed changes in behavior between the cohorts on a variety of behavior measures, including anxiety (open field test), spatial memory (Y maze test), depression (forced swim test), and learning (fear conditioning). Brain tissue was collected following behavioral testing, and immunohistochemistry was performed to assess changes in levels of β-amyloid, PER1, and BMAL1 (a circadian positive arm transcription factor) in each condition. PF-670462 rescues both cognitive and behavioral deficits in these models when compared to controls, and these improvements are associated with decreases in β amyloid aggregation and reduced longer peak in the expression of PER1 across the circadian day. Thus, therapeutic targeting of endogenous modulators of the circadian clock presents a unique, yet efficacious method of symptom reduction for SS in AD.

Disclosures: S. Sundaram: Other; University of South Florida. **D. Gulick:** A. Employment/Salary (full or part-time):; University of South Florida.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.16/J5

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Testosterone improves memory and strength in diabetic mice

Authors: *S. A. FARR[1], M. L. NIEHOFF[2], K. A. ROBERTS[2], D. A. ROBY[2], J. E. MORLEY[2]
[1]St Louis Univ/VA Med. Ctr., Saint Louis, MO; [2]Intrnl. Medicine/Geriatrics, St. Louis Univ. Sch. of Med., St. Louis, MO

Abstract: Background: Diabetes is a costly, multidimensional disease that can lead to significantly increased risks for patients, including those associated with a loss of cognition and physical strength, as well as a decreased level of testosterone in male patients. The goal of this study was to determine whether testosterone treatment would be effective in improving memory and muscle strength in diabetic mice. **Methods:** The subjects were 36 male CD-1 mice. Twenty-five were intravenously injected with streptozotocin, 150mg/kg, to induce a diabetic state. Once the appropriate mice were confirmed to have diabetes, time-release testosterone pellets were implanted (11 nondiabetic mice and 13 diabetic mice received placebos and 12 diabetic mice received testosterone). Four weeks later the mice were tested for memory (novel object recognition and T-maze), activity (open field) and strength (string hang, cage hang, rod, and grip strength meter tests). Following the completion of cognitive and strength testing brain and muscle tissue samples were collected for biochemical analysis. **Results:** In the novel object recognition test, the placebo-treated diabetic mice spent significantly less time investigating the novel object compared to both the diabetic mice that received testosterone treatment and the nondiabetic controls ($p<0.01$). In T-Maze retention, placebo-treated diabetic mice took a greater number of trials to reach criterion compared to the testosterone-treated diabetic mice and the nondiabetic mice. Grip strength test indicated diabetic mice that received a placebo performed significantly worse than the diabetic mice that received testosterone ($p<0.05$) and the nondiabetic mice ($p<0.0001$). In the rod test, placebo-treated diabetic mice spent significantly less time balanced on the rod than nondiabetic mice ($p<0.01$), there was no difference between the testosterone-treated diabetic mice and the placebo-treated nondiabetic mice. During the activity test, the placebo-treated diabetic mice traveled significantly less distance than both the nondiabetic mice and the testosterone-treated diabetic mice ($p<0.05$). **Conclusion**: Testosterone improved memory and strength, in the testosterone-treated diabetic mice compared to the placebo-treated diabetic mice in T-maze and novel object recognition, grip strength, and rod test. The current results suggest testosterone could be a treatment for the memory- and strength-related problems associated with diabetes.

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Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.17/J6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01NS042652

Title: Distribution of insulin in brain after intranasal administration

Authors: *J. J. LOCHHEAD[1], P. RONALDSON[2], T. P. DAVIS, 85716[2]
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Abstract: In the brain, insulin acts as a growth factor, regulates energy homeostasis, and is involved in learning and memory acquisition. Many central nervous system (CNS) diseases have deficits in insulin signaling. Pre-clinical studies have shown intranasal insulin is neuroprotective in models of Alzheiemer's disease, Parkinson's disease, and traumatic brain injury. Clinical trials have shown intranasal insulin elicits beneficial cognitive effects in patients with Alzheimer's disease. Previous studies have shown insulin can be detected within the CNS within minutes following intranasal administration. The anatomical pathways which insulin utilizes to reach the CNS and the cellular targets within the CNS after intranasal administration, however, are not fully understood. In the current study, we intranasally administered fluorescently labeled insulin and imaged its localization within the brain and trigeminal nerves. Our data indicates intranasal insulin is able to reach cellular targets within the CNS along extracellular components of the trigeminal nerve. Upon CNS entry, we found FITC-insulin colocalized with the insulin receptor. These findings suggest the intranasal route of administration is able to rapidly deliver insulin to the CNS and subsequently activate neuroprotective insulin signaling pathways.

Disclosures: J.J. Lochhead: None. **P. Ronaldson:** None. **T.P. Davis:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.18/J7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Fondo Mixto del Estado de Jalisco FOMIXJAL 2014-01-250508

Title: Effect of mesenchymal stem cell-derived exosomes on neurogenesis of Alzheimer's disease mouse model

Authors: *E. E. REZA-ZALDIVAR[1], Y. K. GUTIERREZ-MERCADO[2], S. SANDOVAL-AVILA[2], M. A. HERNANDEZ-SAPIENS[2], A. L. MARQUEZ-AGUIRRE[2,3], A. A. CANALES-AGUIRRE[2]
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Abstract: Alzheimer disease (AD) is the most common type of dementia that affects regions of the central nervous system, which are synaptically plastic and are involved in higher functions such as the acquisition of new information as learning and memory. Currently, an effective cure for AD is not available. Therefore, cell therapy has emerged as an alternative for the treatment of AD. The use of adult stem cells, as neural stem cells and mesenchymal stem cells (MSC) of bone marrow and adipose tissue, has the potential to decrease cognitive deficits, possibly by reducing neuronal loss through blocking apoptosis, increasing neurogenesis, synaptogenesis and angiogenesis. These processes are mediated primarily by secretion of many growth factors, anti-inflammatory proteins, membrane receptors and microRNAs, mainly released into exosomes. These nanovesicles could be used as part of strategy to promote neuroplasticity, improving cognitive impairment and neural replacement in AD due its capacity to encapsulate and transfer several functional factors like proteins, lipids and regulatory RNA. The aim of this study was evaluated effects of MSC-derived exosomes in neurogenesis and cognitive capacity of AD mouse model. The MSC-derived exosomes were obtained from conditioned media using ultracentrifugation and subsequently identified by western blot for CD81 expression. For model establishing, 48 C57BL/6 mice of 6-8 old week were used. The AD model was carried out administering 10 ng/ μL of beta amyloid (βA) in Dentate Gyrus (DG) bilaterally. Morris Water Maze (MWM) and Novel Object Recognition (NOR) tests was performed to evaluate cognitive deficits past 15 days administration. Afterwards, the different treatments were administrated (10 ug/μL exosomes, PBS and $1x10^6$ MSCs) in DG. 14 and 28 days post treatments administration, MWM and NOR were carried out to evaluate cognitive capacity, then, brains were collected, fixed and sliced to determine neurogenesis by immunofluorescence using Nestina, Doublecortina, PSA-NCAM, Tuj-1, and NeuN antibodies. Here, we found that exosomes

administration stimulates neurogenesis in the SVZ, besides of reduce cognitive impairment produced by βA administration, these effects are similar to those shown in the MSC. This may allow the development of cell-free therapeutic strategies for AD. Despite these results, is import understand the molecular signaling in these events of neuroplasticity and how the cognitive improvement is performed.

Disclosures: Y.K. Gutierrez-Mercado: None. **S. Sandoval-Avila:** None. **M.A. Hernandez-Sapiens:** None. **A.L. Marquez-Aguirre:** None. **A.A. Canales-Aguirre:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.19/J8

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Automated cognitive testing in mouse models relevant to Alzheimer’s disease

Authors: *M. LOOS[1], C. M. HELDRING[2], B. KOOPMANS[1], E. REMMELINK[1], M. VERHAGE[3], R. E. VAN KESTEREN[2], A. B. SMIT[2]
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Abstract: Alzheimer’s disease (AD) is characterized by progressive decline in cognitive function. For preclinical testing of novel interventions, for instance against the effects of Aβ or Tau, it is key to develop robust tests in mice that assess cognitive functions relevant to AD. We previously described an automated one-night CognitionWall discrimination learning task that can be used longitudinally. In this automated home-cage (PhenoTyper)-based task, mice obtain a food reward every fifth time they pass through one of three entrances in a wall placed in front of a reward dispenser (CognitionWall). The task likely engages the hippocampus, since it requires short-term and/or working memory as well as pattern separation, which are cognitive functions relevant to AD. A systemic injection of a low dose of MK-801, a non-competitive antagonist of NMDA receptors that attenuates LTP, impaired discrimination learning in wild type mice, as demonstrated by a significantly increased number of entrances to reach the learning criterion (80% through the correct entrance). We investigated whether a phosphodiesterase (PDE9) inhibitor was able to revert this cognitive deficit. We observed that transgenic APP/PS1 mice were significantly slower at reaching the learning criterion, not only around the age at which amyloid plaques start to be visible (26 - 30 weeks of age), but also before plaque formation at 16 weeks of age. We investigated the potential beneficial effect of BACE1 inhibition as well as other proof-of-concept interventions in this task. Characterization of cognitive performance of

Tau models in this task such as the P301S and htau is ongoing. Taken together, this series of studies confirms the idea that this automated cognitive task is instrumental in preclinical testing of interventions targeting AD.

Disclosures: **M. Loos:** A. Employment/Salary (full or part-time):; Sylics (Synaptologics BV). **C.M. Heldring:** None. **B. Koopmans:** A. Employment/Salary (full or part-time):; Sylics (Synaptologics BV). **E. Remmelink:** A. Employment/Salary (full or part-time):; Sylics (Synaptologics BV). **M. Verhage:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sylics (Synaptologics BV). **R.E. Van Kesteren:** None. **A.B. Smit:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sylics (Synaptologics BV).

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.20/J9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R15NS091934

Title: Granisetron, a selective 5-HT3 receptor antagonist, alleviates AD pathology in TgSwDI mouse model through CREB pathway

Authors: *S. B. RIHANI, A. KADDOUMI
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Abstract: Alzheimer's disease (AD), the most common form of dementia, is a progressive neurodegenerative disorder with no available disease-modifying treatment to slow or reverse its progression. Several studies in aging and AD demonstrated a compromised blood-brain barrier (BBB) and disrupted brain intracellular Ca^{2+} homeostasis in patient's brains. Therefore, enhancing the BBB integrity in addition to normalizing intracellular Ca2+ homeostasis could be an effective strategy to treat AD. Recently, we developed a high throughput-screening assay to screen compounds that enhance BBB integrity, which identified multiple hit compounds. Among these hits, granisetron emerged as a potent drug. Granisetron is an FDA approved selective serotonin 5-HT3 receptor antagonist widely used for clinical treatment of chemotherapy-induced nausea and vomiting. The aim of this study was to evaluate granisetron potential as a therapeutic molecule against AD. To study this aim, granisetron was tested in C57Bl/6J young and aged (n=7/group) wild type mice for its effect on BBB tightness, and in TgSwDI mice (n=5/group) as a model for AD. Findings from immunostaining, western blot and ELISA demonstrated the one-

month treatment with granisetron to enhance the BBB integrity in both aged and AD mice. This effect was associated with an overall reduction in Aβ load and neuroinflammation in the brains of TgSwDI mice. Supported by proteomics analysis and findings from in vitro mechanistic studies, granisetron rectified Aβ-induced Ca^{2+} dyshomeostasis by restoring CaMKII/CREB and PKA/CREB pathways in TgSwDI mice brains, which was associated with a significant improvement in the cognitive function. These results support granisetron repurposing as a potential drug to hold, slow and/or treat AD.

Disclosures: S.B. Rihani: None. **A. Kaddoumi:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.21/J10

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Effects of antioxidant in mouse model for Alzheimer's: A behavioral phenotyping and microdialysis study

Authors: *M. MONBUREAU[1], A. F. MALIK[2], P. J. NORTHEY[2], J. ROESER[2], E. HOLLAND[2], C. CIARDIELLO[2], N. MORISOT[2], C. ZHU[2], M. G. VAN DER HART[2], H. B. JANSSENS[2], A. RASSOULPOUR[2]
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Abstract: There is a good amount of evidence that a good antioxidant status may be protective against cognitive decline (Mecocci et al. 2018). However, evidence both supporting and refuting the benefits of antioxidants on Alzheimer's disease and cognitive performance is abundant, leading to uncertainty in the field. In rodents, treatment with Sulforaphane inhibited Aβ oligomer production, reduced tau hyperphosphorylation, oxidative stress, and neuroinflammation and prevented decline in spatial learning and memory in a mouse model for AD and had similar effects in AD-like lesions in a diabetic mouse model (Hou et al., 2018, Pu et al., 2018). On the other hand, exercise, but not antioxidants reversed ApoE4 associated impairments in ApoE mice (Chaudhari et al., 2016). Evidence is not more conclusive in humans. Epidemiology studies suggest diets rich in antioxidants reduce risk of AD (Morris, 2009), while clinical studies showed AD patients treated with antioxidants showed some functional improvement, but no cognitive benefits were observed (Sano et al., 1997, Petersen et al., 2005). A randomized, double blind, placebo-controlled clinical trial in mild to moderate AD patients showed that antioxidant treatment did not influence CSF biomarkers related to amyloid or tau pathology, but the treatment did reach its target, as it lowered CSF F2-isoprostane levels in the brain, a biomarker for oxidative stress. However, the treatment may have caused faster cognitive decline (Galasko

et al., 2012). In the current study, we attempted to elucidate whether an antioxidant could reduce oxidative stress in the brain and whether this has an impact on AD biomarkers and cognitive performance in the Tg2576 mouse model for Alzheimer's disease. To this aim, we treated 12-week-old female Tg2576 mice with Saffron (50 mg/kg daily dose 5-7 days weekly for 8 weeks). Saffron, a potent antioxidant, has been shown to improve learning and memory in an aged mouse model (Papandreou et al., 2011), and the neuroprotective and antioxidant effects of saffron have been previously reported (Papandreou et al., 2011, Linardaki et al., 2012). After 8 weeks of treatment, behavioral phenotype was evaluated in the Y-maze, NOR, open field, EPM, L/D box, and Fear conditioning. Then, microdialysis was conducted in freely moving animals, along with terminal CSF and plasma. In dialysates, Aβ 41, 42, and 38, and Tau along with Ach, 5-HT, NE, DA, GABA, Glu were measured. Further, F2-isoprostane levels were measured in CSF, dialysates, and brain. We found that behavioral deficits and Aβ levels were higher in Tg2576 mice compared to WT, but 8-weeks of treatment with Saffron did not reverse this phenotype.

Disclosures: M. Monbureau: None. **A.F. Malik:** None. **P.J. Northey:** None. **J. Roeser:** None. **E. Holland:** None. **C. Ciardiello:** None. **N. Morisot:** None. **C. Zhu:** None. **M.G. van der Hart:** None. **H.B. Janssens:** None. **A. Rassoulpour:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.22/J11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA (U01 AG054444-01A1)
BrightFocus Foundation
Alzheimer's Drug Discovery Foundation
The Harrington Discovery Institute

Title: A novel, small-molecule activator of glutamate transporter EAAT2 translation delays disease progression in a tauopathy model of Alzheimer's disease

Authors: J. B. FOSTER[1], F. ZHAO[1], R. LASHLEY[1], K. J. HODGETTS[2], *C.-L. G. LIN[1]
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Abstract: Current therapeutics for Alzheimer's disease (AD) are limited in efficacy as they only provide temporary, palliative care, but do not significantly modify disease progression or outcomes. Therefore, there is need to develop novel therapeutics that can stop, slow, or even reverse disease progression. Glutamatergic transmission is essential for numerous neuronal

processes but is elevated in AD patients and can lead to increased tau phosphorylation and excitotoxicity. Excitatory amino acid transporter 2 (EAAT2) is responsible for clearing glutamate from the synaptic cleft and preventing excitotoxicity. We have developed a small-molecule compound series that is capable of increasing EAAT2 expression through a translational induction mechanism and previously showed that it has profound efficacy in an amyloid-β (J20) AD model. Here, we evaluated the efficacy of an advanced compound in rTg4510 mice - an aggressive model that exclusively exhibit tau-related pathology, including increased glutamate release. We hypothesized that long-term compound treatment will delay disease progression, improve synaptic integrity, and restore normal behavior. rTg4510 mice were treated with LDN/OSU-215111 (10 mg/kg P.O. via voluntary consumption) beginning at an early-symptomatic time-point (p60) and were treated to p120 or p240. At a moderate stage of disease, p120 compound-treated rTg4510 mice performed significantly better in cognitive tasks (novel object recognition/T-maze), a working memory test (Y-maze), and showed significantly reduced hyper-exploratory behavior. Even at a late stage (p240), where disease pathology is severe, treated rTg4510 mice still performed better in the novel object recognition task, as well as the Barnes Maze, and display normalized exploratory behavior. Consistent with 8-month behavioral data, hippocampal CA3-CA1 long-term potentiation (LTP) in compound-treated rTg4510 mice was normalized. At both time points, compound treatment partially normalized EAAT2 protein levels and preserved synaptic integrity. It was also determined that compound treatment delayed the deposition of toxic tau-species, provided neuroprotection, and reduced neuroinflammation. Importantly, when treatment was ceased at p240, LTP and behavior remained significantly improved relative to vehicle-treated mice 30d later. We are currently working to better define the mechanism by which this compound-series provides protection in AD. This study suggests that LDN/OSU-215111 may be a viable, clinically-relevant, and disease-modifying treatment for the many facets of AD.

Disclosures: J.B. Foster: None. **F. Zhao:** None. **R. Lashley:** None. **K.J. Hodgetts:** None. **C.G. Lin:** None.

Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.23/J12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: SAF2016-33307
2017SGR106

Title: Neuroprotective effects of the novel nmda channel blocker, rl-208, in samp8 mice model

Authors: *C. G. FERRE[1], J. COMANYS-ALEMANY, Jr[1], A. LARISA TURCU, Jr[2], R. LEIVA[2], S. VÁZQUEZ CRUZ[2], M. PALLÀS[1]
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Abstract: Alzheimer's disease (AD) is the main cause of dementia, a group of brain disorders with behavioral abnormalities and memory loss. Currently, there is no effective therapy able to cure or reduce the AD progression. Memantine, a non-competitive NMDA receptor antagonist improved in cognition and molecular alterations after preclinical treatments. Nevertheless, such neuroprotective effects of memantine in preclinical studies do not translate into clinical results. For this reason, our research group has synthesized a new NMDA channel blocker, RL-208 bearing an amine polycyclic scaffold. The present work evaluated the *in vivo* efficacy of the RL-208 in cognition and cellular pathways in SAMR1 and SAMP8. Males, 5 months-old, were divided into four groups: two control groups, SAMR1 and SAMP8, and two mice treated groups with both strains. RL-208 administered in drinking water, 5 mg/Kg per day during 4 weeks. Behavioral tests (Elevated Plus Maze (EPM), Open Field (OF), Novel Object Recognition Test (NORT) and Object Location Test (OLT)) were applied and molecular analysis was performed through Western blot, RT-PCR and Fluorimetric Assay in hippocampus tissue. After the treatment, behavioral changes in both treated-mice groups were found. Furthermore, better cognitive performance was found in SAMP8 treated with RL-208, whereas SAMR1 maintained cognitive functions. Consistent with behavioral results, RL-208 treated-mice groups significantly reduced protein levels of a neuropathological marker such as Tau hyperphosphorylation (Ser396 and Ser404) and increased gene expression of *Adam10.* Remarkably, the RL-208 increased gene expression of *Neprilysin* contributing to β-amyloid degradation in the brain. Moreover, it was observed increased gene expression of antioxidant protective enzymes *Hmox1 and* GPx1 protein levels as well as the reduction of hydrogen peroxide levels in both treated groups. Taken together, these results demonstrate the neuroprotectant role of RL-208 through specific biological pathways related to aging and neurodegenerative diseases, having a potential therapeutic role in brain disorders.

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Poster

468. Alzheimer's Disease and Other Dementias: Therapeutic Strategies: Preclinical Animal Models III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 468.24/J13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NRF-2012M3A9C4048795
NRF-2017R1A5A2014768

Title: HCE01 prevents memory impairments induced by heat stress in mice

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Kyung Hee Univ., Seoul, Korea, Republic of

Abstract: Under heat stress conditions, prolonged heat stress causes neuroinflammation and neuronal damage, which are well-known causative factors for memory loss in animals' brain. HCE01 has been used for many years as an important traditional medicinal herb for treating fever. However, the effects of HCE01 on hyperthermia-induced memory impairments have not been investigated. In the present study, we investigated the effects of HCE01 on neuropathological changes induced by high temperature. To conduct this study, we treated mice with heat stress (43°C) for 15 min per day, repeated with 3 days. The administration of HCE01 significantly reduced the elevation of mouse body temperatures induced heat stress. Additionally, HCE01 attenuated heat stimuli-mediated stress responses via inhibiting the release of cortisol and upregulation of HSP70 and c-Fos in mice. In the mouse hippocampal CA3 region, HCE01 inhibited thermal stress-triggered gliosis, activation of astrocytes and neuronal loss. HCE01 also reduced the hyperthermia-induced expression of NF-κB, TNF-α and IL- 1β in the hippocampus of mice. For the underlying mechanisms, we found that HCE01 significantly decreased pro-inflammatory mediators such as IL-9 and IL-13 in the hypothalamus of mice. Furthermore, we observed that HCE01 attenuated the cognitive functions impaired by thermal stress. These results indicate that HCE01 improves the heat stress-mediated memory dysfunction and brain damage via reduction of hyperthermia and neuroinflammation in mice. Based on the study, fever-reducing medicinal herb might attenuate heat stress-induced neural damage.

Disclosures: E. Huh: None. **W. Lee:** None. **M. Oh:** None.

Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 469.01/J14

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Quantification of low abundant neurodegenerative biomarkers in blood using Milliplex and SMC high sensitivity immunoassays

Authors: *J. HWANG, L. CHEN, A. SAPORITA, Q. XIAO
R&D, Milliporesigma, Saint Louis, MO

Abstract: Neurodegenerative disorders such as Alzheimer's Disease (AD) have become more prevalent worldwide as population ages. Quantification of protein biomarkers in patients with AD and PD is important for monitoring progression. Monitoring neurodegenerative biomarkers in cerebrospinal fluid (CSF) has led to much of our current understanding of AD. However, due to the invasive nature of collecting CSF samples, new blood biomarkers are needed. Here we report our results from screening biomarkers most commonly associated with neurodegenerative diseases using both Milliplex® multiplex immunoassays for CSF screening and Single Molecule Counting (SMC™) high sensitivity immunoassays for serum and plasma screening. CSF samples from normal versus AD patients displayed significant differences in Aβ40, Aβ42, phosphorylated Tau, GFAP, NSE, UCHL1, PRNP and NRGN levels. However, many of these neurodegenerative disease biomarkers are not detectable in some blood samples due to low abundance and thus require higher sensitivity immunoassays. For example, our Milliplex assays for Aβ42 detect these peptides in CSF, but lack the sensitivity for measurement in blood. To this end, we developed SMC™ Aβ40 and Aβ42 immunoassay kits that can accurately quantitate Aβ40 and Aβ42 levels in human, mouse, and rat blood samples. The limits of detection (LOD) of Aβ40 and Aβ42 in these novel assay kits are 0.67pg/mL and 1.68 pg/mL, respectively. Using this high sensitivity technology, Aβ40, but not Aβ42, was shown to have significant correlation to AD plasma samples. In summary, SMC high sensitivity immunoassay kits can provide a powerful non-invasive biomarker tool in studying the pathogenesis of neurodegenerative diseases such as Alzheimer's disease.

Disclosures: J. Hwang: A. Employment/Salary (full or part-time):; MilliporeSigma. **L. Chen:** A. Employment/Salary (full or part-time):; MilliporeSigma. **A. Saporita:** A. Employment/Salary (full or part-time):; MilliporeSigma. **Q. Xiao:** A. Employment/Salary (full or part-time):; MilliporeSigma.

Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 469.02/K1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R44AG050454
R43AG058350

Title: Novel molecular structures that detect amyloid β associated with Alzheimer's disease

Authors: *S. RASOOL[1,2], L. RANDOLPH[1], J. NGOLAB[2], R. D. SOUZA[1], J. YANG[1], S. SARRAF[1], R. A. RISSMAN[3]
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Abstract: The accumulation and deposition of amyloid deposits in the brain is the hallmark of many neurodegenerative diseases including Alzheimer's (AD). To date, late-stage diagnosis of AD is achieved using functional memory and behavioral tests; however, early stage asymptomatic diagnosis remains a challenge. Amydis has synthesized a new family of novel fluorescent molecules and evaluated their capability to bind with amyloid β (Aβ), which is involved in the pathogenesis of AD. Amydis novel probes bind to aggregated Aβ and fluorescently stained amyloid deposits in human brain tissues from patients with AD. Amydis has focused on two key areas: (a) the diagnostic utility of these molecular probes in AD, CAA and other amyloid associated neurodegenerative diseases and (b) the use of amyloid-binding agents to understand pathophysiological mechanism of the disease. These fluorescent amyloid-binding probes display a significant increase in fluorescence emission upon binding with aggregates of Aβ40 and Aβ42 as compared to the emission of the free probe in solution. To assess whether these novel molecular probes can stain amyloid deposits in brain tissue, free floating sections of the hippocampal region of a patient with familial Alzheimer's disease (FAD) were stained with an Aβ sequence specific (6E10) antibody along with our probes followed by fluorescence microscopy. The binding of these probes colocalized with the immunoreactivity of 6E10 dense core plaques. Additionally, we confirmed that our lead compounds were able to stain amyloid deposits from post-mortem CAA patients. Sections of the median frontal cortex and hippocampus from human CAA brain were stained with a fibril specific (OC) antibody along with these new probes. Fluorescence microscopy revealed that these compounds not only bind to amyloid dense core plaques but also to vascular amyloid β present in cerebral vessels, complementing our results from FAD brain tissue. Moreover, positive staining of these probes completely colocalized with OC positive staining in CAA-laden plaques and Aβ in cerebral vessels. In conclusion, these novel fluorescent compounds can be used not only to detect Aβ associated with AD and CAA, but also have a potential for detecting amyloid biomarkers in other neurodegenerative diseases.

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Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 469.03/K2

Topic: C.02. Alzheimer's Disease and Other Dementias

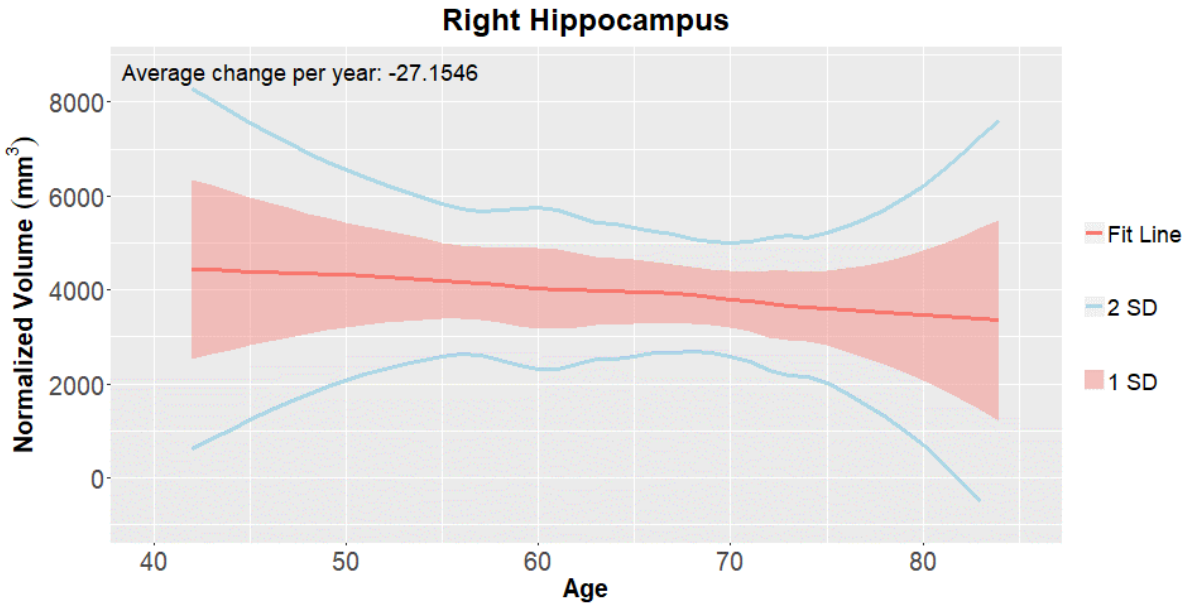
Support: NIH/NIA P50AG005681
NIH/NIA P01AG003991
NIH/NCATS UL1TR000448
R01 EB009352

P30NS098577
NIH/NIA P01AG026276
McDonnell Center for Systems Neuroscience, 22 3922 26239N

Title: Using an amyloid-PET defined cohort to optimize volumetric-based diagnosis of dementia

Authors: *L. N. KOENIG[1], S. KEEFE[1], L. MARPLE[1], B. A. GORDON[1], J. C. MORRIS[1,2], M. MILLER-THOMAS[1], G. S. DAY[1], J. SHIMONY[1], T. L. S. BENZINGER[1]
[1]Washington Univ. In St. Louis, Saint Louis, MO; [2]Knight Alzheimer Dis. Res. Ctr., Saint Louis, MO

Abstract: Background: While hippocampal atrophy is a well-known biomarker of Alzheimer Disease (AD), its use in a clinical setting is limited because atrophy begins years before clinical onset. This preclinical (amyloid positive) stage of AD is undetectable without amyloid biomarkers and is present in over a third of older populations, making it difficult to separate the atrophy of normal aging from AD. Separating atrophy of other dementia types from AD is similarly difficult as the affected regions overlap, though AD-specific patterns of atrophy have been reported. We aim to create atrophy-based biomarkers from structural Magnetic Resonance Images (MRI) that can best distinguish patients with various dementia types. Methods: A cognitively normal (CN) cohort, sourced from the Open Access Series of Imaging Studies (OASIS), was used to determine age-specific norms. Only β-amyloid negative individuals (PiB-PET mean cortical SUVR < 1.42 or AV45-PET < 1.19) who remain CN (CDR=0) for >2 years after neuroimaging were included. Volumes and cortical thicknesses were extracted using the open-source software Freesurfer. After normalizing volumes to intracranial volume, measures were plotted by age and smoothed using a weighted LOESS regression. We next will use an unbiased approach to determine a weighted combination of measures that can best predict clinical diagnoses in symptomatic dementia patients. Results: 184 OASIS subjects age 42 to 84 fit criteria to form the CN cohort. Right and left hippocampal volumes declined an average of 27.15 and 25.90 mm^3 per year, with average volumes of 3897 (535.4) and 3794 (517.8) mm^3. The clinical data from dementia patients is in the process of being extracted. Conclusion: While a single test should not be used for medical diagnoses, structural neuroimaging is routinely obtained in patients with dementia. By increasing the amount of diagnostic information obtained from a structural MRI, our open-source tool will benefit patients and clinicians alike.



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Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 469.04/K3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Alzheimer’s Disease Research Center at Mayo Clinic (AG016574)

Title: Circulating GDF11 is associated with cortical thickness, amyloid burden, and cognitive performance

Authors: *M. J. SCHAFER, A. M. V. WENNBERG, E. J. ATKINSON, P. M. VANDERBOOM, H. R. BERGEN, III, R. C. PETERSEN, M. M. MIELKE, N. K. LEBRASSEUR
Mayo Clin., Rochester, MN

Abstract: Circulating factors that influence neuropathology can be leveraged as clinically useful diagnostic and prognostic biomarkers. Growth differentiation factor 11 (GDF11) is a hypothesized pro-rejuvenative protein that may impart neuroprotective effects through TGF-β signaling. Whether changes in circulating GDF11 levels are associated with cognitive decline

across the Alzheimer's disease (AD) dementia clinical spectrum or are associated with neuroimaging biomarkers of AD, including amyloid PET, cortical thickness on MRI, and hypometabolism measured by FDG-PET, is unknown. Using a highly precise liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay, we explored cross-sectional associations between plasma GDF11 levels and AD imaging biomarkers and cognitive performance among cognitively unimpaired (CU) and mild cognitively impaired (MCI) older adults enrolled in the Mayo Clinic Study on Aging (MCSA). We show that higher GDF11 levels are associated with lower amyloid PET SUVR, as well as greater cortical thickness and brain metabolic activity in AD signature brain regions. Correspondingly, we demonstrate that higher plasma GDF11 levels are associated with better performance in language and memory tests. Our results suggest that circulating GDF11 levels are a potential biomarker of AD-related cognitive aging and early-stage dementia.

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Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

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Title: Changes in EEG due to progression of Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is known as a progressive disease that affects a gradual decline in brain function such as cognitive function, memory capability, and language processing. Recently, many researchers have been tried to early diagnose AD before clinical

symptoms emerge using amyloid-tracer PET and CSF. The biomarkers showed that presymptomatic AD (clinically normal but risk of developing AD) and normal aging can be distinguished. However, these imaging techniques are either very costly or painful due to highly invasive, thus they are difficult to utilize for longitudinal monitoring of disease progression. Electroencephalography (EEG) is a non-invasive neuroimaging technique that can be relatively easy and simple to measure the brain activity changes. In this study, we investigated EEG features and behavior performance according to disease progression from normal controls (NC), presymptomatic AD, prodromal AD to AD. Forty NC (aged 72.4±5.8), twenty patients with presymptomatic AD (aged 75.1±3.8), thirty patients with prodromal AD (aged 76.1±3.5), and eight patients with AD (aged 76.5±3.3) have been recruited in the experiment. All subjects performed three experimental paradigms-visual oddball, 1-back working memory, and verbal fluency task-in a consecutive order during 32-channel wireless EEG with dry electrodes (g.tec, Austria) recording at a sampling rate of 500 Hz. The behavior performances of the oddball and 1-back task were estimated using correct button response. Event-related (de-)synchronization (ERD/ERS) were used as EEG features. In the oddball task, behavior accuracy showed a weak decrease in presymptomatic AD ($p = 0.101$), prodromal AD ($p = 0.082$), and AD ($p = 0.061$) compared to NC. The 1-back performance (both accuracy and reaction time) showed significant decline in AD ($p < 0.05$) compared to the other groups. In addition, reduced beta ERS in centro-parietal area was observed in both prodromal AD and AD compared to NC ($p < 0.1$) during 1-back task. The beta ERS was also decreased in presymptomatic AD, but there was no significant difference compared to NC. We found that there were some differences among NC, prodromal AD, and AD, however, neurophysiological difference between NC and patients with presymptomatic AD was unclear. It may seem to be trivial because we cannot clinically distinguish presymptomatic AD from normal ageing. In further analysis, we will investigate EEG features for each task (cognitive, working memory, and verbal processing) and integrate them into a new biomarker. We expect that integrated features may be helpful for diagnosis of presymptomatic AD, as well as for longitudinal monitoring of disease progression.

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Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 469.06/K5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: National Key Research and Development Program, Ministry of Science and Technology of China Grant No. 2016YFC1300500-03

Title: Mass spectrometry imaging technique reveals a novel visualized metabolism map in the brain of Alzheimer's disease's mouse model

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Abstract: The current therapies for Alzheimer's disease (AD) in clinic are based on neurotransmitters as therapeutic targets. However, using traditional mass spectrometry (MS) coupled to HPLC techniques to analysis the small molecular metabolites in tissue homogenate, it is still not possible to visualize how those neurotransmitters, are generated and metabolized in the whole brain simultaneously during the aging process and AD disease progress. Fully characterization of the disrupted metabolic pathways in aging as well as in the AD brain may provide new diagnostic biomarkers and therapeutic targets for AD. In the present study, we have modified an ambient mass spectrometry imaging (MSI) method based on desorption electrospray ionization (DESI) and we are now able to detect hundreds of small molecular metabolites in situ of whole mouse brain, including the spatial distribution and the relative abundance of metabolites in the brain. We analyzed the alteration of the metabolites in process of ageing and pathogenesis of AD. We observed that more than 100 small molecule metabolites, including neurotransmitter metabolites, i.e. glutamine-glutamate/GABA cycle, were altered at the very early stage in AD model mice (APP23), suggesting the metabolism was disrupted before deposition of Aβ plaques in the brain. Thus, our study reveals metabolic alterations at spatiotemporal resolution that implicated in AD pathogenesis, which may benefit for early diagnosis and drug development for AD.

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Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

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Program #/Poster #: 469.07/K6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AARF-17-533143
NIH-5R01AG048993
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ND EPSCoR UND-0021228
NIH COBRE MS grant 5P30 GM103329 05

Title: Effect of probiotic treatment on metabolic profile of serum and brain prostaglandin and bile acids in a transgenic mouse model of Alzheimer's disease

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Abstract: Increasing evidence suggests the involvement of intestinal dysbiosis and associated metabolic changes in the pathogenesis of various brain disorders. Clinical studies have demonstrated the effectiveness of probiotics for treatment of intestine and brain related diseases. However, the mechanisms by which intestinal microbiota modulate brain functions are unclear. In this study we examined eicosanoids including prostaglandins as well as primary and microbiota-derived bile acids in a mouse model of Alzheimer's disease. Wild type (WT) control C57BL/6 mice were compared to a mouse line that has the human Aβ sequence knocked in to the mouse APP gene along with three disease causing mutations (APP NL-G-F). The animals at 7 months of age were randomly divided into two groups and orally treated with vehicle or probiotic (VSL#3) for 8 weeks. Microbiome analysis was performed to study the effect of probiotic supplementation on intestinal microbiota. Eicosanoids and bile acids were also analyzed in serum and brain using UPLC-MS/MS. The microbiome results showed a significant decrease in the ratio of Firmicutes/Bacteroidetes in vehicle treated AD mice compared to wild type controls suggesting intestinal dysbiosis. VSL#3 supplementation resulted in a dramatic change in microbiota composition in both WT and APP NL-G-F treated lines. Multiple significant decreases in serum and brain bile acids were observed in vehicle treated APP NL-G-F mice as compared to WT controls. Interestingly, VSL#3 feeding significantly altered serum and brain bile acid levels in WT but not APP NL-G-F mice. Various serum eicosanoids were significantly increased in vehicle treated APP-NL-G-F mice as compared to WT controls. However, brain eicosanoids were mostly decreased in vehicle treated APP NL-G-F mice compared to WT controls. Probiotic supplementation had an ability to decrease levels of several serum eicosanoids in APP NL-G-F mice. However, probiotics decreased levels of brain eicosanoids only in WT animals with no effect on APP NL-G-F mice. Our study demonstrates an altered eicosanoid (including prostaglandin) and bile acid metabolome profile associated with intestinal dysbiosis in Alzheimer's disease mice. Moreover, it suggests that probiotic intervention may exert a beneficial effect in AD mice by altering eicosanoid levels in the brain.

Disclosures: H. Kaur: None. **M.Y. Golovko:** None. **C.K. Combs:** None.

Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

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Program #/Poster #: 469.08/K7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NHLBI contract P30-AG010129
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N01-HC-25195
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HL076784

Title: Aging, brain white matter hyperintensities, and structural brain network efficiency in 2257 participants of the framingham heart study

Authors: *S. SEILER[1], E. FLETCHER[1], A. BEISER[2], J. J. HIMALI[2], C. L. SATIZABAL[2], S. SESHADRI[2], P. MAILLARD[1], C. DECARLI[1]
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Abstract: Objective There is evidence that aging and vascular damage affect the structural brain network. Data from large datasets on healthy individuals are scarce. We therefore explored the effects of aging and white matter hyperintensities (WMH) on the structural brain network of 2257 healthy participants of the cross-sectional Framingham Heart Study over a wide age range. Methods We computed the structural brain network of 2257 healthy participants of the Framingham Heart Study (mean age: 54 (13) years, range: 26 to 91 years; 53% female) from diffusion tensor imaging (DTI) probabilistic fiber tractography using the FSL program PROBTRACKX. A connectivity matrix was constructed for 64 automatically segmented gray matter regions, covering the whole cortex. WMH were segmented automatically using published protocols. We calculated global efficiencies for the whole network and nodal efficiencies for 64 individual nodes using the freely available R code “brainGraph”. “brainGraph” is based on published and widely used network analysis protocols. We assessed the relationships between global and nodal efficiencies, age, and WMH volumes using multiple linear regression analyses. To assess regional differences, we computed the structural core of the network using s-core decomposition. All analyses were computed using R and adjusted for age as appropriate, gender, and total cranial volume. Results Lower global efficiency correlated significantly with higher age (β=-0.18, p=9.59x10^{-9}) and higher WMH volume (β-0.14, p=5.11x10^{-7}). Node-wise analysis and s-core decomposition revealed that this relationship was different for nodes belonging to the structural core as compared to more peripheral nodes. Efficiency of core nodes correlated positively with age (β=0.18, p=2.73x10^{-9}), while peripheral nodes showed a negative relationship (β=-0.21, p=2.51x10^{-12}). An age-independent negative effect of WMH volume on efficiency was present in the peripheral network only (β=-0.11, p=5.05x10^{-5}). Conclusion Higher age and larger WMH volumes correlated with lower efficiency of the peripheral network, while the central network shows an opposite relationship. If the age-resistance of the central network expresses the brains scaffolding or a compensatory mechanism in response to age-related changes remains to be determined.

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Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

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Program #/Poster #: 469.09/K8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: H. Lundbeck A/S and Otsuka Pharmaceuticals

Title: Neurophysiological signals as predictive translational biomarkers for Alzheimer's disease treatment: Effects of donepezil on neuronal network oscillations in TgF344-AD rats

Authors: *M. STOILJKOVIC, C. KELLEY, M. HAJÓS
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Abstract: Translational research in Alzheimer’s disease (AD) pathology provides evidence that accumulation of amyloid-β and hyperphosphorylated tau, neuropathological hallmarks of AD, is associated with complex disturbances in synaptic and neuronal function leading to oscillatory abnormalities in the neuronal networks that support memory and cognition. Accordingly, our recent study on transgenic TgF344-AD rats modeling AD, showed an age-dependent reduction of stimulation-induced oscillations in the hippocampus, and disrupted long range connectivity together with enhanced neuronal excitability in the cortex, reflected in greatly increased expression of high-voltage spindles (HVS), an epileptic absence seizure-like activity (Stoiljkovic et al., 2017). To better understand the translational value of observed oscillatory abnormalities in these rats, we examine here the effects of donepezil, an acetylcholine esterase inhibitor clinically approved for AD treatment. Nucleus pontis oralis (nPO) stimulation-induced hippocampal oscillations were recorded under urethane anesthesia in adult (6-months old, n=6) and aged (12-months old, n=5) TgF344-AD and wild-type (WT) rats. Spontaneous cortical activity was monitored in a cohort of freely-behaving aged rats (n=5, for each genotype) implanted with frontal and occipital cortical EEG electrodes. Subcutaneous administration of donepezil significantly augmented stimulation-induced hippocampal theta oscillation in aged WT rats and both adult and aged TgF344-AD rats, which had been previously shown to have diminished response to nPO stimulation. Moreover, in TgF344-AD rats donepezil also significantly increased theta phase-gamma amplitude coupling in the hippocampus during stimulation. However, neither of these effects were significantly changed in adult WT rats. In freely-behaving condition, donepezil treatment had opposite effect on cortical oscillatory connectivity in TgF344-AD and WT rats, and it reduced the occurrence of HVS activity in TgF344-AD rats. Together, these results imply that pharmacologically enhancing cholinergic tone with donepezil could

partially reverse oscillatory abnormalities in TgF344-AD rats, which is in line with its clinical effectiveness in AD patients. Therefore, our study suggests good translational opportunities for these neurophysiological signals recorded in TgF344-AD rats, and their application could be considered in drug discovery efforts for developing therapies with disease-modifying potential.

Disclosures: M. Stoiljkovic: None. **C. Kelley:** None. **M. Hajós:** None.

Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01NS034467
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Zilkha Senior Scholar Support

Title: Impact of APOE4 genetic risk on neurovascular unit biomarkers in early cognitive dysfunction

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Abstract: Abstract:
Vascular dysfunction is increasingly recognized in the pathophysiology of Alzheimer’s disease (AD), and measures of vascular dysfunction can be evaluated using cerebrospinal fluid (CSF) and imaging-based biomarker approaches. A clinical need exists to identify reliable biomarkers for early AD diagnosis, early intervention, and evaluating the efficacy of clinical trials. Here, we quantified novel CSF biomarkers of responses and injury to the neurovascular unit (NVU) – comprising vascular cells, glia, and neurons – using antibody-based single/multiplex assays. CSF was obtained from human subjects of the University of Southern California Alzheimer’s Disease

Research Center (ADRC), Huntington Medical Research Institutes, and the Washington University Knight ADRC. CSF biomarkers of the NVU were analyzed in relation to subjects' cognitive status [no cognitive impairment (NCI) vs. mild cognitive impairment (MCI)] and AD genetic risk factor apolipoprotein E-ε4 (*APOE4*) [carriers vs. non-carriers]. We found that CSF-based biomarkers of the blood-brain barrier/vascular injury are altered in *APOE4* carriers versus non-carriers with NCI and these markers are further altered in *APOE4* carriers versus non-carriers with MCI. Furthermore, preclinical changes in the mural cell vascular injury marker, soluble platelet-derived growth factor receptor-β (sPDGFRβ), is related to early cognitive impairments, independent of CSF amyloid-β $(Aβ)_{42}$ and phosphorylated tau levels, and predict longitudinal decline in cognitive function. These data suggest that CSF biomarkers of cerebrovascular dysfunction are altered early in cognitive impairment and accelerated in *APOE4* carriers. Moreover, vascular biomarkers (e.g., CSF sPDGFRβ) may be a useful predictor of subtle cognitive dysfunction. Altogether these data importantly elucidate the detectable changes in CSF of neurovascular injury across the preclinical-MCI-AD spectrum.

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Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 469.11/K10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R21AG055034
AARG-17-532905
P01AG052350
P50AG005142

Title: Neuropsychological decline improves prediction of dementia beyond ad biomarker and mci diagnoses

Authors: *D. A. NATION[1], J. K. HO[1], S. DUTT[2]
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Abstract: Introduction: Cognitive diagnosis in older adults is traditionally based on a single exam, but serial testing is required to detect cognitive changes in preclinical Alzheimer's disease when cognitive performance is within normal range. We evaluated the prognostic utility of longitudinal diagnosis of cognitive decline in older adults with and without preclinical

Alzheimer's disease. Methods: Regression models quantified 12-month neuropsychological decline relative to normative expectations among dementia-free older adults (N=1074). Progression to Alzheimer's dementia over follow-up (18-120 months) was diagnosed using independent modes of assessment. Baseline brain volumes were compared between older adults with and without longitudinal decline using voxel-based morphometry. Results: In Cox regression models controlling for age, sex, education, apolipoprotein E4, and baseline cognitive diagnosis, neuropsychological decline predicted increased dementia risk,X^2=69.810, p<.001, odds ratio=2.903, even after correction for cerebral spinal fluid biomarkers (amyloid-beta, phosphorylated tau, total tau), X^2=28.202,p<.001, odds ratio=2.364. Voxel-based morphometry analysis indicated smaller hippocampal and medial temporal volume in participants with neuropsychological decline. Discussion: Preclinical decline was detectable and highly predictive of future dementia. Patients showing longitudinal decline exhibited greater evidence of hippocampal and medial temporal lobe atrophy. Assessment of neuropsychological trajectory would improve patient selection and randomization for clinical trials.

Disclosures: D.A. Nation: None. **J.K. Ho:** None. **S. Dutt:** None.

Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

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Program #/Poster #: 469.12/K11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: The UIC Chancellor's Innovation Fund (CIF) Proof of Concept Awards program

Title: Oligomeric abeta as a mechanistic biomarker for alzheimer's disease in human plasma

Authors: *M. LADU[1], N. COLLINS[2], D. BALU[1], C. ESTRADA[1], J. GEORGE[1], L. J. VAN ELDIK[3], A. C. VALENCIA-OLVERA[1]
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Abstract: *APOE4* is the greatest genetic risk factor for Alzheimer’s disease (AD), increasing risk up to 15-fold compared to the more common *APOE3*. Autosomal dominant mutations that increase the peptide amyloid-β (Aβ42) cause the rare familial form of AD. Aβ42 aggregate to form amyloid plaques and soluble oligomeric Aβ (oAβ), the latter considered a proximal neurotoxin. Among *APOE4* carriers, females have an increased AD risk, rate of cognitive loss and accumulation of Aβ42 compared to males. Thus, our hypothesis is that oAβ is a mechanistic biomarker that can track AD progression based on *APOE* genotype and sex. Many current AD biomarkers for are not predictive, reliably diagnostic or easily measured. To test the value of oAβ as a biomarker, we developed a unique monoclonal antibody, MOAB-2, that enabled

development of an ELISA that detects 1pg/ml oAβ. In addition, we developed the EFAD mice, a novel preclinical transgenic mouse that overexpresses human Aβ42 and expresses the human *APOE* genotypes. In EFAD mouse brains, Aβ42 levels correlate with *APOE*-modulated AD pathology, while oAβ levels correlate with *APOE* and sex-modulated AD pathology, as well as and disease progression. Therefore, we measured oAβ levels in brain and plasma from healthy controls and AD patients with *APOE3* or *APOE4* genotypes (n=50-72, from the Alzheimer's Disease Center of the University of Kentucky). In brain and plasma, oAβ levels were higher in AD vs. control. In brain, stratification by genotype and sex within the AD cohort, reveal oAβ levels higher only in *APOE4/4* females. In plasma, stratification of the AD cohort by sex and *APOE* reveal significantly greater oAβ levels in *APOE4* vs. *APOE3* and females vs. males. Importantly, when the data is further stratified by sex within genotype, oAβ levels are higher in female *APOE4/4* vs. male *APOE4/4* and in male *APOE4/4* vs. male *APOE3/4*. These results support our hypothesis that changes in oAβ levels underlie the *APOE4* and female-induced risk for AD. Furthermore, oAβ changes driven by *APOE4* and female sex are detected with higher sensitivity in plasma vs. brain indicating a promising non-invasive novel mechanistic biomarker. Future longitudinal studies will determine thresholds and establish the predictive value of oAβ in plasma as a mechanistic biomarker. Such a mechanistic biomarker is critical for effective prediction of AD and will enable clinical studies to determine the efficacy of predictive therapeutics.

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Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

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Program #/Poster #: 469.13/K12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 973 project: 2015CB755602
The Science Fund for Creative Research Group of China: 61421064
NSFC projects: 91432105, 91432111, 81527901, and 31625013

Title: The lesion analysis of amyloid plaques in the three-dimensional level of whole brain

Authors: *B. LONG, J. ZHANG, X. LI, H. GONG
Wuhan Natl. Lab. for Optoelectronics, Hubei, China

Abstract: Amyloidosis of the central nervous system has been widely proved to be one of the main hallmarks in Alzheimer's disease (AD). According to the amyloid cascade hypothesis, the accumulation of neurotoxic amyloid plaques in the brain is intrinsic and fundamental for disease

onset, however the spatiotemporal origins of the lesions remain unknown. Here, we explored an easy-handling staining method to label whole brain amyloid plaques and imaged with fluorescence micro-optical sectioning tomography system (fMOST). We performed brain-wide comprehensive study of progressive amyloid plaques between the 5XFAD mice and C57BL/6J control mice at different age. The three-dimensional datasets showed that the lateral septum, subiculum and hippocampus were the primary susceptibility to Aβ accumulation in 5XFAD mouse model. Therefore, the combination of the present whole-brain staining method and fMOST technology provided detailed overview of the amyloid plaques in the whole mouse brain, which will contribute to the study of Alzheimer's disease.

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Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

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Program #/Poster #: 469.14/K13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH P50-AG005134
NIH R01-AG039478
NIH R01-NS084965
Challenger Foundation

Title: CMP^3: A CSF multiple pathophysiology panel for clinical trials in Alzheimer's disease

Authors: *B. A. TROMBETTA, B. C. CARLYLE, S. E. ARNOLD
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Abstract: Background
Alzheimer's disease (AD) is a complex disease driven by cycles of protein misfolding, inflammation, and neurovascular and metabolic dysfunction. Although tau and amyloid-β levels in cerebrospinal fluid (CSF) are strong indicators of AD pathology, they are inadequate for measuring disease progression or drug response. To diagnose the disease earlier and expand opportunities for intervention, it is critical to develop more sensitive and diverse biomarkers of AD. Measurement of proteins in pathways that drive AD may provide better biomarkers of disease susceptibility, progression, and therapeutic effects. We investigated a collection of 30 CSF biomarkers that represent diverse pathways active in AD. These analytes will be used to derive a CSF multi-pathophysiology panel ("CMP3") of biomarkers for the diagnosis, staging, and pathophysiological profiling of AD.
Methods
MesoScale Discovery and Quanterix multiplex assays were used to quantify a targeted selection

of CSF protein biomarkers relevant to neurodegeneration, metabolism, oxidative stress, vascular injury, and neuroinflammation. Analyte concentrations were determined in a well-characterized cohort (n=85) of AD cases with mild-stage dementia and well-matched cognitively unimpaired aged controls. CSF samples were collected by the Penn Memory Center and MassGeneral Institute for Neurodegenerative Disease (MIND) Tissue Bank. The cohort was comprised of 40 men and 45 women, predominantly Caucasian (81/85), with a mean age of 67.6 (11.8) years.

Results

Statistical modeling of disease severity correlation, hierarchical clustering of analytes, and analysis of confounding variables were performed. From this preliminary evaluation, we identified several analytes that correlated significantly with core AD biomarkers. We found that creating pathophysiological profiles incorporating these analytes increased the diagnostic accuracy of CSF biomarkers to differentiate between cognitively unimpaired individuals and AD.

Conclusions

Development of a CSF panel that encompasses multiple key pathways in AD could transform CSF outcome measures included in AD clinical research studies. These findings may help clarify the diverse and interrelated changes among various mechanistic pathways of AD onset and progression, with the potential for individual stratification and enabling personalization of treatment approaches. Larger studies are warranted to test the utility of the panel for measuring AD severity across the spectrum of pre-clinical AD, MCI, and late-stage dementia, and compared to other neurodegenerative diseases.

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Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

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Program #/Poster #: 469.15/K14

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JSPS KAKENHI 15K09808
JSPS KAKENHI 16K21207

Title: TOMM40 & APOE gene expression & cognitive decline in Japanese Alzheimer’s disease subjects

Authors: *J. IGA, A. MISE, Y. YOSHINO, K. YAMAZAKI, Y. OZAKI, T. SAO, T. YOSHIDA, T. MORI, Y. MORI, S. OCHI, S.-I. UENO
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Abstract: Background: *TOMM40* is located on chromosome 19, is in linkage disequilibrium with *apolipoprotein E* (*APOE*), and is reported in several genome-wide association studies to be associated with Alzheimer's disease (AD).
Objective: Assess *APOE* and *TOM40* and mitochondrial genes as blood biomarkers for AD.
Methods: We examined *TOMM40, PTEN-induced putative kinase 1* (*PINK1*), *Parkin RBR E3 ubiquitin protein ligase* (*PARK2*), and *APOE* mRNA expression in relation to the methylation rates of CpG sites in the upstream region of *TOMM40* exon 1 in peripheral leukocytes and *TOMM40* 523 polyT genotypes in 60 AD and age- and sex-matched control subjects.
Results: *TOMM40* mRNA expression was significantly lower in AD subjects (0.87 ± 0.18 vs. 1.0 ± 0.23, p = 0.005), and *PINK1* mRNA expression was higher in AD subjects (1.5 ± 0.61 vs. 1.0 ± 0.52, p < 0.001). *TOMM40* mRNA expression was significantly correlated with the Mini-Mental State Examination total score (r = 0.290, p = 0.027). There was no expressional change in peripheral *APOE* mRNA in either AD or control subjects (p = 0.32). Methylation rates in the upstream region of *TOMM40* exon 1 were not different between AD and control subjects (average rate: 1.37 ± 0.99 vs. 1.39 ± 1.20, p = 0.885), and *TOMM40* 523 polyT genotypes were also not different between AD and control subjects (p = 0.67).
Conclusion: *TOMM40* mRNA expression was lower in AD subjects and was correlated with cognitive decline. Significant changes in both *TOMM40* and *PINK1* mRNA may be related to mitochondrial dysfunction.

Disclosures: J. Iga: None. **A. Mise:** None. **Y. Yoshino:** None. **K. Yamazaki:** None. **Y. Ozaki:** None. **T. Sao:** None. **T. Yoshida:** None. **T. Mori:** None. **Y. Mori:** None. **S. Ochi:** None. **S. Ueno:** None.

Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 469.16/K15

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: ApoE-å4 suppresses age-dependent increases in plasma Aâ42 levels

Authors: T. NAKAMURA, *T. KAWARABAYASHI, Y. SEINO, M. HIROHATA, S. MIKIO
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Abstract: Background: There is a great need for biomarkers that could predict onset of cognitive impairment and diagnose early stage of Alzheimer's disease (AD). Some recent publications have been describing the usefulness of plasma Aβ as a biomarker of CNS amyloidosis, but a unified view has not been proposed yet. **Methods**: Plasma Aß40, Aß42 levels are measured by ELISA in 1,109 participants in the first year of the Iwaki Health Promotion (IHP) Project, and plasma Aβ levels are measured every 1 year in 554 out of 1,109 participants

for 4 years. Basic profiles of health of 600 items include height, weight, body fat percentage, ability of exercise, MMSE score, WMS-R, ADL, blood chemistry, whole genome analysis including the ε4 genotype of apolipoprotein E (ApoE). We analyzed whether these items affect levels of plasma Aβ. **Results**: (1) In First year, a significant linear increase with age was observed for Aß40 levels ($Y=0.4724X+79.65$, $r^2=0.2208$, $p<0.0001$), Aß42 levels ($Y=0.02466X+10.04$, $r^2=0.04898$, $p<0.0001$), and the Aß40/42 ratio ($Y=0.02234X+8.113$, $r^2=0.09725$, $p<0.0001$). (2) These linear lines were affected by presence of ApoE-ε4. Age-dependent plasma Aβ42 increases were suppressed by ApoE-ε4 ($p<0.0001$), and plasma Aβ40/42 ratios increases were enhanced by ApoE-ε4 ($p<0.0001$). (3) The same trends were observed for each year follow-up. **Conclusions**: Adjustment for aging and ApoE-ε4 allele are needed to measure plasma Aβ as a biomarker of CNS amyloidosis in the future research.

Disclosures: T. Nakamura: None. **T. Kawarabayashi:** None. **Y. Seino:** None. **M. Hirohata:** None. **S. Mikio:** None.

Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 469.17/K16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01CA16700
NIGMS Medical Scientist Training Program T32GM007347

Title: Aerosol delivery of thioflavin for retinal amyloid-beta plaque detection in Alzheimer's disease mouse model

Authors: *S. BARTON[1], V. A. JANVE[2], E. TO[4], J. MATSUBARA[4], W. PHAM[3]
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by memory loss and executive dysfunction. There are currently no disease modifying therapeutics available and major clinical trials have been unsuccessful. One reason for failure of these trials is at the time of treatment, significant and irreversible neurodegenerative changes have already occurred such that a therapeutic benefit cannot be achieved. Therapeutic efficacy could potentially be improved if initiated in presymptomatic stages of disease. However, techniques to detect AD pathology are expensive or invasive and cannot be readily used in an asymptomatic population. Recent studies have shown β-amyloid (Aβ) plaques, a pathologic feature of AD, are found in the retinas of AD patients and preclinical mouse models. It is hypothesized that retinal plaques could serve as a surrogate biomarker for total plaque burden in the brain and early detection could

identify patients with AD prior to symptomatic onset. As such, we are developing a noninvasive method of retinal plaque detection using thioflavin, a fluorescent Aβ-binding molecule that could be visualized when bound. Thioflavin has poor blood brain barrier permeability and thus limited penetration across the blood-retinal barrier. However, we have shown that delivery of thioflavin via nebulization significantly improves delivery to bind Aβ in the brain. Our current study is to investigate aerosol delivery for detecting Aβ plaques in the retina.
Wild-type (WT) and 5xFAD mice, a transgenic model of AD, were treated with aerosolized thioflavin. Retinal tissue whole-mounts and transverse sections were prepared and analyzed using confocal microscopy. Thioflavin fluorescence was closely associated with ganglion cell bodies in the same retinal layer where Aβ plaques were found in non-treated 5xFAD retinas stained with anti-Aβ antibodies. Importantly, thioflavin was not detected in treated WT retinas. These findings demonstrate that thioflavin retention is plaque-dependent. In future work, retinas from treated 5xFAD mice will be co-stained for Aβ to confirm thioflavin is bound to plaques. Treated 5xFAD mice will also be imaged *in vivo*, using a retinal imaging microscope to determine if thioflavin fluorescence can be detected noninvasively. If successful, aerosolized thioflavin could be used to evaluate retinal Aβ plaques as a predictive biomarker for development of AD and facilitate early intervention to improve therapeutic outcomes.

Disclosures: S. Barton: None. **V.A. Janve:** None. **E. To:** None. **J. Matsubara:** None. **W. Pham:** None.

Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 469.18/K17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: ARDRAF Award No. 17-2
Christopher Newport Summer Scholars Program
No Rho Psi Undergraduate Research Grant

Title: Determining the fatty acid/lipid profiles of 3xTg-AD mice in plasma and in red blood cell membranes

Authors: S. HOULE[1], B. GENOVESE[2], R. A. QUINLAN[2], L. S. WEBB[2], *D. A. MITRANO[2]
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Abstract: Alzheimer's disease (AD) is the most common form of dementia, accounting for anywhere between 60 to 80 percent of all dementia cases in the United States. The disease is progressive and has no cure, making it the sixth most common cause of death in the United States. While the disease is progressive, those who suffer may have AD for several years before

they begin to notice its hallmark symptoms. With only two FDA- approved treatments available, early diagnosis is paramount in the effort to improve the quality of life for those with AD. Recently, several studies have identified 10 lipid biomarkers found in the blood that can be used to predict (with 90% accuracy) a shift from normal cognitive function to mild cognitive impairment. These biomarkers (particularly phosphatidylcholine) are predictive of a downturn in cognition due to their nature as a component of lipoproteins. For this reason these molecules interact with ApoE; of which the ApoEε4 allele is known to be a genetic risk factor for familial Alzheimer's disease. This study, therefore, ultimately seeks to further validate the 3xTg-AD mouse model for human Alzheimer's by creating blood lipid profiles through establishing and analyzing standard curves from high pressure liquid chromatography and mass spectrometry (HPLC-MS) of the plasma and red blood cell membranes of the 3xTg-AD mice to one day aid in the development of a blood biomarker that can be used to diagnose AD in humans.

Disclosures: S. Houle: None. **B. Genovese:** None. **R.A. Quinlan:** None. **L.S. Webb:** None. **D.A. Mitrano:** None.

Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 469.19/K18

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Young to middle-aged dogs with high Abeta-levels show higher pTau levels in CSF

Authors: *H. BORGHYS, B. VAN BROECK, C. THEUNIS, F. TEKLE, D. DHUYVETTER
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Abstract: Understanding the relevance of changes in Alzheimer's disease biomarkers that occur before the pathology becomes evident, can contribute to the development of a treatment for Alzheimer's disease. A longitudinal follow-up of an animal species with a similar amyloid pathology in the brains as in humans may contribute to this research. Amyloid plaque formation is one of the two main neuropathological hallmarks of Alzheimer's disease in humans. Dogs are similar to man with respect to amyloid precursor protein (APP)-processing and age-related amyloid plaque deposition. Dogs also are used as a natural model of age-dependent cognitive dysfunction. In our colony of beagle dogs Aβ-concentrations in cerebrospinal fluid (CSF), sampled in awake animals from the lateral ventricle, were regularly measured over a period of years. We identified dogs showing low or high Aβ42 levels and formed two groups of eight animals each. The age of the animals, which ranged from 2-6 years, was comparable between both groups. Since dogs normally start to develop amyloid plaques from an age of 9-10 years onwards, these dogs are assumed to have no or minimal amyloid plaque formation.To assess baseline pTau levels in these animals, four CSF samples were taken within a period of 8 days. In

the same samples Aβ 1-37/1-38/1-40 and 1-42 were measured. We have found that the dogs with high Aβ levels in CSF also show high pTau levels.

Disclosures: H. Borghys: A. Employment/Salary (full or part-time):; Janssen. **B. Van Broeck:** A. Employment/Salary (full or part-time):; Janssen. **C. Theunis:** A. Employment/Salary (full or part-time):; Janssen. **F. Tekle:** A. Employment/Salary (full or part-time):; Janssen. **D. Dhuyvetter:** A. Employment/Salary (full or part-time):; Janssen.

Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 469.20/L1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: VA I21BX002215
NIH 1R01ES024165
VA IO1 BX003527
Cure Alzheimer's Fund

Title: Linking Alzheimer's disease with a history of traumatic brain injury

Authors: B. MORRIS-EPPOLITO[1], M. LI[3], S. QIAN[2], J. REISMAN[2], *L. MOO[1], L. KAZIS[2], B. L. WOLOZIN[4], W. XIA[1]
[1]GRECC, [2]CHOIR, Bedford VA Med. Ctr., Bedford, MA; [3]Mathematical Sci., Bentley Univ., Waltham, MA; [4]Pharmacol, Boston Univ. Schl Med., Boston, MA

Abstract: Since there is no single established causative factor in over 95% of Alzheimer’s cases, understanding the roles of various Alzheimer’s disease (AD) risk factors will be essential in reducing the prevalence of AD and developing therapeutic treatments. The occurrence of non-fatal traumatic brain injury (TBI) in military personnel has increased with the widespread use of improvised explosive devices in recent wars. TBI has been identified as a risk factor for developing dementia later in life, but the molecular mechanisms underlying associations between TBI history and AD risk remains to be elucidated. In this study, we perform a retrospective analysis on TBI history and clinical Alzheimer’s diagnosis data from a sample of 1.1 million veterans from VA healthcare systems nationwide through the VA Informatics and Computing Infrastructure (VINCI). Patient’s history of TBI and AD status were determined by ICD-9 and ICD-10 diagnosis codes. We found 160,581 patients with at least 1 diagnosis of TBI and 60,704 of these patients were over the age of 50 with at least 2 confirmed TBI diagnoses. Additionally, we analyzed TBI history, Alzheimer’s status and plasma amyloid β protein (Aβ) levels in a group of 75 veteran AD and older control patients. No statistically significant association was identified between the plasma Aβ42 levels within either the AD or control group based on TBI

history. In conclusion, we demonstrate that a notable fraction of the veteran population with a history of TBI has a diagnosis of AD, suggesting that TBI and AD are closely associated. Further research, including further testing of other AD biomarkers in plasma, is needed to fully explore the contribution of TBI history to AD risk. This study was supported by the Veterans Affairs Office of Research and Development (WX), NIH (LM), and the Cure Alzheimer's Fund (WX).

Disclosures: B. Morris-Eppolito: None. **M. Li:** None. **S. Qian:** None. **J. Reisman:** None. **L. Moo:** None. **L. Kazis:** None. **B.L. Wolozin:** None. **W. Xia:** None.

Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

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Program #/Poster #: 469.21/L2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: This work was supported in part by a Grant to CABMC (Control of Animal Brain using MEMS Chip) funded by Defense Acquisition Program Administration (UD140069ID)
This research was supported by the Brain Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Science and ICT (2017M3C7A1029485).

Title: Abnormal inhibitory attention in patients with idiopathic REM sleep behavior disorder reflected in theta- and beta-band activities

Authors: *S. HEO[1], D. YEO[1], K. CHA[1], P. SEO[1], H. KIM[1], S. CHOI[1], J. CHOI[1], K.-Y. JUNG[2], K. KIM[1]
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Abstract: Idiopathic rapid-eye movement (REM) sleep behavior disorder (IRBD) is a sleep disorder characterized by dream enactment behavior and the loss of muscle atonia during REM sleep. IRBD patients are known to be associated with high risk of developing neurodegenerative diseases, such as Parkinson's disease, multiple system atrophy, and dementia with Lewy bodies. Visuospatial abilities, attentional and executive functions have also been reported to be impaired in IRBD. We investigated the dysfunctional visuospatial attention of IRBD patients, focusing on the inhibition of return (IOR), based on event-related electroencephalograms (EEGs) and their cortical current sources in frequency domain. Sixteen drug-naïve idiopathic RBD patients (age: 64.9±6.9 years, F: 3, M: 13) and nineteen healthy controls (age: 63.4±7.3 years, F: 5, M: 14) performed Posner's cueing task while sixty-channel EEGs were recorded. When the target is presented in cued location, the condition is "valid". If the target appears on the contralateral side

of the cue, the condition is “invalid”. Cortical source current densities were estimated using weighted minimum norm estimate method, and then, time-frequency analysis were performed to obtain event-related spectral perturbation (ERSP). To investigate IOR effect, ERSP was compared between validity using mass univariate analysis method.The IOR effect in behavior was found in controls but not in the IRBD group. The IOR effects in theta-band and beta-band ERSP were found only for the control subjects, in visual cortex at 100-300 ms, and in motor regions at 200-500 ms, respectively. The theta- and beta-band activities seems to reflect visual perception and motor processes, which are essential for the attention-mediated target processing. The lack of IOR effects in ERSP may indicate cortical dysfunction for attentional inhibition associated with IRBD.

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Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

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Program #/Poster #: 469.22/L3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: VA I21BX002215
VA IO1 BX003527
Cure Alzheimer Fund

Title: Proteomic profiles of plasma and post-mortem brain tissues from Alzheimer’s patients

Authors: M. CHEN[1], G. SURPRIS[2], T. D. STEIN[3], *W. XIA[4]
[1]Bedford VA Hospital, Harvard TH Chan Sch. of Publ. Hlth., Bedford, MA; [2]Bedford VA Hosp., Bedford, MA; [3]Boston VA Med. Ctr., Boston, MA; [4]GRECC, Pharmacol. & Exptl. Therapeut., Bedford VA Hospital, Boston Univ., Bedford, MA

Abstract: Alzheimer’s disease (AD) is one of the most common neurodegenerative disorders in US. Inflammation has been shown to be a major factor in late onset Alzheimer’s disease (LOAD). Increased inflammatory profile of blood lymphocytes, and the inflammation mediated diseases such as AD converge on vulnerabilities caused by an aging immune system. The current biomarkers for AD in cerebrospinal fluid (CSF) are limited by the relatively invasive nature of CSF sampling. Studies in human plasma have been conducted in searching for reliable biomarkers of AD. The purpose of this study is to use mass spectrometry (MS)-based analysis to find the connection between the peripheral and central nervous system, and to explore proteins associated with neuroinflammation in AD pathogenesis. To accomplish this, we collected blood and at autopsy, post-mortem brain tissue (from superior frontal cortex, inferior cortex and

cerebellum area) from five Alzheimer's disease (AD) patients and five healthy controls. Liquid chromatography/MS was used to analyze plasma proteins and proteins in brain tissues labeled with isobaric mass tags (TMT) for relative protein quantification and differentially expressed proteins were identified. We also examined protein-protein interaction networks associated with the mechanism of AD through a bioinformatics approach. Our study revealed a group of differentially expressed plasma proteins that are associated with AD, including those proteins involved in inflammation, lipid metabolism and disturbed metal homeostasis. Comparative analysis between the plasma proteins and brain tissue proteomics from the same AD patients revealed the top enriched common pathways related to neuroinflammation. In AD brain tissue, oligodendrocyte proteins such as PLP1 and CNPase, and astrocyte proteins GFAP and S100B, proteins associated with increased glial differentiation and activation, were up-regulated, while MAP2, a protein associated with neural dendrites, was reduced. This specifies a change in the proteomic signature of the AD brain that underlies the pathology of reactive gliosis and the loss of synaptic integrity. In conclusion, a group of dysregulated proteins associated with AD was identified in plasma and three brain regions from AD. Our comparative proteomic analysis between plasma and brain regions of the same subjects shows the relevance between peripheral compartment and central nervous system.

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Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

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Program #/Poster #: 469.23/L4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH T32 AG057461
National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Grant UL1TR001998
NIA Grant R01 AG004542

Title: A subset of gene expression profiles in human post-mortem brain aging and Alzheimer's disease are robust, concordant, and show exaggerated changes in female Alzheimer's disease subjects

Authors: *K. HARGIS-STAGGS[1], E. S. JOHNSON[2], N. M. PORTER[3], O. THIBAULT[4], E. M. BLALOCK[5]
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Abstract: Sporadic Alzheimer's disease (AD) is increasing in parallel to the aging population, with the majority (~2/3) of AD cases affecting women. AD is a complex disease characterized by amyloid beta and neurofibrillary tangle pathologies, and risk factors include head injury, high blood pressure, high cholesterol, and inheritance of certain gene variants (e.g., ABCA1, APOEe4, APOEe2, etc.). Despite the vast amount of research, successful therapies that modify the disease have yet to be developed. One reason could be that some unmodifiable risk factors, such as aging and sex, contribute to vulnerability and progression in AD as well, but their molecular roles have not been robustly assessed. We hypothesize that a subset of age-related transcriptional changes precede, and are exaggerated by, AD, and further that female AD sufferers will have exaggerated expression compared to males for this restricted subset of robustly identified genes. To address this, we looked at transcriptional profiles of normal human aging (8 profiles) and AD (9 profiles) to test for a statistically significant agreement for Aging or AD changes across independent samples from different labs. We further tested for a statistically significant relationship between robust aging and AD-related changes. We found 85 genes that were significantly changed with age, worsened in AD, and exaggerated in female vs male subjects These genes also showed very strong directional and magnitude-of-change agreement between normal aging and AD. Taken together, this panel of genes likely contains key candidate molecules for intervention testing and rationale therapeutic development.

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Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

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Program #/Poster #: 469.24/L5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Doris Duke Charitable Foundation
National Institutes of Health 1R01NS092062

Title: The role of vesicle trafficking in Alzheimer's disease: Development of exosome biomarkers

Authors: *V. EKUTA, G. LIAN, V. SHEEN
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Abstract: Background Alzheimer's disease (AD) is a progressive neurodegenerative disorder that causes dementia in the elderly. Recent evidence suggests that early AD detection is instrumental for designing appropriate therapeutics. Thus, developing a sensitive and predictive biomarker that detects disease onset is imperative. Our current understanding of AD

development is based on the amyloid hypothesis, which suggests that amyloid-beta fibril formation and aggregation leads to progressive neuronal cell death. Previous research implicates dysfunctional vesicle trafficking and lysosomal clearance in neurodegenerative disease. These observations suggest that vesicular trafficking impairments should precede amyloid-beta aggregation and AD clinical manifestations. Hence, our overall project goal is to determine whether vesicle trafficking-related protein changes may serve as a predictive AD biomarker. **Objective** 1. To determine vesicle trafficking protein serum and exosome composition differences among 4 patients that developed AD, 4 age-matched patients with mild cognitive impairment (MCI), and 4 healthy age-matched controls. 2. To identify putative vesicle trafficking candidate proteins and protein networks that discriminate between AD and healthy controls. **Methods** 1. Western blot analysis of serum samples to examine the expression of trafficking proteins in healthy controls, MCI, and individuals that later developed AD. 2. Western blot analysis of plasma exosome derived vesicle trafficking proteins in the populations noted above. 3. SOMAscan Proteomics to identify vesicle trafficking candidate proteins and novel protein markers in the populations noted above. **Results** 1. Western blot studies showed significantly increased LAMP-1 serum levels in patients that developed AD, relative to age-matched controls and MCI. 2. Western blot studies showed a trend (albeit not statistically significant) for increasing exosome LAMP-1 expression in patients that developed AD compared to healthy controls. 3. SOMAscan Proteomics Platform identified several candidate target proteins involved in lipid processing and vesicle trafficking with potential links to caveolin and filamin A. **Discussion** Our preliminary work suggests several trafficking proteins may be implicated in AD pathogenesis. Furthermore, serum changes in these proteins may be accompanied by exosome protein expression changes. A better mechanistic understanding will facilitate the development of a predictive AD serum biomarker.

Disclosures: V. Ekuta: None. **G. Lian:** None. **V. Sheen:** None.

Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

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Program #/Poster #: 469.25/L6

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Development and Validation of an *in vitro* system for Alzheimer’s disease studies

Authors: W. LUO[1], J. LEE[2], L. MORIARTY[2], *E. JORDAN[2]
[1]Bio-Rad Labs. Canada Ltd., Mississauga, ON, Canada; [2]Bio-Rad Labs., Hercules, CA

Abstract: Alzheimer’s disease (AD) is one of the most common neurodegenerative diseases, which accounts for over 80% of dementia cases in people over 65 years old. The rapid increase in AD cases not only has a significant impact on the economy, but also imposes huge burdens on

families and society due to the disease rendering patients dependent upon others for their health and safety. Many disease models have been established to study AD, including animal models, primary cultures, stem cells models, and cancer cell models. While these models provide good opportunities for exploring and understanding AD development, they are still far from being ideal and are very limited, either due to high expense, difficult maintenance, or low correlation to real life situations. In our study, we developed a model system using easily-maintained human neuroblastoma cells (SH-SY5Y) which can be differentiated into mature neuron-like cells and further induced into AD-like cells. We validated the model system by checking the expression of key neural biomarkers, including AD markers, and demonstrated that this system can be used for AD drug screening tests. Additionally, we screened lncRNA panels to identify lncRNAs that are differentially expressed during the transition of these cells from neuroblastoma to the AD model system. This model system provides a great potential to mimic real AD development models and drug treatment. Based on its ease of establishment and flexibility to incorporate various techniques, it has the ability to be extremely beneficial for a range of biological and pharmaceutical applications.

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Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Australian Linkage Council Linkage Grant LP160100126
Melbourne Neuroscience Institute Interdisciplinary Seed Fund
Melbourne Research Fellowships

Title: Retinal structural and functional changes in mouse models of Alzheimer’s and Parkinson’s disease

Authors: *C. T. NGUYEN[1], J. K. H. LIM[1], V. H. Y. WONG[1], A. J. VINGRYS[1], J. MULLEN[2], D. I. FINKELSTEIN[3], B. V. BUI[1]
[1]Univ. of Melbourne, Parkville, Australia; [2]AstraZeneca Neurosci., Cambridge, MA; [3]Florey Inst. of Neurosci., Parkville, Australia

Abstract: The retina is an accessible outpouching of the central nervous system and may reflect cortical changes that occur with Alzheimer’s and Parkinson’s disease. As retinal assessments such as electroretinography (function) and optical coherence tomography (structure) are simple and inexpensive to conduct they may prove useful as biomarkers of cortical disease that can be used to streamline drug discovery from animal to human studies. This work aims to examine

whether retinal function and structure are altered in animal models of Alzheimer's and Parkinson's disease across a range of timepoints. A transgenic mouse model of familial Alzheimer's Disease (5xFAD) and their wild-type (WT) littermates were studied at 6, 12 and 17 months of age (n = 10 - 17 / group). A toxin model of Parkinson's disease was induced in C57BL6/J mice using MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, 4x i.p. injections, 20mg/kg) and vehicle control and examined at day 21 and 45 post-induction. Another MPTP group was administered L-DOPA (0.2 mg/ml) or vehicle in their drinking water and assessed at day 45 (n = 12 - 15 / group). All structure and function assessments were conducted under ketamine:xylazine (80:10 mg/kg).

5xFAD mice revealed early changes to retinal ganglion cell function compared to WT (6 & 12 m.o., positive scotopic threshold response, $p < 0.05$). At the oldest age there was also deeper retinal dysfunction of the bipolar and photoreceptoral cells (17 m.o., positive scotopic threshold response, b-wave, a-wave, $p < 0.05$). These early functional changes paralleled structural thinning of retinal ganglion cell axons (retinal nerve fibre layer; 6, 12, 17 m.o. $p < 0.05$) whilst other retinal layers remained intact. In contrast, MPTP mice exhibit a different retinal phenotype. At 21 days no retinal changes were found. At 45 days slower amacrine (oscillatory potential, $p < 0.05$) and bipolar cell responses were found (b-wave, $p< 0.05$) whereas other retinal components were preserved. These functional changes were reversed with L-DOPA treatment ($p< 0.05$). No significant structural changes were found in MPTP mice.

This is the first exploratory study to examine the time course of retinal structure and function in the 5xFAD Alzheimer's disease and MPTP Parkinson's disease model. That these animal models recapitulate key changes which have been reported in human Alzheimer's and Parkinson's disease pave the way for their utility as useful translational biomarkers. Moreover, reversal with therapeutics (L-DOPA) also indicate for their use as a preclinical screening tools in drug development. This important step will enable better and faster development of treatments for these diseases.

Disclosures: **C.T. Nguyen:** 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.; AstraZeneca, Biogen. **J.K.H. Lim:** None. **V.H.Y. Wong:** None. **A.J. Vingrys:** 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.; AstraZeneca, Biogen. **J. Mullen:** A. Employment/Salary (full or part-time):; AstraZeneca. **D.I. Finkelstein:** None. **B.V. Bui:** 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.; AstraZeneca, Biogen.

Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 469.27/L8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Ministry of Education, Singapore

Title: Non-canonical structural variants of sphingosine 1-phosphate are altered in the plasma of patients with vascular dementia, but not with Alzheimer’s disease

Authors: *D. R. HERR, W. S. CHEW, M. K. P. LAI, 117600
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Abstract: Sphingosine-1-phosphate (S1P) has been shown to regulate a variety of processes in central nervous system cells, such as differentiation, survival, and excitability of neurons, activation of astrocytes, and processing of amyloid precursor protein. Therefore, it is plausible that S1P signaling is dysregulated in individuals suffering from dementia, leading to measurable, quantitative changes in circulating S1P levels. To test this hypothesis, we obtained plasma from 384 individuals that had normal cognition, mild cognitive impairment, or dementia; and were subclassified by the presence or absence of cerebrovascular disease. Each sample was evaluated by mass spectrometry for the concentrations of the four most abundant S1P isoforms: d16:1, d17:1, d18:0, and d18:1. We found that S1P was significantly reduced in dementia patients, but only with respect to d16:1 S1P and not with any other isoform. When dementia was stratified into Alzheimer’s disease (AD) vs. vascular dementia (VaD), only VaD was negatively correlated with d16:1 S1P. To understand how a reduction of d16:1 S1P may contribute to the pathology of VaD, we evaluated the effects of d16:1 S1P on S1P receptors and on astrocytic cells *in vitro*. The potency of d16:1 S1P in activating $S1P_{1\text{-}3}$ was comparable to that of d18:1 S1P, but d16:1 S1P displayed a possible reduction in efficacy toward some receptor subtypes. Although both isoforms caused an increase in the expression of pro-inflammatory cytokines, the effect of d16:1 S1P was significantly less than that of d18:1 S1P. Importantly, we demonstrate that the presence of d16:1 S1P can attenuate the effect of d18:1 S1P. This suggests that d16:1 S1P can act as an immunomodulatory compound by “fine tuning” the pro-inflammatory effect of d18:1 S1P. Therefore, the reduction of d16:1 S1P in vascular dementia patients may dis-inhibit S1P-mediated astrogliosis and exacerbate neuroinflammatory cognitive decline.

Disclosures: D.R. Herr: A. Employment/Salary (full or part-time):; National University of Singapore. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Ministry of Education, Singapore. **W.S. Chew:** A. Employment/Salary (full or part-time):; National University of

Singapore. **M.K.P. Lai:** A. Employment/Salary (full or part-time):; National University of Singapore.

Poster

469. Alzheimer's Disease and Other Dementias: Biomarkers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 469.28/L9

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: EEG biomarkers for frontotemporal dementia

Authors: S. WANINGER[1], M. BENESH[1], *C. BERKA[1], E. RATTI[2], P. VON ROSENSTIEL[2], M. MENDEZ[3], A. VERMA[4]
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Abstract: Objective: There is a critical unmet need for reliable, cost effective and noninvasive biomarkers to detect and monitor disease progression of frontotemporal dementia (FTD). Neurophysiological metrics including quantitative EEG may provide sensitive metrics for tracking disease progression and assessing efficacy of novel interventions for dementia as well as assist in differential diagnosis of FTD versus Alzheimer's disease (AD).
Methods: Resting state EEG data was acquired from 8 behavioral variant (bvFTD) participants (average age 66, 50% female), 10 AD participants (average age 77, 52% female), and 10 healthy control (HC) (average age 65, 50% female) for 5 minutes for eyes open (EO) and 5 minutes for eyes closed (EC). Power spectral density (PSD) and low resolution brain electromagnetic tomography (LORETA) analysis were performed using Neuroguide software. Statistical analysis for PSDs and LORETA was performed by independent t-test. Discriminant function analysis (DFA) classifiers were used to fit a multivariate normal density to bvFTD, HC, and AD classes with a pooled estimate of covariance. The trained model was evaluated using leave-one-participant-out cross-validation to evaluate the model's generalization capabilities.
Results: Compared to HC, bvFTD participants showed significant increases in delta and theta PSD bands during EO, particularly over the frontal region. LORETA revealed significant increases for the bvFTD in the delta band for the medial and superior frontal gyrus and anterior cingulate during EC and increases in delta and theta in temporal, frontal, parahippacampal gyrus and anterior cingulate during EO. Significant differences between bvFTD and AD were also observed, particularly in alpha and beta in the superior frontal region and anterior cingulate during EC. The DFA model correctly classified all but one bvFTD versus healthy participants with 94 % accuracy/87 % specificity and all of the FTD versus AD participants with 100 % accuracy/specificity.
Conclusions: The data suggest that EEG may provide a powerful tool for assessing FTD, have

potential as a sensitive and robust biomarker for tracking disease progression, and provide an adjunct diagnostic tool for differentiation from AD.

Disclosures: S. Waninger: A. Employment/Salary (full or part-time):; Advanced Brain Monitoring. **M. Benesh:** A. Employment/Salary (full or part-time):; Advanced Brain Monitoring Inc. **C. Berka:** A. Employment/Salary (full or part-time):; Advanced Brain Monitoring Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Advanced Brain Monitoring Inc. **E. Ratti:** A. Employment/Salary (full or part-time):; Biogen. **P. von Rosenstiel:** A. Employment/Salary (full or part-time):; Biogen. **M. Mendez:** A. Employment/Salary (full or part-time):; University of California Los Angeles. **A. Verma:** A. Employment/Salary (full or part-time):; United Neuroscience.

Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 470.01/L10

Topic: C.03. Parkinson’s Disease

Support: NRF-2017R1D1A1B03033814

Title: Nucleolin degrades alpha synuclein via the autophagy-lysosome pathway

Authors: *D.-H. HO, S. JEONG, D. NAM, W. SEOL, I. SON
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Abstract: Alpha-synuclein (aSyn) is a major component of Lewy body (LB), which is known as a pathogenic marker of Parkinson’s disease (PD). The accumulation of aSyn is caused by dysfunction of protein degradation machinery, including ubiquitin-proteasome system (UPS), Chaperone-mediated autophagy (CMA) and lysosome activity. Misfolded aSyn or chemically modified aSyn would have a resistance to the degradation and is responsible for the generation of oligomeric aSyn in cytosol or vesicles, such as late endosome, autophagosome or lysosome. Proteins, which could enhance degradation of aSyn, are a potential therapeutic target, in as much as accumulated aSyn is the culprit of the pathogenesis of PD. Nucleolin (NCL) is one of the major components of a nucleolar structure. NCL is correlated with oxidative stress-mediated induction of heat shock proteins (Hsp), especially Hsp70, a chaperone for aSyn via CMA. A hexanucleotide repeat expansion in *C9orf72* (*C9orf72*-HRE) is a critical cause of amyotrophic lateral sclerosis (ALS), and increased nucleolar stress via disruption of NCL by the *C9orf72*-HRE in ALS-patients’ cells. A previous study demonstrated that NCL was reduced in PD brain, and overexpression of NCL alleviated rotenone-induced neural toxic effects; knock-down of NCL vice versa. These results suggest that malfunctioning of NCL would exacerbate ALS or PD

pathology. Thus, we hypothesized that artificial expression of ectopic NCL could rescue the synucleinopathy in PD. Overexpression of Flag-aSyn was decreased by co-expression of GFP-NCL in mouse embryonic fibroblast (MEF) compared to GFP protein but co-expressed p21 was not decreased by GFP- NCL. Not only co-transfection of Flag-aSyn and GFP-NCL but also serial transfection of GFP-NCL after Flag-aSyn degraded Flag-aSyn in Triton X-100-soluble and -insoluble fraction. Induction of GFP-NCL increased LC3B mRNA levels significantly and LAMP2, HSP70, and Cathepsin D mRNA levels. Cathepsin D activity also increased in GFP-NCL transfection. Interestingly, bafilomycin A1, the blocker of docking between autophagosome and lysosome, eliminated degradation of Flag-aSyn by GFP-NCL. NH_4Cl showed a similar result to the bafilomycin A1 treatment. However, MG132 treatment showed enhanced degradation of both Flag-aSyn and GFP-NCL. These results support that ectopic expression of NCL degrades aSyn via autophagy-lysosome pathways. We are confirming results of rat primary neuron and validating the Nucleolin-mediated degradation of aSyn fibril form exogenously added.

Disclosures: **D. Ho:** A. Employment/Salary (full or part-time):; Wonkwnag University, Sanbon Medical Center. **S. Jeong:** None. **D. Nam:** A. Employment/Salary (full or part-time):; Wonkwnag University, Sanbon Medical Center. **W. Seol:** A. Employment/Salary (full or part-time):; Wonkwnag University, Sanbon Medical Center. **I. Son:** A. Employment/Salary (full or part-time):; Wonkwnag University, Sanbon Medical Center.

Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 470.02/L11

Topic: C.03. Parkinson’s Disease

Support: I2A Intramural DZNE funding

Title: Improve treatment of Parkinson’s disease

Authors: *J. JATHO-GRÖGER[1], P. BREUER[1], D. PISTON[1], I. SCHMITT[1], P. DENNER[2], D. STAPPERT[2], U. WÜLLNER[1]
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Abstract: The protein α-synuclein (α-syn) is a key component in both familiar and sporadic Parkinson’s disease (PD) pathophysiology. Point mutations in the α-synuclein gene (*SNCA*) and multiplication of wildtype *SNCA* cause familiar parkinsonian syndromes and the overall *SNCA* levels were shown to directly correlate with the severity of the symptoms. Thus, α-syn dyshomeostasis can be considered as key process to contribute to the susceptibility to PD. Given the strong effects of increased α-syn protein expression on PD severity observed in patients with

multiplications of wildtype *SNCA*, decreasing α-syn could be an important therapeutic improvement. Therefore, the pivotal aim of this study was to establish and perform a novel automated screening assay for the reliable detection of modulators of α-syn expression.
To that end we generated stable human neuroblastoma SH-SY5Y *SNCA*-full-length knock-in GFP/firefly luciferase fusion protein cell lines using CRISPR/Cas9-mediated gene editing. This model system enables us to quantify endogenous α-syn expression by measuring luciferase signal intensity in cell lysates. A second cell line with a randomly integrated luciferase construct served as a specificity control. As a proof of concept experiment Valproic acid (VPA), which is known to induce a parkinsonian like phenotype in patients, was used as lead compound and revealed a 3-fold induction of luciferase activity and the respective increase of α-syn at protein level.
Next, we tested 1.650 bioactive (FDA approved) compounds in a fully automated, robust screening assay (intra-assay variability <10 %, inter-assay variability <10-15 %) in a 96-well plate format and after statistical and candidate definition we obtained a list of 153 potential *SNCA* expression inhibitors and 164 potential *SNCA* expression activators. These compounds were tested for their potential to induce cell death and/or proliferation and dose-response experiments were performed. All compounds inducing either cell death or proliferation or not displaying a dose-response were ruled out. In total 16 *SNCA* expression activators and 5 inhibitors remained.
Direct translational benefit can be drawn from this project, since the identification of compounds that increase or reduce intracellular α-syn protein levels allows the direct re-assessment of PD patients' overall medication and the substitution of risk-bearing drugs.

Disclosures: J. Jatho-Gröger: None. **P. Breuer:** None. **D. Piston:** None. **I. Schmitt:** None. **P. Denner:** None. **D. Stappert:** None. **U. Wüllner:** None.

Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 470.03/L12

Topic: C.03. Parkinson's Disease

Title: *In vitro* simulation of traumatic brain injury induces apoptosis and decreases dopamine levels in human neurons

Authors: *S. F. ALI[1], S. M. LANTZ[2], E. CUEVAS[3], S. Z. IMAM[4], H. ROSAS-HERNANDEZ[5]
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Abstract: Traumatic brain injury (TBI) is defined as damage to the brain that consequently disrupts normal function. One of the hallmarks of TBI is neuronal death, but has also been related with the development of neurodegenerative disorders, including Parkinson's disease (PD), where loss of dopaminergic neurons and dopaminergic dysfunction are observed. To date, no *in vitro* model exists in which the dopaminergic damage observed in TBI is replicated. In the present study, we evaluated the effects of *in vitro* simulated TBI on human dopaminergic neurons. To simulate TBI, neurons were subjected to 0%, 10%, 15%, 25% and 50% deformation. Twenty-four hours after injury, cell viability and apoptosis were determined by lactate dehydrogenase (LDH) release and DNA fragmentation as well as ethidium homodimer and caspase 3/7 staining. Dopamine (DA) levels were determined by ELISA. Only 50% stretch increased LDH release and ethidium homodimer staining, suggesting the induction of necrosis. On the contrary, 25% and 50% stretch increased DNA fragmentation while 15%, 25% and 50% increased caspase 3/7 staining, suggesting that moderate and severe TBI promote neuronal apoptosis. Finally, levels of intracellular DA decreased in a stretch-dependent manner with 15%, 25% and 50% stretch, while extracellular levels were increased only at 50%. These data support the use of stretch as a model to simulate TBI *in vitro* in dopaminergic neurons, replicating the acute effects of TBI in the dopaminergic system. This method can be used to study the long-term consequences of TBI, including PD and other neurodegenerative disorders.

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Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 470.04/L13

Topic: C.03. Parkinson's Disease

Support: Michael J Fox Grant
Parkinson's Research Consortium Fellowship

Title: Investigating an alpha-synuclein binding aptamer as a potential treatment avenue to prevent protein fibril formation in Parkinson's disease

Authors: *K. VENTURA[1], E. MCCONNELL[2], J. CALLAHAN[2], V. HUNT[2], A. KOUDRINA[2], M. C. DEROSA[2], M. R. HOLAHAN[1]
[1]Neurosci., [2]Chem., Carleton Univ., Ottawa, ON, Canada

Abstract: A key component of the neurodegenerative processes underlying Parkinson's Disease (PD) is the aggregation of alpha-synuclein (α-Syn). One current hypothesis is that misfolded native or mutant α-Syn protein dimers become oligomers and can form insoluble fibrils

eventually leading to aggregation into inclusions. These fibrils and inclusions have been found to trigger apoptotic and other toxic signals leading to neuron death. The ability to prevent this aggregation during the disease process would have enormous potential for slowing the neurodegenerative cascade in PD.
Using bionanotechnology strategies, we have sought to determine whether a DNA aptamer, targeted to bind to alpha-synuclein monomers, can inhibit protein aggregation and reduce Parkinson's-related neurodegeneration. Specifically, we have identified a DNA aptamer that can recognize, bind, and block the aggregation of α-Syn protein. Our DNA aptamer selectively bound to the α-Syn monomer and prevented α-Syn fibril formation in vitro. Next, we assessed the ability of the α-Syn binding aptamer in vivo in transgenic mice expressing the human A53T variant of α-Syn. We examined the colocalization of the anti-alpha-synuclein (phosphor S129) antibody and Cy3.5 labelled α-Syn aptamer on ex vivo tissue slices using fluorescent microscopy. Our results suggest that we have been successful at targeting and binding to α-Syn both in vitro and in vivo. The ability to inhibit protein aggregation with an exogenous treatment during aging would be a key strategy in studying and potentially slowing the neurodegenerative process in PD.

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Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 470.05/L14

Topic: C.03. Parkinson’s Disease

Support: Kahn Neurotechnology Development Grant

Title: Downregulation of SNCA expression by targeted editing of DNA-methylation: A potential strategy for precision therapy in PD

Authors: *B. KANTOR[1], L. TAGLIAFIERRO[2], J. GU[2], M. E. ZAMORA[2], E. ILICH[3], C. GRENIER[4], Z. Y. HUANG[4], S. MURPHY[4], O. CHIBA-FALEK[2]
[1]Duke U, Chapel Hill, NC; [2]Neurol., [3]Neurobio., [4]Div. of Gynecologic Oncology, Dept. of Obstetrics and Gynecology, Duke Univ., Durham, NC

Abstract: *SNCA* gene has been associated with Parkinson’s disease (PD) and accumulating evidence suggest that elevated levels of wild-type *SNCA* are pathogenic. On the other hand, robust reduction of *SNCA* level showed neurotoxicity, demonstrating that normal physiological levels of *SNCA* are needed to maintain neuronal function. Thus, there is an unmet need to develop new therapeutic strategies targeting the regulation of *SNCA* expression. DNA

methylation at *SNCA* intron 1 contributes to the regulation of *SNCA* transcription, and differential methylation levels at *SNCA* intron 1 were found between PD and controls. These evidences established DNA-methylation at *SNCA* intron 1 as an attractive therapeutic target mediated by manipulation of *SNCA* levels. In this study, we developed a system that comprises of an all-in-one lentiviral vector for targeted editing the methylation in the CpG islands along the *SNCA* intron 1. The system is based on CRISPR/deactivated-Cas9 nuclease (dCas9) fused with the catalytic domain of the DNA methyltransferase 3A (DNMT3A). Applying the system to human induced pluripotent stem cells (hiPSC)-derived dopaminergic neurons from a PD-patient with the triplication of *SNCA* locus, resulted in targeted DNA-methylation of *SNCA* intron 1 that enabled fine-tuned downregulation of *SNCA*-mRNA and protein. Furthermore, we showed that the reduction in *SNCA*-mRNA levels by the gRNA-dCas9-DMNT3A system rescued cellular disease related phenotypes characteristics of the *SNCA*-triplication hiPSC-derived dopaminergic neurons, *e.g.* mitochondrial ROS production and cellular viability. Our findings established that DNA hypermethylation at particular CpG islands within *SNCA* intron 1 allows an effective and sufficient tight-downregulation of *SNCA* expression levels, suggesting the potential of this target sequence combined with the CRISPR/dCas9 technology as a novel epigenetic-based therapeutic approach for PD.

Disclosures: B. Kantor: A. Employment/Salary (full or part-time):; Viral Vector Core. **L. Tagliafierro:** None. **J. Gu:** None. **M.E. Zamora:** None. **E. Ilich:** None. **C. Grenier:** None. **Z.Y. Huang:** None. **S. Murphy:** None. **O. Chiba-Falek:** None.

Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

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Program #/Poster #: 470.06/L15

Topic: C.03. Parkinson’s Disease

Support: NIH/NIAAA R03AA022479
NIA/NIH 1R25AG047843-01
NIEHS R01ES10653

Title: Nicotine protects against manganese and iron-induced toxicity in SH-SY5Y cells: Implication for Parkinson's disease

Authors: B. GETACHEW[1], A. B. CSOKA[2], K. N. MCPIKE[2], M. ASCHNER[3], *Y. TIZABI[1]
[1]Dept. of Pharmacol., [2]Dept. of Anat., Howard Univ. Col. of Med., Washington, DC; [3]Mol. Pharmacol., Albert Einstein Col. of Med., Bronx, NY

Abstract: Manganese and iron are trace elements that are needed in minute quantities for proper growth and physiological functions, as both play critical roles in a variety of enzymatic reactions.

At high concentrations, however,they can be toxic and cause neurodegenerative disorders, particularly Parkinson-like diseases. Nicotine, on the other hand, has been shown to have neuroprotective effects against various endogenous or exogenous toxins that selectively damage dopaminergic cells. For example, we have previously reported that exposure of neuroblastoma-derived SH-SY5Y cells (used as a cellular model of central dopaminergic neurons) to salsolinol, an endogenous dopaminergic selective toxicant, results in significant cell loss and that pre-treatment with nicotine can protect against this toxicity. In this study, we sought to determine whether nicotine might also protect against manganese or iron induced toxicity in these cells. Exposure of SH-SY5Y cells for 24 hours to manganese (10 µM) and iron (10 µM) resulted in approximately 55% and 50% toxicity, respectively. Pretreatment with nicotine (1 µM) reduced the toxicity for both manganese and iron by approximately 35%. Though the mechanism(s) of neuroprotective effects of nicotine against manganese and iron are under investigation the current findings further support the utility of nicotine in Parkinson-like neurodegenerative disorders. Supported by: NIH/NIAAA R03AA022479 (YT), NIA/NIH 1R25AG047843-01 (ABC), NIEHS R01ES10653 (MA)

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Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 470.07/L16

Topic: C.03. Parkinson’s Disease

Support: NINDS Grant NS 047198

Title: Neuroprotective effect of a novel dopamine agonist, D-512 in a rotenone model of Parkinson's disease

Authors: *D. YEDLAPUDI, P. RAVIPATI, L. XU, A. K. DUTTA
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Abstract: Parkinson’s disease (PD) is the second most common neurodegenerative disorder after Alzheimer’s disease affecting nearly 1% of the population over the age of 60. Neuropathologically, it is defined by death of dopaminergic neurons and the presence of intracellular inclusion bodies called Lewy bodies. In this study, we explored the effect of a multifunctional novel potent dopamine D2/D3 receptors agonist, D-512 in a rotenone model of PD *in vitro*. In this regard, we have previously shown that D-512 has potential in symptomatic and neuroprotective treatment of PD as it exhibited protection from neurotoxins like 6-OH DA and MPTP both *in vitro* and *in vivo* models of PD (1).

However, since rotenone based models have been known to recapitulate multiple symptoms of PD like dopaminergic neuronal death, alpha synuclein aggregation and Lewy body formation (2), we wanted to check if D-512 was able to reduce the toxicity caused by Rotenone in MN9D and PC12 cells.
Pre-treatment with D-512 showed a reduction in the toxicity caused by Rotenone in both MN9D and PC12 cells. Neuroprotection was found to coincide with a decrease in ROS levels, caspase-3 cleavage and activation of phospho-tyrosine hydroxylase levels in MN9D cells. D-512 was also able to inhibit the activation of ERK and restore the mitochondrial membrane potential caused by treatment of rotenone in PC12 cells. These observations suggest that D-512 might constitute a novel therapy for PD. This work is supported by a grant from NINDS (NS 047198, AKD).
1. Shah, M.; Rajagopalan, S.; Xu, L.; Voshavar, C.; Shurubor, Y.; Beal, F.; Andersen, J. K.; Dutta, A. K. The high-affinity D2/D3 agonist D512 protects PC12 cells from 6-OHDA-induced apoptotic cell death and rescues dopaminergic neurons in the MPTP mouse model of Parkinson's disease. J. Neurochem. 2014, 131,74−85
2. Johnson, M. E. and L. Bobrovskaya (2015). "An update on the rotenone models of Parkinson's disease: their ability to reproduce the features of clinical disease and model gene environment interactions." Neurotoxicology 46: 101-116.

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Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 470.08/L17

Topic: C.03. Parkinson's Disease

Title: Development of a novel therapeutic for treatment of synucleinopathies

Authors: *J. DELA CRUZ
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Abstract: Using a human pigmented cell line as an in vitro model of neuromelanin-containing neurons, we uncovered a pathway that results in the accumulation of alpha-synuclein and subsequent neurodegeneration providing a target for novel therapeutic approaches. We have identified a peptide with functions in pigment modulation, inflammation and energy homeostasis. It is produced and released by activated microglia and is elevated in the cerebrospinal fluid of patients with Parkinson's disease (and multiple system atrophy). Injection of this peptide within the rat midbrain dopaminergic neurons results in significant decreases in striatal dopamine. Indeed, treatment with a similar peptide exacerbated symptoms in PD patients. Although, pharmacologic reduction of the peptide improved symptoms, it did not halt the progression of disease. We found that upon exposure to the peptide, the pigmented cell line

displayed the cardinal features of synuclein pathology: a) accumulation of intracellular alpha-synuclein, b) decreased melanin production and c) increased cell death by apoptosis. We conclude that the peptide disables cellular autophagy. Mice impaired in neuronal cell autophagy invariably develop neurodegenerative disease and we observed progressive motor deficits in mice administered the peptide by intranasal route. Collectively, these observations point to the peptide as the likely culprit in synucleinopathies making it a very compelling therapeutic target. We have now shown that the biologic inhibitor of the peptide is able to block and more importantly reverse the effects of the peptide in vitro. The biologic inhibited the accumulation of intracellular alpha-synuclein and restored cellular autophagy, melanin production and preserved cell viability. As a therapeutic, the inhibitor may reverse the adverse effects of the peptide in synucleinopathy and promote an environment ideal for recovery and cell restoration therapies. Our current goals are to prepare a brain targetable biologic, demonstrate delivery of the inhibitor to the brain of monkeys and evaluate efficacy in melanin-containing parkinsonian monkeys.

Disclosures: J. Dela Cruz: None.

Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 470.09/L18

Topic: C.03. Parkinson’s Disease

Support: ERC-2014-CoG-646923_DBSModel

Title: Closed-loop deep brain stimulation using local field potential features in a computational model of the cortico-basal ganglia network

Authors: *J. E. FLEMING, E. DUNN, M. LOWERY
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Abstract: Deep Brain stimulation (DBS) is an established surgical treatment for Parkinson’s disease (PD) when medication is no longer effective. Setting stimulation parameters is a difficult and time-consuming process, requiring a skilled clinician to find optimal stimulation parameters over several parameter tuning sessions. Closed-loop DBS has been suggested as a solution to this, where disease biomarkers are monitored and utilized to set stimulation parameters. Local Field Potential (LFP) recordings from the basal ganglia have shown increased power in the beta frequency band (10-30 Hz) during PD. This increase correlates with motor impairment during the disease, and its suppression, by levodopa or during DBS, with improved motor function and has been suggested as a possible biomarker for PD. Computational modelling allows the simulation and investigation of this complex behaviour and testing of alternative DBS strategies which are not yet suitable for clinical testing. The objective of this study was to investigate the

effectiveness of different LFP features for use in closed-loop DBS strategies using a computational model of the cortico-basal ganglia (CBG) network.
The CBG network was modelled using single-compartment Hodgkin-Huxley type neuron models. Cortical neurons were modelled with multiple compartments, with cortical soma, axon and collateral segments. Local field potentials were simulated for the cortex and subthalamic nucleus (STN). The DBS extracellular field was modelled and applied directly to cortical collateral segments to simulate antidromic cortical stimulation through the hyperdirect pathway. Model parameters were set so the network displayed bursting in the beta band corresponding to a dopamine depleted state, as observed clinically. Four features were estimated for use in a closed-loop DBS strategy. From the STN LFP, the beta band average rectified value (ARV) and sample entropy were estimated. The vector strength and magnitude of beta band coherence between the cortical and STN LFPs was also estimated. These features were utilized by a proportional-integral-derivative controller to modulate the DBS amplitude and drive each feature to a predefined target value.
An approximately linear relationship between feature values and the DBS amplitude was observed for currents between 1 mA – 2 mA. The controller was capable of modulating the proportional error of the features within this region. The controller performance was affected by the measurement window length. Beta ARV modulation performed well for window lengths of 100 milliseconds, while the other features required longer window lengths to accurately estimate their value.

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Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 470.10/M1

Topic: C.03. Parkinson’s Disease

Title: Effect of carbon monoxide releasing molecule-2 on 6-hydroxydopamine-induced cell death in C6 glioma cells

Authors: D. CHOI[1], H. MOON[2], J.-H. JANG[3,4], T. JANG[4], *G. PARK[1]
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Abstract: Carbon monoxide (CO) was regarded as toxic gas in the past. Recently, it has been reported that low concentration of CO exerts therapeutic actions under various pathological conditions such as liver failure, heart failure, gastric cancer, and cardiac arrest. However, the

effect of CO in neuronal diseases like Parkinson's disease (PD) has remained to be elucidated. To test whether CO could have neuroprotective effect against oxidative cell death in PD, we examined the effect of CO-releasing molecule (CORM)-2 on 6-hydroxydopamine (6-OHDA)-induced cell death in C6 glioma cells. Treatment of CORM-2 significantly attenuated 6-OHDA-induced apoptotic cell death in a dose-dependent manner. CORM-2 treatment decreased Bax/Bcl2 ratio and caspase-3 activity, which had been increased by 6-OHDA. CORM increased phosphorylation of NF-E2-related factor 2 (Nrf2) which is a transcription factor regulating antioxidant proteins. Subsequently, CORM-2 also increased the expression of heme oxygenase-1 and superoxide dismutases, which were antioxidant enzymes regulated by Nrf2. Taken together, it is suggested that CO released by CORM-2 treatment may have protective effects against oxidative cell death in PD through the potentiation of cellular adaptive survival responses via activation of Nrf2 and upregulation of heme oxygenase-1, leading to increasing antioxidant defense capacity.

Disclosures: D. Choi: None. **H. Moon:** None. **J. Jang:** None. **T. Jang:** None. **G. Park:** None.

Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

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Program #/Poster #: 470.11/M2

Topic: C.03. Parkinson's Disease

Support: NIH Grant RO1 NS084998

Title: Development of a novel FRET-based cellular biosensor to monitor alpha-synuclein protein-protein interactions

Authors: *A. R. BRAUN[1], D. D. THOMAS[2], J. N. SACHS[1]
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Abstract: We have developed a pair of cellular, fluorescence-lifetime (FLT) FRET-based biosensors capable of monitoring early-stage oligomeric aSyn-aSyn interactions. Misfolded alpha-Synuclein (aSyn) is the pathological hallmark for numerous alpha-synucleinopathies (e.g. Parkinson's Disease-PD, Dementia with Lewy-bodies-DLB, and Multiple-systems atrophy-MSA). Native aSyn is an intrinsically disordered protein, predominantly localized to synaptic terminals. Under disease-associated conditions, misfolded aSyn assembles into kinetically metastable "on-" or "off-pathway" oligomers, ultimately forming fibrillar aSyn deposits (i.e., Lewy bodies and Lewy Neurites). Increasing evidence suggests that the oligomeric forms of aSyn are the toxic species responsible for neurodegeneration associated with PD, DLB, and MSA.

Due to their kinetically unstable nature, aSyn oligomers pose significant challenges to isolate and characterize their biophysical properties and mechanism of action. Developing a cellular biosensor to monitor aSyn-aSyn interactions provides a novel tool to target this important, pathological protein-protein interaction, and establishes a platform for future therapeutic discovery.
Using GFP- and RFP-aSyn fusion proteins expressed in HEK293 and SH-SY5Y cells, we have developed two classes of aSyn biosensors sensitive to either inter-molecular or intra-molecular FRET signals. Our FLT-based biosensor affords a 30-fold increase in sensitivity relative to conventional intensity-based FRET measurements. Pilot high-throughput screens of small-molecule libraries have identified a series of tool compounds that demonstrate sensitive FRET dose response and rescue cytotoxicity induced by aSyn-overexpression. These compounds will be used to develop a deeper understanding of the mechanism of aSyn oligomer-induced cytotoxicity.

Disclosures: A.R. Braun: None. **D.D. Thomas:** None. **J.N. Sachs:** None.

Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

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Program #/Poster #: 470.12/M3

Topic: C.03. Parkinson’s Disease

Support: The work described was funded by Mission Therapeutics

Title: Development and validation of a high content-based assay to measure Tom20 loss in dopaminergic human neurons differentiated *in vitro*

Authors: *F. VERKAAR[1], R. DE WIT[1], M. WATSON[2], P. THOMPSON[2], S. DIJKSTRA[1]
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Abstract: Parkinson’s disease (PD) pathogenesis has been linked to mitochondrial dysfunction through several lines of research, starting with the finding that the mitochondrial complex I inhibitor rotenone induces parkinsonism. In addition, mutations in genes encoding proteins involved in the selective clearance of mitochondria (mitophagy), such as PARK2 and PINK1, are present in the majority of autosomal recessive cases of PD. Phenotypic readouts to measure mitochondrial (dys)function in disease-relevant cellular backgrounds are therefore thought to represent powerful predictive tools to probe PD pathobiology and identify potential therapeutics. Here, we describe the development of a high content-based assay to measure loss of the mitochondrial marker TOMM20 (Tom20) in differentiated ReNcell VM cells, which represent a replenishable source of human dopaminergic neurons. Using immunocytochemical detection coupled to high-throughput image acquisition with an IN Cell 6000 plate-based imager,

concentration-dependent reductions in mitochondrial Tom20 content were observed following treatment with a range of mitochondrial stressors, such as CCCP, oligomycin/antimycin (O/A) and valinomycin. Specificity of the readout for mitochondria was validated by co-staining with MitoTracker mitochondrial dye, and the assay was successfully miniaturized to 96-well format. Loss of Tom20 with mitochondrial damaging agents most likely represents mitophagy. The assay is expected to facilitate hit-to-lead- or target validation programs in the PD space by enabling compound profiling in a human neuronal background.

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Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

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Topic: C.03. Parkinson's Disease

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Title: A druggable genome screen identifies modifiers of α-synuclein levels via a tiered cross-species validation approach

Authors: *G. VAZQUEZ-VELEZ[1,2,10,3], M. W. ROUSSEAUX[4,10], I. AL-RAMAHI[10,4], H.-H. JEONG[4,10], A. S. BAJIC[5,10], J.-P. REVELLI[4,10], H. YE[4,10], E. PHAN[4,10], J. DEGER[4,10], A. PEREZ[4,10], J.-Y. KIM[4,10], L. LAVERY[4,10], Q. XU[11], M. LI[11], H. KANG[4,10], J. SHULMAN[4,10,6,7], T. WESTBROOK[4,8,9], S. ELLEDGE[11,12], Z. LIU[5,10], J. BOTAS[4,10], H. Y. ZOGHBI[4,10,3,5,13]
[2]Med. Scientist Training Program, [3]Program in Developmental Biol., [4]Dept. of Mol. and Human Genet., [5]Dept. of Pediatrics, [6]Dept. of Neurol., [7]Dept. of Neurosci., [8]The Verna and Marrs McLean Dept. of Biochem. and Mol. Biol., [9]Therapeut. Innovation Ctr. (THINC), [1]Baylor Col. of Med., Houston, TX; [10]Jan and Dan Duncan Neurolog. Res. Inst. at Texas Children's Hosp., Houston, TX; [11]Dept. of Genet., Harvard Med. Sch., Boston, MA; [12]Howard Hughes Med. Inst., Boston, MA; [13]Howard Hughes Med. Inst., Houston, TX

Abstract: Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons of the *substantia nigra pars compacta* (SNc), and by the formation of Lewy bodies composed chiefly

of alpha -Synuclein (*SNCA*). Importantly, duplications and triplications of the *SNCA* locus cause familial forms of PD, single nucleotide polymorphisms in *SNCA* are major risk factors for PD, and correlate with higher *SNCA* transcript levels. Additionally, beta-adrenergic receptor agonists reduce alpha-Synuclein levels and PD risk. Thus, increased alpha -Synuclein levels are intrinsically tied to PD pathogenesis, this underscores the importance of identifying the factors that regulate its levels. To find these factors, we conducted a pooled RNAi screen of a collection of 7,787 druggable genes which identified 351 putative modifiers of alpha-Synuclein levels. Of these, we validated 60 candidates and selected 10 for further testing. Using a cross-species approach, we identified six strong modulators of alpha -Synuclein levels and toxicity in cell lines, Drosophila, human neurons and mouse brain. More broadly, the strategy employed here can be used for other diseases caused by dosage sensitive proteins.

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Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

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Program #/Poster #: 470.14/M5

Topic: C.03. Parkinson’s Disease

Support: CIHR MOP-153068
NSERC 2018-06264
NSERC 2018-522690
Junior II career award FRQ-S

Title: Post-mortem analysis of a Parkinson's disease brain after 11 years of deep brain stimulation of the subthalamic nucleus

Authors: *F. DESMEULES[1], C. LECOURS[2], S. CARRONDO COTTIN[3], A. M. NOECKER[4], P. V. GOULD[3], S. SAIKALI[3], M. LANGLOIS[3], M.-E. TREMBLAY[2], C. C. MCINTYRE[4], M. PRUDHOMME[3], L. CANTIN[3], M. PARENT[1]
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Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is widely used to treat Parkinson’s disease (PD). This procedure does not cure the disease but radically alleviates motor symptoms and leads to a significant reduction of dopamine medication and severe

associated adverse effects such as dyskinesia, improving the quality of life of PD patients. The cellular and molecular mechanisms of DBS as well as its long-term effects on cerebral tissue are still poorly understood. Through this case report, we aim to describe fine neuroanatomical and neurochemical alterations of stimulated brain parenchyma and associate these changes to clinical outcomes of STN DBS. Our case report deals with the detailed post-mortem investigation of a PD patient's brain treated with DBS for 11 years, the longest STN stimulation period ever reported. Clinical data indicates significant positive outcomes of STN DBS on physical functioning with a score going from 48 to 11 on UPDRS III, along with a 70% daily reduction of dopamine medication. A 3D reconstruction of patient's brain indicates that the active contacts were placed in the dorsolateral region of the STN, corresponding to its sensorimotor functional territory. This 3D virtual environment was then used to model current spreading throughout the tissue. As expected, we observed a 300 µm-width gliosis around the electrode leads showing high immunoreactivity for GFAP (specific marker of astrocytes), for the proliferating cell nuclear antigen (PCNA) and for the neurotrophic factor GDNF. We also identified astrocytes endowed with highly varicose processes, exclusively in the STN stimulated area. A significant reduction of the number of Iba1+ microglia was also observed near the active contacts, the vast majority being immunoreactive for CD68, supporting the hypothesis of altered neuroinflammation induced by DBS. We also found a 23% increase of the length of GLUT1+ capillaries in the STN stimulated area compared to non-stimulated STN regions. Immunoreactivity for the vascular endothelial growth factor (VEGF) was low in this STN stimulated region, indicating that angiogenesis occurred rather early following the surgery, but stabilized with time. Moreover, the subventricular zone in this particular DBS implanted brain was thicker than in non-implanted PD brains and similar to non-pathological brains, suggesting that DBS may restore normal neural cell proliferation in PD. Interestingly, we also noted a significant reorientation of serotonin (SERT+) axons near the active contacts. We hope that this case report will provide new insights for a better understanding of the long-term effects of DBS, including its mechanisms of action.

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Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

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Program #/Poster #: 470.15/M6

Topic: C.03. Parkinson's Disease

Title: Inhibiting phosphoinositide 3-kinase/mammalian target of rapamycin signaling reduces cellular phosphorylation of protein kinase B to increase macro- and chaperone-mediated autophagy and mitigate alpha synuclein-induced neurotoxicity

Authors: *J. K. BOWDEN-VERHOEK[1], E. STOCKING[1], J. L. WONG[1], E. ARIAS-PEREZ[2], N. FUSSI[3], M. HÖLLERHAGE[3], G. HOEGLINGER[3], A. M. CUERVO[2], W. WRASIDLO[1], D. PRICE[1], M. GILL[1], D. BONHAUS[1]
[1]Neuropore Therapies, San Diego, CA; [2]Albert Einstein Col. of Med., Bronx, NY; [3]DZNE - German Ctr. for Neurodegenerative Dis. within the Helmholtz Assn., Munich, Germany

Abstract: Synucleinopathies are a family of central nervous system (CNS) degenerative disorders characterized by deposition of insoluble alpha-synuclein-containing protein aggregates, neuronal and/or glial cell death and inflammation. Neurons, astrocytes and microglia activate cellular clearance mechanisms to dispose of misfolded, monomeric or aggregated proteins and damaged organelles. These clearance mechanisms are referred to collectively as autophagy, of which macro-autophagy and chaperone-mediated autophagy handle a large component of the cell's protein clearance. Macro-autophagy involves the bulk degradation of organelles and protein aggregates through engulfment in a membrane-bound vesicle which ultimately fuses with the lysosome, while chaperone-mediated autophagy selectively degrades proteins, identified by an amino acid pentamotif, through chaperone-mediated translocation into the lysosome via the LAMP2A multimeric complex. The phosphoinositide 3-kinase/mammalian target of rapamycin (PI3K/mTOR) signaling pathway can modulate cellular phosphorylation of protein kinase B (pAkt) and has been well-characterized for its role in activation of macro-autophagy. Recent publications suggest pAkt negatively regulates the activation of chaperone-mediated autophagy. Together, these data support reduction of pAkt as a means to increase both macro-autophagy and chaperone-mediated autophagy to reduce cellular protein aggregation. Neuropore Therapies (NPT) has developed novel, potent and kinome-selective PI3K/mTOR inhibitors which are orally bioavailable and are brain penetrant. Using a combination of in vitro rodent reporter cell systems and human microglia, these compounds reduced cellular pAkt and induction of HIF-1α, as well as activated macro- and chaperone-mediated autophagy. Indeed, we uncovered a strong correlation between a compound's cellular pAkt inhibition potency and the compound's ability to reduce HIF-1α induction, and activate macro- and chaperone-mediated autophagy. Importantly, compounds, which significantly activated macro- and chaperone-mediated autophagy, also significantly reduced cell death in a viral alpha synuclein-mediated neurotoxicity

model. Preliminary in vivo data with a reference PI3K/mTOR inhibitor demonstrate a separation between pAkt target engagement and systemic hyperglycemia, supporting a path forward for mechanism-of-action-related efficacy studies. Proprietary NPT compounds are in queue for in vivo evaluation of target engagement and pre-clinical PD model efficacy experiments.

Disclosures: J.K. Bowden-Verhoek: A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc. **E. Stocking:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc. **J.L. Wong:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc.. **E. Arias-Perez:** None. **N. Fussi:** None. **M. Höllerhage:** None. **G. Hoeglinger:** None. **A.M. Cuervo:** None. **W. Wrasidlo:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc. **D. Price:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc. **M. Gill:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc. **D. Bonhaus:** A. Employment/Salary (full or part-time):; Neuropore Therapies, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuropore Therapies, Inc..

Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 470.16/M7

Topic: C.03. Parkinson’s Disease

Support: Cedars-Sinai Board of Governors Regenerative Medicine Institute

Title: Human iPSC-based models to study gastrointestinal dysfunction in Parkinson’s disease

Authors: *M. J. WORKMAN[1,2], S. SANCES[1], A. LAPERLE[1], R. HO[1], R. J. BARRETT[1,3], C. N. SVENDSEN[1,2]
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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder that is typically characterized by various motor symptoms and the progressive loss of dopaminergic (DA) neurons in the substantia nigra. However, PD is also associated with numerous non-motor symptoms. Many PD patients suffer from gastrointestinal (GI) abnormalities such as constipation, microbial dysbiosis, and intestinal inflammation that precede motor system dysfunction by many years. Additionally, α-synuclein accumulation has been reported in the enteric neurons of the GI tract in PD patients and it is thought that this possibly contributes to the accumulation of α-synuclein and subsequent DA neuron cell death in the CNS. Here we have developed a platform to investigate GI dysfunction observed in PD based upon our previously published protocol of induced pluripotent stem cell (iPSC)-derived human intestinal organoids (HIOs) containing a functional enteric nervous system (ENS). The vast majority of PD cases have no known genetic mutations, prompting the need to develop sporadic Parkinson's disease models. Through the Cedars-Sinai iPSC Core, we have generated numerous iPSC lines from sporadic PD patients using non-integrating episomal plasmids, along with gender-matched control iPSC lines from the Lothian Birth Cohort, a group of individuals which are free of any known neurodegenerative diseases. Using these lines, we have successfully generated HIOs with an incorporated ENS (control n=4; PD n=3) and have performed transcriptomic profiling, revealing disease-specific changes in gene expression. Additionally, we have combined iPSCs with a scalable microphysiological system (MPS) known as the Organ-Chip (Emulate, Inc). Using the micro-engineered poly(dimethylsiloxane)-based Organ-Chip platform, we have developed a co-culture system of intestinal epithelium and enteric neurons that permits the study of host-microbial interactions. Using this approach, we aim to identify disease-specific changes in iPSC-derived intestinal tissue from PD patients and to characterize the role of gut microbiota in promoting disease progression.

Disclosures: M.J. Workman: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **S. Sances:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **A. Laperle:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **R. Ho:** None. **R.J. Barrett:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **C.N. Svendsen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder.

Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 470.17/M8

Topic: C.03. Parkinson's Disease

Title: Drug-like small molecules that modulate catalyzed assembly and toxicity ofalpha-synuclein in cell culture models of pd

Authors: S. SELVARAJAH[1], A. MÜLLER-SCHIFFMANN[2], K. PAULVANNAN[1], R. MARREIROS[2], N. DEYARMAN[1], *V. R. LINGAPPA[1], C. KORTH[2]
[1]Prosetta Biosciences, Inc, San Francisco, CA; [2]Heinrich Heine Univ. Düsseldorf, Düsseldorf, Germany

Abstract: Background: We use an unconventional *de novo* cell-free protein synthesis (CFPSA)-based phenotypic screen to interrogate catalyzed assembly as an essential, but previously inaccessible, step in gene expression, applicable across therapeutic areas. Assembly has been found to be carried out by multi-protein complex (MPC) putative "assembly machines" that are normally hard to detect by conventional proteomics due to their transience/lability. This appears to be a critical weak link in the pathophysiology of many diseases, including PD, in which assembly machine protein composition is found to be strikingly aberrant. A collection of approximately 300 diverse drug-like chemotypes, identified by their modulatory activity against various assembly events, were interrogated for activity in modulating a-synuclein.
Method: We developed a cellular model for robust α-synuclein aggregation in SH-SY5Y and NLF cells using proprietary nucleic acid sequences. We performed toxicity assays in differentiated dopaminergic human LUHMES cells. Rotenone induced toxicity model was used to explore primary rat dopaminergic neuron viability. Drug resin affinity chromatography (DRAC) followed by MS-MS was used for identification of MPCs.
Results: Our cell models revealed different assembly states of α-synuclein, including small aggregates and ring-like structures of α-synuclein associated with lipid droplets. Interestingly, the most potent ring- inducing compound showed the least degree of aggregated α-synuclein, was protective against rotenone and dopamine induced synaptic loss or toxicity. Early structure-activity relationship studies already led to optimized compounds with an EC50 below 200nM. The compounds prevented α-synuclein mediated synaptic loss or cell death of dopaminergic neurons via a novel molecular mechanism, i.e. the increased association of toxic α- synuclein aggregates with LDs, thereby presumably facilitating degradation of α-synuclein.
Conclusions: Assembly modulation is a novel and productive approach to PD therapeutics. DRAC has allowed identification of the protein components of assembly machines and it is composed of proteins previously identified as part of the PD disease interactome – but not previously known to be transiently together as a MPC.

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Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 470.18/M9

Topic: C.03. Parkinson's Disease

Support: PIND Pilot Projects

Title: Are they still dopaminergic? A re-examination of various dopaminergic cell lines

Authors: *J. D. JAUMOTTE[1], S. L. CASTRO[1], A. D. SMITH[3], M. J. ZIGMOND[1], D. B. DEFRANCO[2]
[1]Neurol., [2]Dept. of Pharmacol. and Chem. Biol., Univ. of Pittsburgh, Pittsburgh, PA; [3]V.A. Pittsburgh Healthcare Syst., Pittsburgh, PA

Abstract: Cell lines have provided an invaluable tool in biological research since the isolation of the first immortal cells, HeLa, in 1951. Their use allows for more rapid experimental output, testing of multiple conditions, and reduces the number of animals used. However, it is critical that cell lines are used appropriately and have the best characteristics for the diseases in which they are used to model. One such example is in Parkinson's disease (PD) for which a variety of cell lines are available: PC12, MN9D, SH-SY5Y, N27. Although each of these cell lines has been used in published articles there have been conflicting levels of expression in many of the key proteins associated proteins associated with the dopaminergic (DAergic) cells that are affected in PD, including tyrosine hydroxylase (TH) and dopamine transporter (DAT) reported. Variations should not be unexpected if one takes into account the manner in which the cells were initially produced, the number of times the cells are passed, and the conditions in which they are cultured. We have done an extensive investigation of three DAergic cell lines used in our lab: MN9D, SH-SY5Y, and N27. We used western analysis, qRT-PCR, and immunofluorescence to examine expression of TH, DAT, dopamine beta hydroxylase, α-synuclein, and estrogen receptor β and HPLC to measure DA synthesis, and DA levels, as well as overall morphology of undifferentiated cells over several passages and compared to what has been previously observed across the literature.

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Poster

470. Parkinson's Disease: Therapeutic Strategies: Cellular Models

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Program #/Poster #: 470.19/M10

Topic: C.03. Parkinson's Disease

Support: University of Georgia Physiology and Pharmacology
REM Seed Grant
MJFF Target Advancement Grant

Title: Human natural killer cells clear extracellular alpha-synuclein while their effector functions are inhibited

Authors: *J. LEE[1], J. CHUNG[1], R. H. EARLS[2], K. BAKER[2]
[1]Dept. of Physiol. and Pharmacol., Univ. of Georgia Col. of Vet Med., Athens, GA; [2]Neurosci., Univ. of Georgia, Athens, GA

Abstract: The pathological hallmarks of Lewy body dementia and Parkinson's disease (PD) are the presence of Lewy bodies (LBs), which are composed of intracellular fibrillar inclusions of aggregated alpha-synuclein (α-syn). Additionally, the levels of extracellular α-syn are higher in the serum and cerebrospinal fluid in these patients, and have been implicated in modulating immune responses in both the CNS and the periphery. The number of circulating natural killer (NK) cells are modulated in neurodegenerative disorders and their activities are related with disease severity. Nevertheless, the role of NK cells in modulating PD severity has received little attention. Here, we demonstrate that extracellular α-syn attenuates NK cell cytotoxicity in a dose-dependent manner by reducing the level of perforin. The extracellular α-syn also attenuated production of interferon (IFN)-γ, a major proinflammatory cytokine produced by NK cells. Remarkably, NK cells efficiently uptake and degrade extracellular α-syn species via the endosomal/lysosomal pathway. Importantly, NK cells also efficiently uptake and degrade extracellular Aβ species. Our study has demonstrated a novel function of NK cell in clearing extracellular abnormal protein aggregates while extracellular α-syn aggregates did not activate but instead inhibited NK cell effector functions. Our results suggest that NK cell may be a candidate for cell-based therapy due to their capability to clear extracellular protein aggregates without aberrant activation.

Disclosures: J. Lee: None. **J. Chung:** None. **R.H. Earls:** None. **K. Baker:** None.

Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.01/M11

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Mouse model of manganism: Towards understanding of the phenotype

Authors: *C. G. JANUS[1], G. GIRALDO[1], R. WEISKIRCHEN[3], M. KNUTSON[2]
[1]CTRND and Dept. of Neurosci., [2]Food Sci. & Human Nutr., Univ. of Florida, Gainesville, FL; [3]Univ. Hosp. RWTH Aachen, Aachen, Germany

Abstract: In humans, exposure to excess manganese can result in manganese accumulation in the brain, as well as in neurological and motor disturbances resembling a parkinsonian-like disorder known as manganism. We recently published findings confirming that *Slc39a14*$^{-/-}$ knockout mice have elevated manganese concentrations in the blood, brain, and bone. Brain manganese accumulation in *Slc39a14*$^{-/-}$ mice was associated with locomotor impairments. Additionally, most *Slc39a14*$^{-/-}$ mice also displayed postural abnormalities in the form of torticollis, a condition in which the muscles in the neck contract, causing the head to twist slightly to one side. In this study, we investigated whether this postural defect could confound the performance of mice in the administered locomotor tests, and thus bias the interpretation of the obtained results. To this end, we compared the performance of *Slc39a14*$^{-/-}$ mice which showed torticollis with the performance of the *Slc39a14*$^{-/-}$ mice without any identifiable signs of torticollis and with the performance of the control, wild type mice. The results of our comparative analyses across a variety of locomotor tests demonstrated the unequivocal motor impairment of *Slc39a14*$^{-/-}$ mice in each of these tests, and that the combined index of performance across the tests did not differentiate between *Slc39a14*$^{-/-}$ mice with and without torticollis. Thus, we conclude that in this study torticollis did not significantly confounded the locomotor performance of *Slc39a14*$^{-/-}$ mice in the tests.

Disclosures: C.G. Janus: None. **G. Giraldo:** None. **R. Weiskirchen:** None. **M. Knutson:** None.

Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.02/M12

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Young Investigator SCA Research Grant

Title: *In vivo* analyses on ubiquitin and proteasomal activity in SCA3

Authors: *J. SCHMIDT[1,2], A. GRUN[1,2], T. MEFFERT[1,2], O. RIESS[1,2], T. SCHMIDT[1,2]
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Abstract: Spinocerebellar ataxia type 3 (SCA3) or Machado-Joseph disease (MJD) is an inherited neurodegenerative disorder caused by the expansion of a CAG repeat within the *ATXN3* gene resulting in an expanded polyglutamine repeat in the encoded protein ataxin-3. SCA3/MJD therefore belongs to the group of polyglutamine diseases. Up to now, no treatment is available for this disease. One hallmark of this and other neurodegenerative diseases is the formation of inclusion bodies (protein aggregates) in the brain. For the affected protein ataxin-3 deubiquitinating activities have been proven. Ubiquitin has a central role in many cellular pathways. E. g., K48-linked ubiquitin chains represent the main signal for proteasomal degradation. In order to further study the role of ubiquitination in SCA3, we crossed one of our previously generated mouse models for SCA3 with mice transgenic for mutated ubiquitin (K48R mice). The mutation in K48R mice (Lysin at position 48 is replaced by Arginin) leads to premature termination of K48 poly-ubiquitin chain assembly, hence to the formation of higher amounts of short K48-linked ubiquitin chains. Performing rotarod tests to measure the motor-coordinative abilities, we observed that transgenic SCA3 mice which simultaneously express a mutant ubiquitin transgene (MJD/K48R) showed an alleviated motor phenotype compared to single transgenic SCA3 mice. Western blot and immunohistochemical analyses furthermore revealed that transgenic SCA3 mice with mutated ubiquitin (MJD/K48R) showed less transgenic ataxin-3 protein as well as less ataxin-3 positive inclusion bodies. We hypothesize that the presence of higher amounts of short K48-linked ubiquitin chains leads to a higher proteasomal turnover of the expanded transgenic ataxin-3 protein resulting in the alleviated phenotype in MJD/K48R mice. We are currently conducting analyses (e.g. measurement of proteasomal activity) to further explore this hypothesis and the feasibility to translate this approach into a therapeutic strategy.

Disclosures: J. Schmidt: None. **A. Grun:** None. **T. Meffert:** None. **O. Riess:** None. **T. Schmidt:** None.

Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.03/M13

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Deep brain stimulation of the ventral intermediate nucleus/zona incerta as an off-label treatment for anti-GAD65 antibody-positive stiff-person-syndrome-induced tremor

Authors: *K. MARKOPOULOU[1,2], A. LOGGINI[2], P. WARNKE[3]
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Abstract: Introduction Intention tremor is a frequent manifestation of the disruption of cerebello-thalamo-cortical circuits with variable underlying etiologies and is often medication-refractory. Deep brain stimulation (DBS) has been used to treat uncommon tremor disorders e.g., multiple sclerosis associated intention tremor, Holmes tremor, rubral tremor, neuropathic tremor, orthostatic tremor, fragile-X associated tremor/ataxia syndrome (FXTAS) with good outcomes. Stiff person syndrome (SPS) can present with severe intention tremor. Here, we present the first case of anti-GAD65 positive-antibody SPS-associated intention tremor treated successfully with bilateral Vim DBS.
Methods A 79 year-old male with history of anti-GAD65 antibody-positive SPS, of five-year disease duration, characterized by severe ataxia and intention tremor that was refractory to repeated courses of high dose IV methylprednisolone, oral prednisone, IVIG and symptomatic therapy with baclofen and clonazepam underwent bilateral insertion of deep brain stimulator leads at the border of the ventral intermediate nucleus of the thalamus (Vim) and the zona incerta (Zi) using a Medtronic wide-spaced lead (3387). No intra-operative complications were observed as documented by intra-operative CT. A late appearing small (3cc) intra-parenchymal hematoma along the proximal end of the left DBS lead tract caused a transient alteration of consciousness that resolved spontaneously. Tremor was assessed with the Fahn-Tolosa-Marin (FTM) rating scale and video-recorded with DBS OFF and DBS ON.
Results With DBS ON complete elimination of postural tremor was achieved bilaterally. Kinetic tremor resolved completely on one side whereas its severity decreased from severe to moderate on the other. DBS OFF FTM score was 58 and DBS ON 15. With frequent reprogramming sessions at on-average bimonthly intervals, the beneficial effect on the tremor has been maintained with some fluctuation in severtiy for more than two years, without adverse effects.
Conclusion Bilateral Vim/Zi nucleus DBS is a safe and effective off-label symptomatic treatment of medically-refractory intention tremor in anti-GAD antibody positive SPS. The therapeutic effect obtained in this as in other uncommon tremor disorders suggests that irrespective of the underlying pathophysiological mechanisms, the modulation of common cerebellar-thalamo-cortical circuits can result in good tremor control. Thus, DBS Vim/Zi therapy in medication-refractory intention tremor associated with SPS further expands the spectrum of uncommon tremors that can be effectively treated with DBS.

Disclosures: K. Markopoulou: None. **A. Loggini:** None. **P. Warnke:** None.

Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.04/M14

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Neurotoxic effect of a polyglutamine expansion in human TATA-binding protein in SCA17 modeled in *Drosophila melanogaster*

Authors: *M. CARDENAS-TUEME[1], C. ALTAMIRANO-TORRES[2], V. GONZALEZ-VILLASANA[2], D. RESENDEZ-PEREZ[2]
[1]Developmental Biol., Univ. Autonoma De Nuevo Leon, Nuevo Leon, Mexico; [2]Developmental Biol., Univ. Autonoma de Nuevo Leon, Nuevo Leon, Mexico

Abstract: Spinocerebellar ataxias (SCAs) are progressive disorders in which the cerebellum and brain stem slowly degenerate. Spinocerebellar ataxia 17 (SCA17) is caused by an expansion of the CAG / CAA trinucleotide in the gene that encodes for the polyglutamine (polyQ) regions in the TBP gene (TATA Binding Protein). Since our laboratory focuses on the study of protein-protein interactions of transcription factors in *D. melanogaster*, and SCA17 is caused by a transcription factor we decided to model it in *Drosophila melanogaster* to study the effect of hTBP polyglutamine expansion and its consequences at brain and motor level. To analyze the neuropathological effect of hTBP with the extended poly 90Q compared with wild type poly 34Q, we addressed expression using the brain tissue-specific promoter ELAV-Gal4 in *D. melanogaster*. Afterwards protein aggregation, cell death and climbing ability were analyzed at 2, 10, 20 and 50 days of age. The expression of hTBP90Q reduced the life of *D. melanogaster* in comparison with the *wild type* fly. As expected, the tissue-specific expression of hTBP with the expansions of 34 and 90 Q, in a span of 50 days, showed a degenerative phenotype in the eye. According to our results, the aggregation of these proteins is present in the brains of both flies hTBP34Q and hTBP90Q with a clear dependence on the age and length of the polyQ expansion. The confocal images did not show aggregates in the *D. melanogaster* brain at an early age, in the case of both 34Q and 90Q expansions; however, starting at ten days of age, hTBP90Q formed protein aggregates in *D. melanogaster's* brain, which increased over time. In contrast, the expansion with 34Q began to form aggregates up until 50 days of age, which demonstrated the dependence of the length of the expansion of polyQ and its correlation with the age of the fly. Cell death was present in a greater proportion in brains expressing hTBP90Q compared to hTBP34Q, and flies expressing hTBP90Q were more affected in the climbing tests compared to flies expressing hTBP34Q. The modeling of SCA17 in *D. melanogaster* allowed to clearly conclude the neurotoxic effect of hTBP80Q in the brain of the fly which shortened its life time and locomotor capacity due to the formation of protein aggregates and cell death. Our results have opened the possibility to evaluate the type of cell death produced in the affected neurons

and the molecular behavior of these polyQs expansions in the neurodegenerative pathology SCA17.

Disclosures: M. Cardenas-Tueme: None. **C. Altamirano-Torres:** None. **V. Gonzalez-Villasana:** None. **D. Resendez-Perez:** None.

Poster

471. Ataxias

Location: SDCC Halls B-H

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Program #/Poster #: 471.05/M15

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Utilizing apigenin to attenuate the degenerative effects of oxidative stress in the spastic Han-Wistar rat, a model of ataxia

Authors: *M. OLMOS[1], M. A. GILHUYS[2], A. LEMUS[2], R. W. COHEN[2]
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Abstract: Oxidative stress is an accumulation of reactive oxygen species (ROS) to toxic cellular levels resulting in damage to DNA and proteins, which ultimately impedes proper neuronal function. ROS, including superoxide, hydroxyl and hydrogen peroxide arise through a deviant process in which high energy electrons are released during oxidative phosphorylation. Direct correlations have been established between oxidative stress and neurologic disorders such as Parkinson's and Alzheimer's diseases. Important to this presentation, oxidative stress has also been linked to progressive cell death in Purkinje cells in ataxia. Apigenin is a bioflavonoid with anti-oxidant, anti-tumorigenic, and anti-inflammatory properties. Specifically, apigenin exhibits its anti-oxidant ability by donating electrons to ROS to produce more stable and lower energy compounds. Apigenin has been used to treat neurologic diseases that present oxidative stress effects, such as Parkinson's and Alzheimer's Disease. By utilizing apigenin, this study aimed at attenuating the ataxic symptoms of the *spastic* Han-Wistar (*s*HW) rat characterized by fore limb tremors, decreased motor coordination, and hind limb rigidity. At 25-30 days of age, an equal mix of male and female mutant and normal *s*HW siblings were administered intraperitoneal injections with 40 mg/kg apigenin or vehicle (20% ethanol in mammalian saline) three times per week for three weeks. Three behavioral assays were utilized in this study and were performed three times per week: weight was utilized to assess overall animal health, open field test elucidated motor function, and rotarod data determined cerebellar motor coordination. Weight assay data showed apigenin-treated mutants displayed weights similar to untreated normals ($p > 0.05$). Data collected from open field activity tests showed that apigenin-treated mutants were able to retain their motor function when compared to vehicle-treated mutants ($p < 0.05$), implying Purkinje cell survival in apigenin-treated mutants. Data from rotarod activity tests indicated no statistical significance in motor coordination between apigenin-treated mutants and

vehicle-treated mutants ($p > 0.14$). At 60-65 days of age, all animals were sacrificed and perfused in order to collect cerebellar tissue for Purkinje cell counts. Increased Purkinje cell counts in the cerebellum correlated with sustained increased mobility in the apigenin-treated mutants. This study demonstrated the potential effectiveness of apigenin by delaying the onset of neurologic symptoms against neurodegenerative damage caused by oxidative stress.

Disclosures: M. Olmos: None. **M.A. Gilhuys:** None. **A. Lemus:** None. **R.W. Cohen:** None.

Poster

471. Ataxias

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Program #/Poster #: 471.06/M16

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Firb 2013 N. RBFR132BKP (MIUR)
Platypus (EU H2020-MSCA-RISE-2016 734227)

Title: Reaching strategies when the eye-hand configuration varies in direction and depth in a patient with lesions of the posterior parietal cortex

Authors: *A. BOSCO[1], V. PISERCHIA[1], C. BERTINI[2], E. LADAVAS[2], P. FATTORI[1]
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Abstract: The accuracy in reaching to targets can be affected by lesions of the posterior parietal cortex (PPC), like those that are observed in Optic Ataxia (OA). OA is a high-order disorder that occurs with unilateral or bilateral PPC lesion; the sites of the lesion typically involve the Parietal Occipital Junction (POJ), the superior parietal lobule (SPL) and areas around the intra parietal sulcus (IPS). Here, we report the case of a female left-handed patient (age: 61) with right posterior parietal lobe damage where we studied the influence of different eye/hand configurations varying in depth and direction on her reaching trajectories and accuracy. The reaching performance of the patient was compared with 5 left-handed healthy controls (4 females, mean age: 47). Trajectories and accuracy were measured by a motion capture system (Vicon) while participants were tested in visually-guided reaching movements to targets presented at different depths and directions in foveal and peripheral viewing conditions. The peripheral and foveal viewing conditions consisted in 3 eye/hand configurations: in the constant-gaze configuration, the eye fixated a central fixation target and the hand reached one of the peripheral reaching targets, in the constant reach configuration, eyes fixated one of the peripheral targets and the hand reached always the central target, and in the foveal reach configuration, the fixation and reaching targets were coincident. The patient showed significant higher reaching errors with respect to controls both in depth and direction and in all the three eye/hand configurations (t-test, $P < 0.05$). In the eye/hand configurations with peripheral viewing, the

patient did not correct the trajectory at the end of movement as the controls (t-test, $P < 0.05$). In the configuration where the targets were foveated, she was able to adjust her behavior in the same direction of controls, although significantly less (t-test, $P < 0.05$). We suggest that the reaching inaccuracies observed in the configurations where the direction of gaze and reach direction differed can be explained by the lack of the "automatic pilot" which is able to adjust in healthy conditions the predefined motor plan. In particular, this lack is specific of the second part of the reaching movement.

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Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.07/M17

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Adeno-associated virus-mediated knockdown of Gba in the central nervous system models neuronopathic Gaucher disease

Authors: *K. JACKSON[1], C. VIEL[1], J. C. MATTHEWS[1], J. BU[1], M. CHAN[1], B. WANG[2], L. S. SHIHABUDDIN[1], S. P. SARDI[1]
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Abstract: Pathological mutations in GBA, encoding the lysosomal hydrolase glucocerebrosidase (GCase), cause Gaucher disease (GD). GD is a multi-system disease with great phenotypic variation between individuals. It has been classified into type 1 with primarily systemic involvement and types 2 and 3 with varying degrees of neurological involvement. Type 2 GD progresses rapidly with severe neurological symptoms and death typically by 2 years of age. Type 3 GD has an increased life expectancy compared to type 2 and a slower progression of neurological impairments, including ataxia and tremor. GD is characterized by decreased GCase activity leading to accumulation of lipid substrates, glucosylceramide and glucosylsphingosine. Current murine models of neuronopathic GD mostly replicate the acute aspects of the neurological disease showing rapid progression and early lethality, thus presenting a short window for therapeutic testing. In order to develop a model of chronic neuronopathic GD, we reduced GCase in the central nervous system (CNS) of a mild GD mouse model (Gba(D409V/D409V)) by intracerebroventricular administration of an adeno-associated virus encoding a microRNA to Gba (AAV-miR-Gba). Gba(D409V/D409V) mice have significantly reduced activity of GCase and marginal substrate accumulation in the CNS. Phenotypically, these mice are similar to type 1 GD and only display cognitive impairments. Administration of AAV-miR-Gba into Gba(D409V/D409V) pups in the CNS caused progressive lipid substrate

accumulation. Phenotypically, these AAV-miR-Gba-treated mice were indistinguishable from their littermates until 10 weeks of age, when they started developing progressive neurological impairments, including hyperactivity, abnormal gait, and head retroflexion. Importantly, these impairments can be prevented by simultaneous administration of a miR-resistant GCase, demonstrating that the pathological effects are specifically due to Gba mRNA reduction. This novel model of neuronopathic GD offers several advantages including slower progression of neurological complications and an increased lifespan, which make it more amenable to therapeutic testing.

Disclosures: K. Jackson: None. **C. Viel:** None. **J.C. Matthews:** None. **J. Bu:** None. **M. Chan:** None. **B. Wang:** None. **L.S. Shihabuddin:** None. **S.P. Sardi:** None.

Poster

471. Ataxias

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Topic: C.04. Movement Disorders other than Parkinson's Disease

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National Key Research and Development Program of China Stem Cell and Translational Research (2017YFA0105101, 2017YFA0105102, 2017YFA0105103, and 2017YFA0105104

Title: Age dependent neurodegeneration and symptoms in a transgenic pig model of SCA3

Authors: *S. YAN[1], Z. TU[1], Q. YAN[2], Z. LIU[2], Y. ZHAO[2], X. ZHANG[1], S. LI[3], L. LAI[2], X.-J. LI[1,3]
[1]Guangdong-Hongkong-Macau Inst. of CNS Regeneration, Jinan Univ., Guangdong, China; [2]Guangzhou Inst. of Biomedicine and Health, Chinese Acad. of Sci., Guangzhou, China; [3]Dept. of Human Genet., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Spinocerebellar ataxia type 3 (SCA3) is caused by a CAG repeat expansionin the *ATXN3* gene, which encodes for ataxin-3 protein containing an expandedpolyglutamine (polyQ). SCA3 is characterized by age-dependent neurodegeneration, which preferentially occurs in the cerebellum. SCA3 patients usually show clinical symptoms in their middle lifewith the typicalsymptom. A number of genetic mouse models of SCA3 have been established and show age-dependent neurological symptoms. However, these models do not show obvious neuronal

cell death and resemble human neurological phenotypes. Using lentiviruscarryingmutant ataxin 3 with 80Q and somatic cell nuclear transfer (SCNT) technology, we generated a transgenic SCA3 pig model.The founder SCA3 transgenic pig shows age-dependent ataxia, and MRI study also revealed cerebellum atrophy in the pig brain.Western blotting using the polyQ specific (1C2) antibody showed that the SCA3 transgenic pig expresses the polyQ-expanded ataxin-3 protein. We have now bred the F0 pigs to obtain F1 SCA3 pigs and areinvestigating these F1 SCA3 pigs.

Disclosures: S. Yan: None. **Z. Tu:** None. **Q. Yan:** None. **Z. Liu:** None. **Y. Zhao:** None. **X. Zhang:** None. **S. Li:** None. **L. Lai:** None. **X. Li:** None.

Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

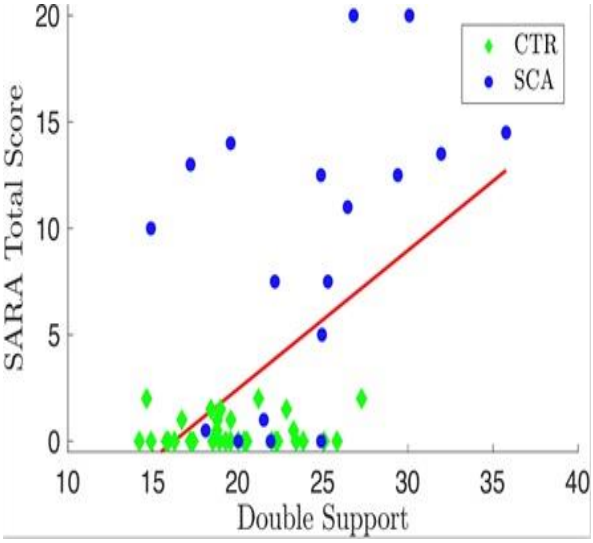
Program #/Poster #: 471.09/N1

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Objective measures of ataxic gait using wearable inertial sensors

Authors: *K. SOWALSKY[1], C. M. GOMEZ[2], F. B. HORAK[3], M. MANCINI[4], M. EL-GOHARY[1]
[1]Res. and Develop., APDM Wearable Technologies, Portland, OR; [2]Dept Neurol., Univ. of Chicago, Chicago, IL; [3]OHSU, Portland, OR; [4]Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Clinical trials on spinocerebellar ataxias are hampered by the lack of objective measures to precisely measure the disease severity, progression, and clinical efficacy. Gait impairments precede symptoms in patients with spinocerebellar ataxia (SCA) and may be valid surrogate markers of disease severity. We investigated whether gait measures from wearable inertial sensors were sensitive to ataxia and related to SARA scores in patients with SCA. Twenty one patients with SCA (mean age 61 years) and 34 control subjects (mean aged 58 years) underwent SARA testing. SARA total scores ranged from 0 (prodromal) to 25. The subjects wore 2 inertial sensors (Opals by APDM) on their feet and walked for 2 minutes at their normal walking pace. Step duration, double support time, and foot angle at heel strike were all very sensitive to ataxia ($p<.02$). In addition to these gait measure, other gait measures including gait speed, cadence, foot elevation at mid-swing, and toe off angle were significantly ($p<.003$) related to the total SARA score ($r=.53$ -- $.82$). The figure shows the relationship between the total SARA score and double support, calculated as the percentage of gait cycle while both feet are in contact with the ground. Future analysis will determine the most sensitive measures of gait in prodromal SCA, examine test-retest reliability of gait measures, and evaluate sensitivity to progression of disease.
Objective measure of gait with wireless inertial sensors provides promising, practical measures of severity cerebellar ataxia for clinical trials and clinical practice.



Disclosures: **K. Sowalsky:** A. Employment/Salary (full or part-time):; APDM. **C.M. Gomez:** None. **F.B. Horak:** A. Employment/Salary (full or part-time):; APDM. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); APDM. **M. Mancini:** None. **M. El-Gohary:** A. Employment/Salary (full or part-time):; APDM. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); APDM.

Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.10/N2

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Ataxia UK
Ataxia Charlevoix-Saguenay Foundation

Title: Loss of the ataxia protein sacsin impacts on focal adhesion dynamics and cell migration

Authors: L. E. L. ROMANO, *J. P. CHAPPLE
Queen Mary Univ. of London, London, United Kingdom

Abstract: Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) is a childhood-onset neurological disease with pyramidal spasticity and cerebellar ataxia. ARSACS results from mutations in the SACS gene that encodes sacsin. Previously we have identified that loss of sacsin results in reduced mitochondrial health and altered organization of the intermediate filament cytoskeleton.

Sacsin is a modular protein with conserved domains that indicate a molecular chaperone linked function. We therefore hypothesized that loss of sacsin would alter solubility of client proteins and/or their interactors. Using a proteomics approach, we identified that cytoskeletal proteins and proteins associated with focal adhesion formation accumulated in an insoluble fraction from sacsin null cells. Confocal microscopy revealed that the number and structure of focal adhesions was altered in sacsin null SH-SY5Y cells (generated by CRISPR/Cas 9 genome editing). Moreover, fluorescence recovery after photobleaching demonstrated that focal adhesion dynamics were altered relative to wild-type controls. Directional cell migration was also impaired in sacsin null cells.
To understand mechanisms underlying the altered focal adhesion dynamics and migration we investigated activation of the focal adhesion kinase signaling pathway. This showed a reduction in phosphorylation of Focal Adhesion Kinase (FAK), c-Jun N-terminal kinases (JNK) and Paxillin. We also observed that levels of Phosphatase and Tensin homolog (PTEN), which is a negative regulator of FAK signalling, were increased in sacsin null cells. Together these data suggest that altered expression of PTEN and FAK signalling contributes to the sacsin null cell adhesion and migration phenotype.
ARSACS has a neurodegenerative phenotype characterized by Purkinje cell loss, however, it is also thought to have a neurodevelopmental component. Normal neurodevelopment is dependent on cell migration and is orchestrated by a multitude of adhesion molecules and their downstream signalling. We are currently investigating if sacsin null cells differentiated along neuronal lineages exhibit altered migration, as this could be relevant to understanding the neurological phenotype of ARSACS patients.

Disclosures: L.E.L. Romano: None. **J.P. Chapple:** None.

Poster

471. Ataxias

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Program #/Poster #: 471.11/N3

Topic: C.04. Movement Disorders other than Parkinson's Disease

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Nu Rho Psi Undergraduate Research Grant
Georgia State University Assistantship Program
NSF S-STEM Award: 1644034

Title: Role of Rnf216/Triad3 on neurondevelopment and degeneration

Authors: *A. CHARLES[1,2], A. MABB[2]
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Abstract: The balance between the production of proteins and their breakdown is acknowledged as protein turnover. E3 ubiquitin ligases are a group of enzymes that directly participate in protein turnover by covalently attaching ubiquitin to target substrates. Obstructions in this pathway can lead to a multitude of neurological disorders that span the spectrum from neurodevelopment to neurodegeneration. RNF216/TRIAD3 is an E3 ubiquitin ligase that is disrupted in individuals with Gordon Holmes syndrome (GHS). GHS is characterized by dysarthria, underdevelopment of secondary sex organs, and neurodegeneration in the cerebrum and cerebellar regions. There are no effective therapeutic interventions for GHS. Scientific studies have pinpointed disruption in the ubiquitin pathway as a cause of these symptoms, but it remains unclear how this disruption affects neural development and neurodegeneration in select regions of the brain. To determine how Rnf216/Triad3 alters neuronal morphologies and survival, we selectively deleted the Rnf216/Triad3 gene in cortical neurons using the CRISPR-Cas9 system and a conditional knockout approach. Results from our studies will provide insight into the changes in neural properties that might occur in GHS and will contribute to the development of therapeutic strategies for GHS patients.

Disclosures: A. Charles: None. **A. Mabb:** None.

Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.12/N4

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CONACYT ACM 326042
CONACYT JFR 220871
PAPIIT-UNAM JFR IN214716
The Beltran-Morgado Foundation for the Advancement and Communication of Neuroscience in Veracruz

Title: Longitudinal analysis of gray matter neurodegeneration and its correlation with cognitive and motor performance in patients with Spinocerebellar Ataxia Type 7 (SCA7)

Authors: *A. CONTRERAS MARTÍNEZ[1], C. MORGADO-VALLE[2], C. R. HERNANDEZ-CASTILLO[3], R. DÍAZ-PÉREZ[4], J. FERNANDEZ-RUIZ[4], L. BELTRAN-PARRAZAL[2]
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Abstract: SCA7 is a neurodegenerative and autosomal dominant disorder caused by the expanded repetition of CAG. Clinical manifestations in SCA7 patients include cerebellar ataxia, visual acuity impairment, ophthalmoplegia, extrapyramidal signs, swallowing difficulties and dysarthria. Transversal MRI studies in SCA7 patients have shown atrophy in olivo-ponto-cerebellar and cortical areas, compared to healthy subjects. However, neurodegenerative progression is currently unknown due to lack of longitudinal studies. Here, we characterized the progressive neurodegeneration in patients with SCA7 and identified whether atrophy in specific brain structures correlates with clinical motor or cognitive assessment. Fourteen SCA7 patients were assessed with the Rey Auditory Verbal Learning Test (RAVLT), the Montreal Cognitive Assessment blind version, and the Scale for the Assessment and Rating of Ataxia (SARA), and subjected to a 3T MRI scan. T1 images were acquired and we performed a VBM (FSL library) analysis to provide intra-subject and inter-subject image alignment and voxel-wise comparison to detect progressive structural changes. Two years later, we performed a follow-up of all tests. Results: SCA7 group exhibited statistically significant progressive gray matter volume reduction in bilateral superior frontal gyrus, left medial frontal gyrus, right superior temporal gyrus, right transverse temporal gyrus, left and right cingulate gyrus, right parahippocampal gyrus, left insula, left cerebellar culmen and midbrain. We found a positive correlation of SARA scores with the loss of gray matter in the right middle frontal gyrus, whereas cognitive performance was non-correlated.

Disclosures: A. Contreras Martínez: None. **C. Morgado-Valle:** None. **C.R. Hernandez-Castillo:** None. **R. Díaz-Pérez:** None. **J. Fernandez-Ruiz:** None. **L. Beltran-Parrazal:** None.

Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.13/N5

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: KAKENHI 17H05708

Title: Dynactin-1 implicates autophagosome-lysosome fusion defects in the pathogenesis of neurodegenerative diseases

Authors: *H. ADACHI, Z. HUANG, K. OKADA, K. OHNARI, T. HASHIMOTO, T. TOYOTA, Y. IWANAKA
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Abstract: Background and Purposes: Dynactin is a dynein-activator complex required for most of the cellular functions of cytoplasmic dynein. Dynactin is composed of seven to nine polypeptides, including the dynactin-1 (p150Glued) that forms the sidearm of the complex and

binds both to microtubules and to dynein; the Arp1 polypeptide that forms an actin-like filament at the base of the complex; and the dynamitin, or p50, the subunit that localizes to the shoulder between the sidearm and the base. Autophagy is essential for neuronal homeostasis, and its dysfunction has been linked to many neurodegenerative disorders. In this report, we show that regulatory relationship between dynactin-1 and fusion of autophagosomes and lysosomes. Methods: In the present study, we used a combination of molecular biological techniques and morphological methods such as western blot, immunofluorescence, RFP-AcGFP-LC3 reporter assay, and immunoelectron microscopy on lentivirus-mediated dynactin-1 knockdown NSC 34 motor neuron cell line, and we determined the autophagosome-lysosomes fusion efficiency. Results: The levels of dynactin-1 protein expression were decreased in the dynactin-1 knockdown cells. The cell viability was decreased in dynactin-1 knockdown motor neuron cells. The level of the autophagosome marker LC3-II in cell culture was increased and the autophagosome-lysosome fusion was inhibited in dynactin-1 knockdown NSC 34 motor neuron cells. Conclusions: Our study identifies the dynactin-1 as a regulator that controls the fusion of autophagosomes and lysosomes. These findings suggest that dynactin-1 play important roles in the autophagy and implicate autophagosome-lysosome fusion defects in the pathogenesis of neurodegenerative diseases.

Disclosures: H. Adachi: None. **Z. Huang:** None. **K. Okada:** None. **K. Ohnari:** None. **T. Hashimoto:** None. **T. Toyota:** None. **Y. Iwanaka:** None.

Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.14/N6

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NINDS Intramural Research Program

Title: Pathophysiologic insights into ataxia and spasticity through structural imaging of a spinocerebellar ataxia type 7 cohort

Authors: *J. PARKER, S. MERCHANT, S. HOROVITZ, M. HALLETT
Human Motor Control Section, NINDS, Bethesda, MD

Abstract: Spinocerebellar ataxia type 7 (SCA7) is a neurodegenerative disease characterized by progressive cerebellar ataxia, retinal degeneration, ophthalmoplegia, and spasticity. Postmortem analysis reveals widespread atrophy of the brainstem and cerebellum, but our understanding of the evolution of this pathology is limited. Methods that quantify differences in brain structure such as voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) tractography may be used to assess these neurodegenerative changes *in-vivo*. The objective of this study was to

quantify the atrophy of various brain regions and white matter tracts with VBM and DTI tractography, and to correlate these metrics with clinical measures of ataxia and spasticity. Such correlations may identify useful biomarkers of disease progression and provide pathophysiologic insights into the mechanisms of ataxia and spasticity. In a cohort of 7 SCA7 patients (5 female), we measured ataxia using the SARA scale, 9-hole pegboard test, keyboard dexterity test, and Timed-Up-and-Go paradigm. Spasticity was quantified using the vibration inhibition index, a measure of H-reflex suppression with homonymous muscle vibration. T1w, T2w, and diffusion weighted images were acquired from this SCA7 cohort and 6 healthy controls (5 female). VBM was used to localize and quantify cerebral and cerebellar gray matter (GM) volumes. DTI tractography was used to determine fractional anisotropy (FA) in the corticospinal (CST), corticoreticulospinal (CRST), dentatothalamocortical (DTCT), and corticopontocerebellar (CPCT) tracts. Results showed a significant decrease in cerebellar GM volume in patients whereas cerebral GM volume was similar between the groups. An ROI-wise comparison in the cerebellum revealed decreased volume in patients in all 28 ROIs assessed. Bonferroni corrected two-sample t-tests revealed that this decrease was significant in the right and left flocculus and vermis region VIIb. The FA of the CST, CRST, and DTCT were also found to significantly differ between patients and controls through Bonferroni corrected two-sample t-tests. Imaging measures found to be significantly different between the two groups were subsequently correlated with clinical measures on a hypothesis driven approach, but no significant correlations were found with the small number of subjects so far investigated. Using this novel approach, we were able to assess in humans the brain regions and pathways previously implicated by animal studies in the pathophysiology of ataxia and spasticity. Longitudinal studies are warranted to reveal the relevance of these findings as potential biomarkers of SCA7 progression.

Disclosures: J. Parker: None. **S. Merchant:** None. **S. Horovitz:** None. **M. Hallett:** None.

Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.15/N7

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH Grant NS103066
NIH Grant NS108117
LA BioMed Seed Grant 31126-01

Title: Small molecule read-through compounds for the treatment of Ataxia-Telangiectasia

Authors: M. F. ABDALLAH[1], *P. J. MATHEWS[2]
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Abstract: Children stricken with Ataxia-Telangiectasia (A-T) live short (~25 years) lives characterized by a progressive loss of motor function (ataxia), an increased susceptibility to cancer, and immune abnormalities. A-T is an autosomal-recessive disease caused by mutations in the Ataxia-Telangiectasia Mutated (ATM) gene, which encodes a serine/threonine kinase involved in double-stranded DNA repair. In about one-third of A-T patients, the causative mutation is a nonsense mutation that encodes a premature termination codon (PTC) that produces a short-lived, truncated, and nonfunctional protein. There are currently no effective treatments for A-T, in part due to two main roadblocks: 1) we lack therapeutics capable of restoring ATM production, and 2) current animal models of A-T are inadequate for testing new therapeutic strategies. Our ongoing work, which we detail here, seeks to resolve these issues. To restore ATM production we are testing Small Molecule Read-Through (SMRT) compounds recently developed by Dr. Gatti and colleagues that have shown therapeutic promise in overcoming A-T patient-related PTCs, restoring functional ATM protein in both in vitro and ex vivo preparations. Our lab has independently reproduced these findings using human B cell-derived lymphoblastoid cell lines (LCLs) from A-T patients that contain a PTC. Pretreatment of LCLs with SMRT compounds at concentrations at or below 10 μM resulted in the production of ATM protein, and phosphorylation of downstream targets (e.g. p-ATM, p-Chk2, p-H2A-X) after Ultra-Violet (UV) irradiation (50 J/m^2) demonstrating ATM's functionality. To demonstrate that SMRT compounds are capable of restoring ATM production in a living animal we are creating mice harboring a human-related nonsense mutation in the Atm gene (103C>T) to test the drug ─ we denote this mouse as $Atm^{N/N}$ for "N"onsense mutation containing. Unlike wildtype littermates, we find no ATM expression in various tissues including the spleen, forebrain, and cerebellum. Like other mouse models of A-T to date, the $Atm^{N/N}$ mice do not display a progressive loss of motor coordination, thus limiting their use in testing SMRT compounds as a treatment for this characteristic aspect of the disease. For this reason we are utilizing a new genetic strategy to create a new A-T mouse model that preliminarily displays a marked, progressive loss of motor coordination.

Disclosures: M.F. Abdallah: None. **P.J. Mathews:** None.

Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.16/N8

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Whitehall Foundation (Grant 2017-05-35)

Title: Emerging Roles of RNF216/TRIAD3 in the hypothalamic-pituitary-gonadal axis

Authors: *A. J. GEORGE, A. M. MABB
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Abstract: Ubiquitin E3 ligases are substrate-specific enzymes in the ubiquitin pathway that participate in the turnover of proteins in the central nervous system and also control receptor trafficking. Recessive mutations in the E3 ligase *RNF216/TRIAD3* cause Gordon Holmes syndrome (GHS), with symptomologies of hypogonadotropic hypogonadism, cognitive impairment, dysarthria, cerebellar ataxia, and dementia. Individuals diagnosed with GHS have dysfunction at multiple levels of the reproductive endocrine axis also known as the hypothalamic-pituitary-gonadal (HPG) axis. This includes deficiencies in release of hypothalamic gonadotropin-releasing hormone (GnRH) and pituitary gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) with diminished secretion of gonadal hormones, estradiol and testosterone. The role of *RNF216/TRIAD3* in the HPG axis and the selective vulnerability in these neuronal and pituitary cell types is unknown. Previously, we found that RNF216/TRIAD3 localizes at the plasma membrane with clathrin-coated pits in neurons, a region where receptor-mediated endocytosis takes place. Moreover, disruption in RNF216/TRIAD3 was found to alter the trafficking of AMPA receptors. In addition to controlling AMPA receptor trafficking, we found that both knockdown and overexpression of RNF216/TRIAD3 disrupts trafficking of the ubiquitous transferrin receptor suggesting RNF216/TRIAD3 broadly controls receptor trafficking. To test the role of RNF216/TRIAD3 function in regulating receptor trafficking within the HPG axis, we knocked out *RNF216/TRIAD3* using CRISPR-Cas9 in hypothalamic (GT1-7) and pituitary (LβT2) cell lines to determine if the trafficking of key HPG axis receptors such a kisspeptin and GnRH receptors are altered. Taken together, our work will illuminate how disruptions in RNF216/TRIAD3 lead to defects in the HPG axis and will inform translational research for neurological disorders involving HPG axis disruption.

Disclosures: A.J. George: None. **A.M. Mabb:** None.

Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.17/N9

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: National Institutes of Health (R01 NS073872) (Clark/Louis)
R21 NS098930 (Clark)

Title: Functional studies of a missense variant in SLIT3 identified in a family with essential tremor

Authors: *Z. ODGEREL[1], S. SONTI[1], R. TABA[1], E. D. LOUIS[2], L. N. CLARK[1,3]
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Abstract: Essential Tremor (ET) is a prevalent neurological disorder with an estimated prevalence of 5% for individuals aged over 65 and is typically characterized by the presence of an action tremor that occurs during voluntary movements. Genetic factors contribute to the etiology of ET. WGS analysis in ET families (FASET, NS073872) identified the *SLIT3* gene as a candidate gene in one ET family. A disease association of SNPs in the *SLIT3* gene and genetic risk (models: susceptibility, survival and age-at-onset) for Parkinson disease was previously identified in two independent GWAS datasets. Axon guidance pathway molecules are involved in defining precise neuronal network formation during development and in the adult central nervous system play a role in the maintenance and plasticity of neural circuits.
The non-synonymous variant (c.3526G>C, p.Val1176Leu) identified in *SLIT3* is highly conserved evolutionarily, is predicted to be deleterious and damaging by several in silico tools and has an allele frequency of 0.0006407 in ExAC. To determine the functional effect of the *SLIT3* variant identified in an ET family, the variant was expressed in HEK293 and SH-SY5Y cell lines using the pLenti-C-Myc-DKK vector. Our preliminary result shows that there is a difference in the length of dendrites between the cells transduced with wild type SLIT3 compared to those with mutant SLIT3 protein. We are currently performing the Sholl analysis to determine alterations in dendrite morphology including fragmentation of dendrites and changes in branching pattern and will further discuss the findings from the analysis.

Disclosures: S. Sonti: None. **R. Taba:** None. **E.D. Louis:** None. **L.N. Clark:** None.

Poster

471. Ataxias

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Program #/Poster #: 471.18/N10

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH GR006623

Title: Modeling genetic loss of function ataxia phenotypes in zebrafish

Authors: *E. BUGLO, N. MARTUSCELI, E. SARMIENTO, J. DALLMAN, S. L. ZÜCHNER
Univ. of Miami, Miami, FL

Abstract: Introduction: Recessive ataxias are a group of debilitating neurological disorders, which mainly affect balance and movement as a result of cerebellar degeneration. More than

60% of patients are lacking genetic diagnosis due to unknown pathogenic variants. Therefore, many candidate genes require an efficient approach to functional testing. The need for an effective functional approach led us to modeling ataxia in zebrafish, which is a vertebrate system with conserved genetic and circuit homology, as well as optical transparency for convenient visualization of the fluorescently labeled neuronal cells. In this study we model three known ataxia genes with diverse disease phenotypes and mechanisms: slc25a46 involved in mitochondrial dynamics, snx14 involved in lysosomal clearance, and polr3a which works on small RNA transcription. We aim to better understand the commonalities in cellular loss of function phenotypes, and establish cellular and behavioral markers of ataxia in zebrafish.
Methods: We used CRISPR/Cas9 to generate stable knockout lines with frameshift alleles in the targeted genes. We analyzed zebrafish at larval stages up to 6 days by whole-mount immunostaining and confocal imaging of the motor neurons and Purkinje cells of the cerebellum. We performed visual motor response assays to test behavioral swimming phenotypes. The number of animals used for experiments was approximately 500 larvae per gene, with the sample size 30-50 larvae per experiment.
Results: Polr3a mutants show severe brain abnormalities with thinner and flattened cerebellum and forebrain, smaller eyes, deformed gut, and absence of swim bladder. Snx14 and slc25a46 phenotypes, in contrast to previously published reports using morholino knockdown, which showed drastic degeneration of Purkinje cell layer in snx14 morphants and motoneuron degeneration in slc25a46 morphants, our mutant lines show a mild neuronal phenotype: shorter, but well-formed motoneuron axons and smaller, but well-shaped Purkinje cell layer. Neither snx14, not slc25a46 mutants have observed deficiencies in swimming as tested by Noldus Danio Vision movement analysis platform.
Conclusions: The three chosen genes for modeling complex recessive ataxia in zebrafish using CRISPR knockout approach show different levels of cerebellar disruption and behavioral swimming phenotypes. Although snx14 and slc25a46 genetic loss of function is severe in humans, the zebrafish knockout model only has a mild phenotype. Our study serves as an important exploration of zebrafish model of ataxia, and as a checkpoint for discrepancies between knockdown and knockout methodologies for functional gene studies.

Disclosures: E. Buglo: None. **N. Martusceli:** None. **E. Sarmiento:** None. **J. Dallman:** None. **S.L. Züchner:** None.

Poster

471. Ataxias

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Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: National Ataxia Foundation Young Investigator for SCA Research Award 2015 to M.C.C.
Becky Babcox Research Fund, Michigan Medicine, University of Michigan - Pilot research award G015617 to M.C.C.
Protein Folding Disease Initiative, Michigan Medicine, University of Michigan - Pilot drug screen fund 2014 to M.C.C. and H.L.P.
NINDS/NIH R01NS038712 to H.L.P.

Title: Novel genes that modulate levels of mutant ATXN3 in the polyglutamine disorder, Machado-Joseph disease

Authors: N. S. ASHRAF[1], J. R. SUTTON[2], B. RANXHI[2], Y. YANG[1], E. SHAW[1], S. V. TODI[2], H. L. PAULSON[1], *M. COSTA[1]
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Abstract: Machado-Joseph disease (MJD), also known as Spinocerebellar Ataxia type 3, is a polyglutamine (polyQ) neurodegenerative disease caused by a CAG repeat expansion encoding an abnormally long polyQ stretch in the disease protein, ataxin-3 (ATXN3). No preventive treatment is yet available for MJD or any other polyQ diseases. Because expanded polyQ proteins accumulate in diseased brain, a compelling therapeutic approach is to reduce levels of the mutant protein by manipulating pathways that control their production, stability, or clearance. Here we sought to identify molecular pathways that modulate levels of expanded-polyQ ATXN3, with the long-term goal of developing therapies for this fatal and untreatable disease. Using a cell-based assay that provides readout of expanded ATXN3 levels, we screened a collection of siRNAs targeting 3,080 human druggable genes encoding GPCRs, kinases, phosphatases, ions channels and proteins involved in protein quality control. From this initial screen, 100 genes for which knockdown resulted in significantly altered signal were selected for follow-up studies. Thirty-three genes were confirmed to selectively affect luminescence signal in AT3-Luc cells but not in control cells expressing Luc alone, suggesting that they are likely regulators of mutant ATXN3 abundance in cells.. A subset of these genes (n= 17) was subsequently validated by immunoblotting as modulators of ATXN3 levels in an independent cell model expressing expanded ATXN3. Network analysis of the 17 genes revealed three hub genes, including a kinase of the NF-kB pathway. Accordingly, expression of this human kinase in a drosophila model of MJD decreases lifespan compared to flies not expressing the kinase. We are currently further defining the role of this kinase in modulating cellular levels of ATXN3. Genes identified in our siRNA screen as modulators of mutant ATXN3 abundance represent candidate therapeutic targets for MJD.

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grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Cydan Development Inc..

Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.20/N12

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: A Cure For Ellie

Title: Modeling LBSL

Authors: *C. L. NEMETH[1], P. HUBO[1], S. N. TOMLINSON[1], M. R. ROSEN[1], C. F. MURRAY[1], D. WU[2], M. V. JOHNSTON[1], A. TRIFUNOVIC[3], A. FATEMI[1]
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Abstract: Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) results in a rare, progressive, neurological disease that manifests as white matter signal abnormalities in the cerebral white matter and spinal cord, as well as slowly progressive dorsal column spasticity, dysarthria, and ataxia. Most LBSL patients are compound heterozygotes for mutations in *DARS2*, encoding the mitochondrial enzyme aspartyl-tRNA synthetase. Over 50 disease variants have been recorded in patients with LBSL, with the most frequent mutation causing a frame shift prior to the third exon and downstream errors of splicing. As production of *DARS2* is affected throughout the body, it is thought that the extreme energy demands of the central nervous system make the brain especially susceptible to the consequences of reduced *DARS2* functioning. Although no current animal model recapitulates the genetic composition of LBSL patients, we can model some aspects of disease pathology using conditional knock out mouse models. Furthermore, we have created patient-derived induced pluripotent stem cells (iPSCs) to help to elucidate the effects of these specific disease variants. Complete deletion of *DARS2* within CamKIIα expressing neurons of mice results in progressive and severe cortical atrophy, with brain area reduced by 20% by 9 months of age ($p < 0.001$) and corpus callosum thickness reduced at midline by 40%. In addition, neuroinflammation is present in the cortex, signified by microglia with thickened processes and enlarged soma ($p < 0.001$). These changes are paralleled by an age-dependent increase in locomotor activity ($p < 0.001$). Despite the overall reduced area of the corpus callosum, electron microscopy reveals increased axonal area ($p < 0.05$) and thickness of myelin ($p < 0.05$), as well as increased mitochondrial number ($p < 0.005$). In patient iPSCs, preliminary work reveals reduced efficiency of *DARS2* splicing by approximately 50%, a phenotype preserved when these cells are then differentiated

into motor neurons. Together, these models serve to provide insight into the various aspects of LBSL pathology and can be used to study cell-type specific effects of *DARS2* deficiency. These models may further allow for the testing of therapeutics for the treatment of LBSL.

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Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.21/O1

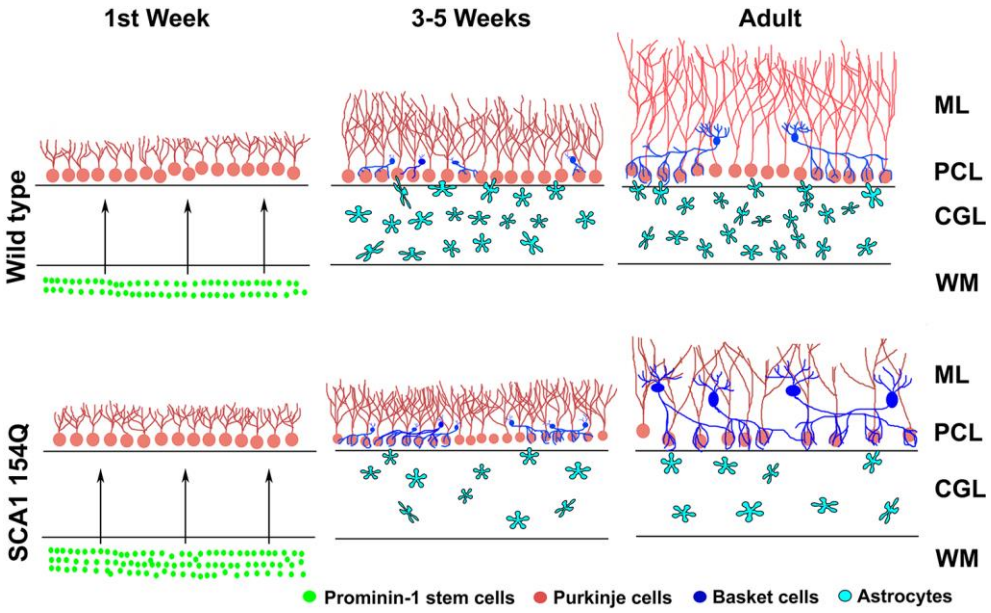
Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Mutant ataxin1 disrupts postnatal cerebellar development in spinocerebellar ataxia type 1

Authors: *C. EDAMAKANTI, J. DO, M. MARTINA, P. OPAL
Neurol., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Background and Objective: Spinocerebellar ataxia type1 (SCA1) is an adult-onset neurodegenerative disease caused by a pathogenic polyglutamine expansion in the protein Ataxin1. Since Purkinje cells bear the brunt of the pathology in SCA1, scientific investigations have focused on characterizing intrinsic deficits within these neurons. Although symptoms appear relatively late in life, primarily in the cerebellum, pathogenesis begins early, with brain-wide transcriptional changes appearing a week after birth in SCA1 knock-in mice. Moreover, delaying expression of Ataxin1 or restoring the aberrant gene expression (YAPdeltaC and RORα) during first three postnatal weeks is enough to ameliorate the pathophysiology of SCA1. During this early period, neurogenesis is still taking place within a niche of postnatal stem cells in the cerebellar white matter, which led us to ask whether early neurodevelopment gone awry in ways that alter the neural circuitry of the cerebellum. Methods: Used SCA1 patients, SCA1 mice (Knock-in, Transgenic and knock-out) and cell culture models to prove hypothesis. Results: We found that the cell-autonomous gain of ATXN1 function stimulates the proliferation of postnatal cerebellar stem cells in SCA1 mice. Using in vitro and in vivo experiments confirmed that these hyper-proliferating stem cells tended to differentiate into GABAergic inhibitory interneurons rather than astrocytes; this significantly increased the GABAergic inhibitory interneuron synaptic connections, disrupting cerebellar Purkinje cell function in a non-cell autonomous manner. We confirmed the increased basket cell-Purkinje cell connectivity in human SCA1 patients. Mutant ATXN1 thus alters the neural circuitry of the developing cerebellum, setting the stage for the later vulnerability of Purkinje cells to SCA1. We propose that other late-onset degenerative diseases in which early transcriptional alterations have been found may also be rooted in subtle

developmental derailments. These interesting findings pave a way to test the novel therapeutic targets in SCA1 field.



Disclosures: C. Edamakanti: None. **J. Do:** None. **M. Martina:** None. **P. Opal:** None.

Poster

471. Ataxias

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Program #/Poster #: 471.22/O2

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Coldwell Foundation

Title: FTY720-derivatives increase neurotrophic factor expression and protects oligodendroglia against hydrogen-peroxide-mediated oxidative stress

Authors: *J. VARGAS, I. SEGURA-ULATE, G. VIDAL-MARTINEZ, B. YANG, R. PEREZ
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Abstract: Multiple system atrophy (MSA) is a lethal demyelinating neurodegenerative disorder for which there are currently no disease-modifying treatments. MSA pathology includes α-synuclein (aSyn) accumulation in glial cytosolic inclusions (GCIs) inside oligodendroglial cells (OLGs), the myelinating cells of brain. This is believed to induce aberrant expression of brain-

derived neurotrophic factor (BDNF) and glial-cell line derived neurotrophic factor (GDNF) in OLGs in MSA brains and MSA mouse models with GCIs. Yet, it is unclear if oxidative stress also impacts OLG cell viability as aSyn-accumulates. Using the OLG cell line, OLN-93, we stably overexpressed human wild type aSyn or an MSA-associated G51D mutant form of aSyn. aSyn OLN-93 lines were more sensitive to oxidative stress than OLN-93 cells lacking aSyn expression. We further evaluated OLN-93 cells treated with FTY720 (Fingolimod), an FDA approved multiple sclerosis drug, and our novel non-immunosuppressive FTY720-derivatives, FTY720-C2 and FTY720-Mitoxy. All three FTY720s cross the blood brain barrier and OLN-93 cell viability was normal after 48 hr treatments with the various FTY720s [160 nM]. The parent compound, FTY720, as well as FTY720-C2 increased nerve growth factor (NGF) expression at 24 hr. In contrast, our mitochondrial-targeted-FTY720-derivative, FTY720-Mitoxy, increased BDNF, GDNF, and NGF expression at 24 hr. Moreover, pretreating OLN-93 cells with FTY720s for 48 hr totally blocked oxidative cell death associated with 2 hr treatment with H_2O_2 [75 µM] and showed a trend toward protection with H_2O_2 [100 µM]. However, pretreating with FTY720s for 12 hr followed by 24 hr H_2O_2 [100 µM] + FTY720s [160 nM] did not block OLN-93 death. These data suggest that excessive oxidative damage in OLG cells cannot be blocked by FTY720s. However, early treatment of MSA patients with FTY720s may protect OLGs by increasing their expression of major trophic factors. Our data further suggest that the therapeutic potential of FTY720-Mitoxy may be even greater than the parent compound as this FTY720-derivative will not induce immunosuppression yet significantly stimulates OLG expression of BDNF, GDNF, and NGF. We are currently assessing FTY720-Mitoxy in MSA mice.

Disclosures: J. Vargas: None. **I. Segura-Ulate:** None. **G. Vidal-Martinez:** None. **B. Yang:** None. **R. Perez:** None.

Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.23/O3

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Coldwell Foundation

Title: FTY720-Mitoxy a novel FTY720-derivative improves movement cognition and sweat function in multiple system atrophy mice

Authors: *R. PEREZ, G. VIDAL, B. YANG, J. VARGAS, I. SEGURA, V. DIAZ-PACHECO, J. DE LEON, J. BARRAGAN, S. CHAPARRO
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Abstract: Multiple system atrophy (MSA) is a progressive neurodegenerative disorder that affects both the central and peripheral nervous systems. MSA pathology occurs due to abnormal alpha-synuclein (aSyn) aggregation inside myelinating glia. Oligodendroglial aSyn-pathology then causes widespread denervation, which in MSA patients' impairs movement, cognition, sudomotor function, and thermoregulation. CNPaS aSyn transgenic (Tg) mice are an MSA mouse model that expresses aSyn under control of the myelinating glia specific 2', 3'-cyclic nucleotide 3'-phosphodiesterase (CNP) promoter. Tg mice form aSyn-containing glial cytoplasmic inclusions (GCI) in brain and spinal cord oligodendroglia between 9 and 12 mo. We have developed FTY720-Mitoxy, which is an analogue of an FDA-approved drug that crosses the blood-brain-barrier and has potent neuroprotective effects in vitro. We hypothesized that FTY720-Mitoxy blocks aSyn pathology to normalize movement, cognition and sudomotor activity. We tested this in wild type (WT) and Tg littermates using Rotarod, Barnes maze, object recognition tests and a iodine-starch sweat test at baseline and after FTY720-Mitoxy or Vehicle control solution. Hindlimb soleus and gastrocnemius muscles were collected to evaluate their potential contribution to movement. At baseline WT and Tg mice performed similarly on all tests. Vehicle treated Tg mice had impaired movement at 10.5 mo with sweat production being reduced only in Tg males. FTY720-Mitoxy treated Tg mice did better on Rotarod and showed an increase in hindlimb muscle mass. Sweat production was restored to normal levels for FTY720-Mitoxy treated Tg males. On cognitive tests, FTY720-Mitoxy treated Tg females were significantly better than Tg males at 11.5 mo. Overall these preclinical data suggest that FTY720-Mitoxy may slow MSA dysfunction making it a promising candidate for clinical development.

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Poster

471. Ataxias

Location: SDCC Halls B-H

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Program #/Poster #: 471.24/O4

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH Grant NS038712
NIH Grant T32-NS007222-33
Becky Babcox Fund G015616
SCA Network

Title: Antisense oligonucleotides ameliorate disease in spinocerebellar ataxia type 3 mice

Authors: *H. S. MCLOUGHLIN[1], L. MOORE[1], R. CHOPRA[1], R. KOMLO[1], M. MCKENZIE[1], K. BLUMENSTEIN[1], H. T. ZHAO[2], H. B. KORDASIEWICZ[2], V. G.

SHAKKOTTAI[1], H. L. PAULSON[1]
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Abstract: ABSTRACT
Spinocerebellar ataxia type 3 (SCA3) / Machado-Joseph Disease (MJD), is the most common dominantly inherited ataxia in the world. It is caused by an expansion of a polyglutamine-coding CAG repeat in the *ATXN3* gene. There currently is no effective treatment for this relentlessly progressive and fatal disease. Because expression of the mutant protein is an early and necessary step in disease pathogenesis, strategies to reduce expression of the disease gene itself are high on the list of potential therapies. Through a collaboration with Ionis Pharmaceuticals, we recently reported the potential for antisense oligonucleotide therapy to reduce mutant ATXN3 protein after a single ASO treatment. Here we follow up that study to longitudinally investigate whether an anti-*ATXN3* ASO can prevent molecular, neuropathological, electrophysiological and behavioral features of the disease in a SCA3 mouse model. The top *ATXN3*-targeting ASO from our published *in vivo* screen was injected intracerebroventricularly into post-symptomatic transgenic YAC transgenic SCA3 mice, which express the full-length human *ATXN3* disease gene and recapitulate key disease features by 6 weeks of age. Following a single *ATXN3*-targeting ASO treatment at 8 weeks of age, treated mice achieved sustained reduction of polyQ-expanded ATXN3 up to 16 weeks of age. The *ATXN3*-targeting ASO also prevented high molecular weight species and nuclear accumulation of ATXN3 up to 22 weeks of age. To assess effects of ASOs on SCA3 mouse behavior, mice received an additional ASO injection at 21 weeks and were evaluated longitudinally up to 29 weeks for motor performance. Longitudinal ASO therapy led to a complete rescue of motor impairment in SCA3 mice by 29 weeks of age. This behavioral rescue was associated with a recovery of defects in Purkinje neuron firing frequency and afterhyperpolarization in SCA3 mice. Overall, our assessment of an *ATXN3*-targeted ASO established efficacy and supports further efforts to develop ASOs for human SCA3 clinical trials.

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Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.25/O5

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: FARA Center of Excellence (DL)
CHOP Foerderer Grant for Excellence (HL)

Title: Dysregulated IP3R-mediated endoplasmic reticulum-mitochondria calcium signal pathways contribute to mitochondrial bioenergetic deficits and cell death in Friedreich ataxia

Authors: *H. LIN[1,2], E. M. CLARK[2], S. GHURA[2], N. WARREN[1], A. SALOVIN[1], J. MAGRANE[3], D. R. LYNCH[1,2]
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Abstract: Friedrich ataxia (FRDA) is an autosomal recessive neurodegenerative disease caused by deficiency of a mitochondrial protein frataxin. Mitochondrial dysfunction and dysregulated calcium homeostasis have been implicated in FRDA. IP_3Rs are IP_3-activated Ca^{2+} release channels located on the endoplasmic reticulum (ER) that are crucial for regulating cell survial and death by controlling Ca^{2+} transfer from the ER to mitochondria through mitochondria-associated ER membranes (MAMs). The pathophysiological role of IP3R-mediated ER-mitochondrial Ca^{2+} signaling in FRDA remains unclear. Here we report that dysregulated IP3R-mediated ER-mitochondrial Ca^{2+} signal pathways contribute to mitochondrial bioenergetic deficits and cell death in FRDA patient cellular and animal models. In normal mice and human fibroblasts, type 1 and 3 IP3Rs are highly expressed and widely distributed as puncta in mouse cerebellar Purkinje neurons and human fibroblasts. IP3Rs interact with mitochondrial chaperone protein GRP75 in a multiprotein complex and appear in close contact with GRP75-labeled mitochondrial network. In FRDA mouse cerebellum and patient fibroblasts, IP3R levels, IP3R interactions with GRP75 and contacts with GRP75-labeled mitochondrial network as well as ER-mitochondria contacts are significantly reduced compared with controls. Furthermore, in the isolated MAM fractions of KIKO brains, ER-mitochondria tethering protein MFN2 and mitochondrial calcium uptake proteins VDAC1 and MICU1 are significantly decreased compared with controls, suggesting that impaired IP3R-mediated mitochondrial Ca^{2+} signaling may contribute to mitochondrial Ca^{2+} deficiency and bioenergetic deficits in FRDA. Interestingly, staurosporine- or H_2O_2-induced stress in patient fibroblasts leads to a larger increase in IP3R levels, IP3R contacts with fragmented mitochondrial network and cleaved caspase 3 than in controls. This suggests that FRDA patient fibroblasts may be more vulnerable to stress-induced increase in IP3R-mediated mitochondrial Ca^{2+} signaling, thereby leading to mitochondrial Ca^{2+} overload and cell loss in FRDA. Taken together, our findings demonstrate that dysregulated IP3R-mediated ER-mitochondrial Ca^{2+} signal pathways contribute to mitochondrial bioenergetic deficits and cell death in FRDA, thereby providing novel pathogenic mechanisms underlying selective neuronal vulnerability and potential therapeutic strategies for FRDA patients.

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Poster

471. Ataxias

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Program #/Poster #: 471.26/O6

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Supported by NIH grants R21NS081182, R01NS097903, R37NS033123, and U01NS103883.

Title: Transcriptome sequencing of spinocerebellar ataxia type 2 (sca2) mouse spinal cord toward identifying therapeutic targets for amyotrophic lateral sclerosis (als)

Authors: *D. R. SCOLES, W. DANSITHONG, L. PFLIEGER, S. PAUL, K. FIGUEROA, S. PULST
Dept. of Neurol., Univ. of Utah, Salt Lake City, UT

Abstract: Objectives: To characterize the spinal cord (SC) transcriptome of spinocerebellar ataxia type 2 (SCA2) mice toward identifying therapeutic targets and biomarkers for amyotrophic lateral sclerosis (ALS). **Background:** CAG repeat expansions in the *ATXN2* gene are the cause of SCA2 and increase the risk of ALS. Patients with SCA2 also often present with motor neuron disease characteristic of ALS. Our past work demonstrated that lowering the expression of *ATXN2* using an antisense oligonucleotide (ASO) delivered to the lateral ventricle improved motor, molecular and neurophysiological phenotypes of two different SCA2 mouse models. In addition, reduction of *Atxn2* expression genetically or by ASO improved the survival of TDP-43 ALS mice. These observations suggest that knowledge of the SCA2 spinal cord transcriptome might aid in understanding targets for ALS therapy and biomarkers useful for drug development. **Methods:** RNA-seq of SC and cerebellar (CB) RNAs was performed using BAC-ATXN2-Q72 mice vs wildtype littermates, including mice of 20-34 wks of age (total *N*=16). Differentially expressed genes (DEGs) were analyzed by weighted gene co-expression network analysis (WGCNA), and pathway analysis (GO, KEGG, IPA). **Results:** The DEG cutoff used was $P<0.05$, $|\log2(FC)| > 0.585$. 12.6% of DEGs were shared between SC and CB. WGCNA identified three SC gene modules significantly correlated with SCA2. Top pathways of each were immune system processes, cholesterol biosynthesis and lipid biosynthesis, three pathways that are dependent on insulin induced gene 1 (*Insig1*) that was significantly downregulated in SCA2 mouse spinal cord. We also identified 9 DEGs in SCA2 mouse SC that are related to ALS pathology, including genes encoding angiotensinogen (*Agt*), EAAT2 (*Slc1a2*), Pcp4, and Fus. **Conclusions:** This study provides new insights into the underlying molecular basis of ALS motor neuron phenotypes observed in SCA2. The presence of ALS-related genes in the SCA2 mouse SC transcriptome validates the SCA2 mouse as an ALS model. This study also suggests

possible therapeutic targets for ALS given that reduction of *Atxn2* increased TDP-43 ALS mouse survival. <!--EndFragment-->

Disclosures: D.R. Scoles: None. **W. Dansithong:** None. **L. Pflieger:** None. **S. Paul:** None. **K. Figueroa:** None. **S. Pulst:** None.

Poster

471. Ataxias

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Program #/Poster #: 471.27/O7

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: National Ataxia Foundation, Spinocerebellar Ataxia Research Award
Landesgraduiertenförderung Baden-Württemberg
TALEN Library Resource

Title: The impact of ataxin-3 isoforms on the pathogenesis of Spincerebellar Ataxia Type 3

Authors: *T. SCHMIDT[1,2], D. WEISHAEUPL[1,3,2], J. SCHNEIDER[1,2], B. PINHEIRO[1,2], C. RUESS[1,2], S. DOLD[1,2], F. VON ZWEYDORF[4,5], C. J. GLOECKNER[4,5], J. SCHMIDT[1,2], O. RIESS[1,2]
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Abstract: Ataxin-3 is a deubiquitinating enzyme involved in the ubiquitin-proteasome system and transcriptional regulation. The encoding gene *ATXN3* is alternatively spliced leading to two full-length isoforms which differ in their number of ubiquitin interacting motifs. Both isoforms are additionally modified by single nucleotide polymorphisms that cause amino acid changes and a premature stop in one isoform. An expansion of the polyglutamine repeat within ataxin-3 causes Spinocerebellar Ataxia Type 3 (SCA3), also known as Machado Joseph Disease (MJD), a progressive neurodegenerative disorder. Clinically, SCA3/MJD is characterized by a variability of the age at onset and disease severity. In this study we associate this variability to the combination of different ataxin-3 isoforms. We examined the significance of ataxin-3 isoforms and the effect of the premature stop mutation on major aspects of the physiological function of ataxin-3 as well as their impact on main disease mechanisms. On the physiological level we could show that alternative splicing and the premature stop cause changes in the stability of ataxin-3 isoforms and that ataxin-3 isoforms differ in their enzymatic deubiquitination activity, subcellular distribution and interaction with other proteins. On the pathological level we found that the expansion of the polyglutamine repeat leads to a stabilization of the respective isoform

and that ataxin-3 isoforms differ in their aggregation properties on multiple levels. Interestingly, the interaction of ataxin-3 alleles modifies physiological as well as pathophysiological properties of ataxin-3. Taken together our current data indicates that alternative splicing as well as the mutual interaction of ataxin-3 isoforms affects major aspects of the normal ataxin-3 function as well as the pathogenesis of SCA3/MJD. We believe that our data will lead to an improvement in the prediction of disease severity and age at onset by taking into account the specific combinations of ataxin-3 isoforms which thus may become important additional markers in therapeutic interventions.

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Poster

471. Ataxias

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 471.28/O8

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH R21 NS104799-01
National Ataxia Foundation Postdoc Fellowship
University of Utah Neuroscience Initiative Pilot Project Award

Title: Low-frequency dentate nucleus deep cerebellar stimulation treats cerebellar ataxia

Authors: *C. ANDERSON[1], K. P. FIGUEROA[1], A. D. DORVAL[2], S. M. PULST[3]
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Abstract: Background: Degenerative cerebellar ataxias affect 1 in 5,000 people worldwide, presenting with motor symptoms including incoordination, tremor, and falls. Despite more than twenty years since the first Spinocerebellar ataxia genes were discovered, treatment strategies are limited. Many ataxia forms share the loss of Purkinje cells, a major source of input to the deep cerebellar nuclei. This degeneration dysregulates the dentatothalamocortical network, resulting in reduced transmission of information related to properly coordinated movement. Thus, we have developed an electrical stimulation-based therapy for degenerative ataxias by targeting the dorsal dentate nucleus, aimed at enhancing the throughput of motor-relevant signaling through the dentatothalamocortical network. **Materials and Methods**: We tested this therapeutic strategy in the Wistar Furth *shaker* rat model of degenerative cerebellar ataxia, which presents with a full-body cerebellar tremor, progressing to a shaking ataxia, with frequent falling. We bilaterally, chronically implanted a cohort of *shaker* rats with stimulating electrodes to test the hypothesis

that electrical stimulation targeted to the dorsal dentate nucleus can reduce motor symptoms. We tested a spectrum of frequencies from very low to high frequency, testing the hypothesis that low frequency deep cerebellar stimulation would most optimally reduce motor symptoms. We quantified symptoms in an operator-independent manner via novel methods of our design and characterized the behavioral response to the spectrum of stimulation frequencies. Further, we are currently coupling *in vivo* single unit and local field potential recordings in the dentate nucleus with therapeutic and non-therapeutic stimulation to improve mechanistic understanding. **Results**: We tested dentate nucleus stimulation across a large domain of frequencies, and we found that 20-30 Hz stimulation most effectively reduced motor symptoms. Interestingly, stimulation frequencies over 100 Hz, commonly used for Parkinsonism and essential tremor, were tied to worsened incoordination, while very low frequencies within the tremor physiologic range (sub 10 Hz) contributed to increases in tremor. We will further present results related to the network effects of stimulation and discuss the network effects of stimulation that result in symptomatic improvement. **Conclusions**: Low-frequency deep cerebellar stimulation may provide a novel method for treating the motor symptoms of some forms of degenerative cerebellar ataxia.

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Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.01/O9

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R01 AR066003

Title: Loss of mkp-5 prevent fibrosis accumulation in dystrophic muscle disease

Authors: *T. M. GYLES[1], K. MIN[2], A. M. BENNETT[2]
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Abstract: Duchenne muscular dystrophy (DMD) is a degenerative skeletal muscle disease induced by mutations in dystrophin gene. The disease is characterized by progressive skeletal muscle degeneration and cardiac muscle weakness which result in premature death. It has been established that excessive accumulation of fibrosis is a prominent contributor to skeletal muscle dysfunction in DMD. The mitogen-activated protein kinases (MAPKs) are required to promote skeletal muscle myogenesis and function. The MAPKs are negatively regulated by the MAPK phosphatases through direct dephosphorylation. Recently, our group demonstrate that MKP-5 is involved in the progression of dystrophic muscle disease. However, the pathophysiological mechanisms of how MKP-5 regulates the progression of dystrophic muscle disease are unclear.

Therefore, we are investigating the role of MKP-5 in development of fibrosis in dystrophic muscle disease using genetic mouse models. Our data show that phosphorylation of Smad2 was significantly decreased in skeletal muscle from $m;k;p;5^{-/-}$〖mkp5〗^(-/-) mice in response to injury. In order to investigate the role of MKP-5 in TGF-β signaling in dystrophic muscle disease, we intercrossed $m;k;p;5^{-/-}$〖mkp5〗^(-/-) mice into the mdx background in order to generate $m;d;x;m;k;p;5^{+/+}$〖mdxmkp5〗^(+/+) and $m;d;x;m;k;p;5^{-/-}$〖mdxmkp5〗^(-/-) . Our data show that gene expression of fibrosis markers such as Col1a1, Col3a1, and FN1 was significantly decrease in skeletal muscle from $m;d;x;m;k;p;5^{-/-}$〖mdxmkp5〗^(-/-) compared with $m;d;x;m;k;p;5^{+/+}$〖mdxmkp5〗^(+/+) mice. These results may indicate that MKP-5 negatively regulate the signaling of fibrosis in dystrophic muscle disease

Disclosures: T.M. Gyles: None. **K. Min:** None. **A.M. Bennett:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.02/O10

Topic: C.06. Neuromuscular Diseases

Support: UK Medical Research Council
Motor Neurone Disease Association
Americal ALS Association
Thierry Latran Foundation

Title: Knockin mouse models to understand ALS pathomechanism

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Abstract: Research objective and rationale: Amyotrophic lateral sclerosis (ALS) is a relentless degenerative disease of the motor system, for which there are few treatments and no cures. In order to understand pathomechanisms, we need a multiplicity of systems including mouse models, through which we can study tissue:tissue interactions, for example, over the full course of lifespan. In ALS, approximately 10% of cases are familial, usually autosomal dominant, and we can create mouse models based on the >20 genes that have been found to be causative for this disorder. **Methods and results**: We have a long-term interest in creating knock in mouse models of disease, in order to avoid any confounds from the overexpression that arises

in transgenic models. From our experience we tend to produce mice with milder phenotypes and slower disease course than transgenics, and this enables us to study early stage disease. Here we present new mouse models of ALS (validated by specific tests as below) and new data. (1) the *Sod1*^{D83G} mouse (Joyce et al, 2015); (2) the FUS Delta14 mouse (Devoy et al, 2017); (3) an allelic set of *Tardbp* (TDP-43) mutants, including a new strain with spinal cord motor neuron degeneration, novel splicing changes that we also find in human mutant *TARDBP*-ALS cells, and no other visible phenotype (Fratta et al, 2018), and we give information on other models that we are producing/characterising. **Sample sizes, replication, controls:** Our methods of creating mice range from chemical mutagenesis through to sophisticated humanised targeting constructs for embryonic stem cells. We characterise statistically significant cohorts, separated by sex, via a longitudinal panel of tests including behaviour, physiology, histology, and transcriptomics - which are then validated in human tissue/cell lines. Mice are kept on more than one inbred background which is carefully monitored and all controls are wildtype littermates, age-and sex-matched in comparable cohort sizes.

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Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: 472.03/O11

Topic: C.06. Neuromuscular Diseases

Title: Accelerated disease progression in a mouse model of amyotrophic lateral sclerosis after Ephrin-A5 knockdown

Authors: L. RUE[1,2], M. TIMMERS[1,2], A. LENAERTS[1,2], L. VAN DEN BOSCH[1,2], P. VAN DAMME[1,2,3], R. LEMMENS[1,2,3], *W. L. ROBBERECHT[4,1]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects lower motor neurons in brainstem and spinal cord, and the upper motor neurons in the motor cortex, and leads to a progressive muscle phenotype in patients. Its considerable genetic and clinical heterogeneity indicate that there must be factors that modify the phenotypic expression of the disease. One such modifying factor is the tyrosine kinase receptor EphA4. Genetic and pharmacological inhibition of EphA4 rescued the motor neuron phenotype in zebrafish and rodent models of ALS, and an inverse correlation was found between EphA4 expression levels and disease onset and survival in patients. We aimed to identify whether ephrin ligands would contribute to the EphA4 modifying effect in ALS. Most ephrin-A and ephrin-B ligands are able

to bind and activate EphA4. Here, we determined the contribution of ephrin-A5 in ALS, by genetic knockdown in a mouse model of ALS, the $SOD1^{G93A}$ mouse. We followed the mice during disease progression to determine the decline in their motor behavior as well as their latency to reach an end-stage point of the disease. Although we did not observe differences in disease onset, survival and disease duration were significantly reduced in the mice with lower ephrin-A5 levels. In situ hybridization of ephrin-A5 in the spinal cord of $SOD1^{WT}$ and $SOD1^{G93A}$ mice revealed that this ephrin ligand is mainly expressed in neurons, both ChAT positive and negative. However, a reduction of its levels did not lead to further nerve conduction deficits nor deficits in the percentage of innervated neuromuscular junctions in the gastrocnemius muscle. Finally, no differences could be detected in the expression levels of several biomarkers of neuronal function, astroglial reactivity and microglial activation in the spinal cord of $SOD1^{G93A}$ mice with normal or reduced levels of ephrin-A5. These results suggest that, in contrary to EphA4, ephrin-A5 expression might be beneficial during ALS disease progression. Further work is needed to understand the mechanism of this beneficial role of ephrin-A5 in ALS, and to reveal if its effect on disease progression is EphA4-dependent or independent.

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Poster

472. Studies of ALS in Animal Models

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Program #/Poster #: 472.04/O12

Topic: C.06. Neuromuscular Diseases

Support: Thierry Latran Foundation
ALSA
ARSLA
ERA-NET NEURON TracInflam
NRJ-Institut de France
ARMC

Title: Implication of peripheral macrophages in amyotrophic lateral sclerosis (als)

Authors: A. CHIOT[1], S. ZAIDI[1], C. ILTIS[1], M. RIBON[1], F. BERRIAT[1], L. BERNARD[1], L. SCHIAFFINO[1,2], M. MALLAT[1], D. BOHL[1], S. MILLECAMPS[1], C. S. LOBSIGER[1], *S. BOILLEE[3,1]
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Abstract: Amyotrophic Lateral Sclerosis (ALS) is the most common motor neuron disease leading to progressive paralysis. Previous studies using mouse models expressing mutant hSOD1 (the second most frequent mutated gene in ALS) highlighted the implication of microglial cells/ macrophages in ALS disease progression without, however discriminating their respective role. A special feature of spinal cord motor neurons is that their axon extends at the periphery and is therefore surrounded by peripheral macrophages while their cell body, is surrounded by microglia. Although microglia and peripheral macrophages share common characteristics, both populations have different developmental origins and are localised in different cellular environments, which could lead to different implications in the disease. Since degeneration of motor neuron axons happens early and macrophages at the periphery would be more easily accessible than microglia in the CNS, we studied the potential of peripheral macrophages as therapeutic targets in ALS mice. First, we showed strong and progressive macrophage activation in the sciatic nerve of $hSOD1^{G93A}$ (fast progressing) and $hSOD1^{G37R}$ (slow progressing) ALS mice, suggesting an active role of macrophages in the pathology. We developed a protocol using bone marrow graft to replace macrophages at the periphery without affecting microglia. We replaced mutant hSOD1-expressing macrophages by control (GFP+) macrophages or macrophages with more trophic or less toxic potentials. Our protocol allowed an efficient replacement of monocytes/ macrophages (GFP+) in the blood and in peripheral tissues affected in ALS. We showed that infiltration of peripheral cells remained low during disease, as only few GFP+ peripheral cells were transiently found in the spinal cord of grafted ALS mice and seemed dependant of disease duration. These results were further confirmed by immunostaining of specific markers and by using transgenic reporter mice. The effect of peripheral macrophages in ALS therefore rather comes from the periphery, and this allowed us to perform distinct transcriptomic studies of spinal cord microglial cells, and sciatic nerve macrophages during disease course in ALS mice to find differentially expressed markers in the two populations and according to disease stages. Finally, replacement of mutated macrophages by cells more trophic or less toxic led to an improvement of several pathophysiological markers and delayed the symptomatic stage of ALS grafted mice. In conclusion, we provide new evidence suggesting an active role of peripheral macrophages in ALS, supporting future therapeutic strategies by targeting peripheral macrophages.

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Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.05/O13

Topic: C.06. Neuromuscular Diseases

Title: Identification and evaluation of disease relevant biomarkers of progressive neurodegeneration in preclinical models of amyotrophic lateral sclerosis

Authors: *J. SUGAM, J. WONG, S. NIROOMAND, H. ZARIWALA, D. ZHOU, R. GENTZEL, Y. HU, T. ROSAHL, S. PARMENTIER-BATTEUR
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Abstract: Amyotrophic Lateral Sclerosis (ALS) is fatal neurodegenerative disorder characterized by the selective loss of motor neurons in the brain and spinal cord that leads to progressive motor dysfunction. Several mechanisms have been found to be underlying causes of this motor neuron degeneration including increases in oxidative stress, endoplasmic reticulum stress pathway activity, and neuroinflammation. In order to develop therapeutic strategies that can modify the progression of the disease, it is necessary to identify and validate translatable biomarkers that could reflect this motor dysfunction and neurodegeneration. To this end, two transgenic animal models of ALS consisting in SOD1 G93A mice and TDP43 Tar 6/6 mice were characterized using motor (accelerated rotarod/grip strength), histological (neuromuscular junction denervation), electrophysiological (compound muscle action potential (CMAP)), and biochemical (phospho-neurofilament heavy chain levels (pNF-H), muscle atrophy markers, MAPK pathway activity) assays. The measures of all these markers were performed at various ages in order to determine their relationship with the progression of the disease. In SOD1 mice, we found an age related dysfunction in multiple biomarkers including an increase in pNF-H and in neuromuscular junction denervation that was associated with the progressive decrease in motor functions evaluated by the CMAP, rotarod and grip test scores. Interestingly, these markers all overlapped with each other to effectively reflect disease onset, progression, and terminal limb paralysis. These disease biomarkers were further validated by studying the effect of the administration of the new FDA approved therapy, Edaravone, to SOD1 mice. In contrast to the SOD1 mice, the TDP43 Tar6/6 mice showed moderate modification in a subset of these markers including pNF-H and motor impairments using rotarod, but no changes in CMAP scores or markers of muscle atrophy, suggesting that the muscle function and lower motor neuron-muscle connections were not altered. These data validate multiple disease markers reflecting the major pathological mechanisms of ALS including the motor dysfunction and neurodegeneration. The results in the two ALS mice models also highlights the importance of understanding the specific characteristics of different preclinical models of neurodegenerative diseases to choose the most appropriate model for the evaluation of novel therapeutic strategies.

Disclosures: **J. Sugam:** A. Employment/Salary (full or part-time):; Merck and Co., Inc. **J. Wong:** A. Employment/Salary (full or part-time):; Merck and Co., Inc. **S. Niroomand:** A. Employment/Salary (full or part-time):; Merck and Co., Inc. **H. Zariwala:** A. Employment/Salary (full or part-time):; Merck and Co., Inc. **D. Zhou:** A. Employment/Salary (full or part-time):; Merck and Co., Inc. **R. Gentzel:** A. Employment/Salary (full or part-time):; Merck and Co., Inc. **Y. Hu:** A. Employment/Salary (full or part-time):; Merck and Co., Inc. **T. Rosahl:** A. Employment/Salary (full or part-time):; Merck and Co., Inc. **S. Parmentier-Batteur:** A. Employment/Salary (full or part-time):; Merck and Co., Inc.

Poster

472. Studies of ALS in Animal Models

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Topic: C.06. Neuromuscular Diseases

Support: NIH grant NS088653
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Title: RNA-Seq analysis of spinal cord tissues from hPFN1^{G118V}transgenic mouse model of ALS

Authors: *M. KIAEI[1], C. BARHAM[1], D. FIL[2], S. D. BYRUM[3], Y. RAHMATALLAH[4], G. GLAZKO[4]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that leads to the loss of motor neurons. The molecular mechanisms of motor neuron degeneration are largely unknown and there are currently no effective therapies to treat this disease. We have conducted a whole transcriptome profiling using RNA-Seq technology and sequencing cDNA from the total RNA isolated from the spinal cords of mutant transgenic hPFN1^{G118V} mice and their wildtype transgenic hPFN1^{WT} controls. The aim of this study was to identify molecular changes in spinal cords of the hPFN1^{G118V} ALS mouse model at presymptomatic and end stages. To our knowledge, this is the first study to use next-generation RNA-Seq to measure differential gene expression in hPFN1^{G118V} mice at presymptomatic and end stages. The analysis of genes identified in this study revealed that end-stage hPFN1^{G118V} mice had 890 deferentially expressed genes (747 upregulated, 143 downregulated) when compared to presymptomatic hPFN1^{G118V} mice, and they had 836 deferentially expressed genes (742 upregulated, 94 downregulated) when compared to age-matched hPFN1^{WT} controls. Presymptomatic hPFN1^{G118V} mice were not significantly different from age-matched hPFN1^{WT} controls. We further analyzed the genes and their corresponding proteins form the database using ingenuity pathway analysis (IPA) and identified inflammatory pathways significantly activated in end-stage hPFN1^{G118V} samples, suggesting an excess of glial activation at end-stage disease. We have also analyzed the data for gene expression for cell type specificity (astrocytes, microglia, oligodendrocytes, neurons and

motor neurons) and validated the RNA-Seq data by qRT-PCR using randomly selected 12 candidate genes. We will present our RNA-Seq data and graphical representations showing valuable and promising leads into the identification of molecules and pathways revealing the mechanism of neurodegeneration that could potentially serve as therapeutic targets for ALS.

Disclosures: M. Kiaei: None. **C. Barham:** None. **D. Fil:** None. **S.D. Byrum:** None. **Y. Rahmatallah:** None. **G. Glazko:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.07/O15

Topic: C.06. Neuromuscular Diseases

Support: MNDA Grant Fisher/Oct14/876-792

Title: Humanising the mouse Tardbp gene

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Abstract: Amyotrophic lateral sclerosis (ALS) is a terminal, adult onset neurodegenerative disease causing gradual degeneration of upper motor neurons (UMNs) and lower motor neurons (LMNs) leading to paralysis of the muscles and death within 5 years from the disease onset. About 10% of ALS patients show familial inheritance of the disease (fALS) while 90% are sporadic (sALS). Cytoplasmic inclusions containing truncated and ubiquitinated/hyperphosphorylated forms of the TAR DNA binding protein (TDP-43), encoded by the *TARDBP* gene, are found in almost all ALS cases. TDP-43 is a ubiquitous nuclear RNA/DNA binding protein that shuttles between the nucleus and the cytoplasm and is involved in different steps of the RNA processing and modification. Furthermore mutations in *TARDBP* are causative for ALS. Because cytoplasmic mislocalisation and nuclear depletion of this protein appears to have an important role in the neurodegenerative process, a better understanding of the pathogenic mechanisms is essential. For this reason, we are generating a humanised knock-in TDP-43 mouse which will express the human protein at endogenous levels. Mouse *Tardbp* will be replaced by the corresponding human orthologous *TARDBP* from the start codon (ATG) in exon 2, to the stop codon (TAG) in exon 6. The 5' and 3' UTR's will be maintained as mouse, thus likely maintaining correct gene expression and avoiding the toxicity caused by overexpression of TDP-43. Using a gene targeting strategy which involves the use of Bacterial Artificial Chromosomes (BACs) and BAC recombineering in *Escherichia coli*, we have created

our final modified BAC vector successfully replacing the *Tardbp* gene, from exon 2 to exon 6, with the corresponding sequence from human *TARDBP* together with large flanking homology arms against *Tardbp*. Using the *humanised* BAC, we are currently targeting mouse embryonic stem cells, with the aim of producing a humanised knock-in mouse via homologous recombination. This new model will express a fully human wild type TDP-43 protein under the control of the endogenous mouse promoter. In parallel, we will use CRISPR/Cas9 genome editing technology to introduce ALS/FTD causative point mutations within the *humanised TARDBP* to study normal and pathological functions of human TDP-43.

Disclosures: F. De Giorgio: None. **A. Devoy:** None. **C. Milioto:** None. **F. Zhu:** None. **K. Mackenzie:** None. **A. Acevedo arozena:** None. **E. Fisher:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.08/O16

Topic: C.06. Neuromuscular Diseases

Support: ALS Canada
Brain Canada

Title: Modelling the ALS-causing TDP-43 [A382T] variant in zebrafish

Authors: *Z. HARJI[1], V. PETEL-LÉGARÉ[3], E. C. RODRIGUEZ[3], G. A. B. ARMSTRONG[2]
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Abstract: Mutations in *TARDBP*, encoding TARDNA-Binding Protein of 43 kDa (TDP-43), cause amyotrophic lateral sclerosis (ALS). Until recently, modelling ALS in animals has relied upon transgenic overexpression of either human mutant or wild type *TARDBP*. Though these models have permitted investigations and added to our understanding of the disease mechanisms, endogenous gene expression many impact the evaluation of disease-causing variants. With the advent of the CRISPR/Cas9 system, researchers now have the opportunity to generate analogous disease-causing mutations in endogenous genes of model system. Using this method, we have a created a zebrafish model of ALS that carries the equivalent A382T TDP-43 (zebrafish A379T tdp-43) variant. The A382T variant shows complete penetrance by the age of 80 and is recognized as the most commonly found disease-associated TDP-43 variant. We believe that this mutant zebrafish line will allow us to more accurately recapitulate the genetic aetiology of familial ALS and permit us to examine both cellular and physiological defects that arise in this neurodegenerative disease. The zebrafish genome contains a paralog of *tardbp* (*tardbpl*), from which a unique splice variant (*tardbpl V1*) can compensate for the loss of zebrafish tdp-43. We

will examine defects that arise in zebrafish that carry the A379T variant both in the *tardbpl*$^{+/+}$ and *tardbpl*$^{-/-}$ genetic background. We anticipate that zebrafish expressing the A379T variant will develop motor deficits and predict that zebrafish with the A379T variant in the *tardbpl*$^{-/-}$ background will develop a more severe motor phenotype.

Disclosures: Z. Harji: None. **V. Petel-Légaré:** None. **E.C. Rodriguez:** None. **G.A.B. Armstrong:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: 472.09/P1

Topic: C.06. Neuromuscular Diseases

Support: Als Canada
Brain Canada

Title: Amyotrophic lateral sclerosis models of CHCHD10 in zebrafish

Authors: *V. PETEL LEGARE[1], G. A. B. ARMSTRONG[2], Z. HARJI[3]
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Abstract: Introduction: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the progressive degeneration of lower and upper motor neurons. While most forms of the disease occur sporadically in the population (sALS), a small subset (~5-10%) is inherited (fALS), which has allowed researchers to model this disease in simple animal models. Recently, dominantly inherited missense mutations in the nuclear encoded gene *CHCHD10* (encoding the mitochondrial protein CHCHD10) were identified in both sALS and fALS cases, implicating mitochondrial dysfunction in ALS pathogenesis. These include the predicted variants P80L, S59L, and A35D. As the function of this protein remains largelyunknown, we propose to use zebrafish (*Danio rerio*) to explore *in vivo* cellular defects that arise following the expression of analogous disease-causing variants in the zebrafish ortholog of *CHCHD10*. **Goal:** To investigate the cellular and pathophysiological consequences of the analogous zebrafish *chchd10* variants: P83L, A35D, and S60L. **Methodology:** Using the clustered regularly interspaced short palindromic repeats (CRIPSR) and CRISPR associated protein 9 mutagenic system along with homology directed repair, we will knockin analogous missense mutations, as well as generate a *chchd10* knockout model. We will characterize motor phenotypes in both knockout (KO) and knockin (KI) models and examine neuromuscular junctions (NMJs). NMJs, will be assessed by examining co-localization of the pre- (synaptogamin 2) and the post-synaptic NMJ marker (α-bungarotoxin-conjugated to sulforhodamine). In addition, we will evaluate differences oxidative

metabolism in both KO and KI models. **Hypothesis:** We hypothesize that the KI mutant zebrafish will display age-related defects, characterized by the loss of muscle connectivity, motor impairment, and premature death, as well as a defect in oxidative metabolism. We believe that KO of *chchd10* will express a phenotype at earlier stages in development, supporting the loss-of-function disease mechanism that is believed to occur in patients expressing CHCHD10 variants. **Results:** A KO model was recently identified and confirmed by Western Blot in one of our founder lines. We are in the process of further characterizing the consequences arising from the loss of *chchd10* expression and are currently screening for KI mutations. **Conclusion:** The data generated from this project will be beneficial to further our understanding of the cellular defects that arise in ALS cases with mutations in *CHCHD10*, as there are currently no KI animal models of *CHCHD10*.

Disclosures: V. Petel Legare: None. **G.A.B. Armstrong:** None. **Z. Harji:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: 472.10/P2

Topic: C.06. Neuromuscular Diseases

Support: NINDS/NIH R21 NS100055
Children's Hospital of Pittsburgh RAC grant

Title: Matrin 3 expression leads to neuromuscular degeneration and RRM-mediated toxicity in *Drosophila*

Authors: *N. RAMESH, I. CASCI[1,2], U. B. PANDEY[1,2]
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Abstract: Amyotrophic Lateral Sclerosis (ALS) is an adult-onset, fatal neurodegenerative disease with progressive loss of upper and lower motor neurons. Mutations in Matrin 3 (MATR3), a DNA/RNA-binding protein, have been found in familial and sporadic forms of ALS, as well as in distal myopathy. In addition, Matrin 3-positive cytoplasmic inclusions have been observed in C9orf72 hexanucleotide repeat expansion mediated- as well as sporadic ALS. However, the underlying molecular mechanisms of MATR3-mediated neuromuscular degeneration are still poorly understood. We have developed novel *Drosophila* models of MATR3 that recapitulate key features of neuromuscular degeneration. We found that expression of MATR3 leads to reduced lifespan accompanied by progressive motor defects in flies. Furthermore, we found that ubiquitous expression of MATR3 in *Drosophila* causes early lethality. Strikingly, deletion of the RNA-recognition motif (RRM2) strongly mitigates MATR3 toxicity, suggesting that MATR3 causes degeneration through its RNA-binding properties.

Furthermore, using candidate-gene approach, we have identified *rump*, *Drosophila* homolog of human hnRNP M, as a potential modifier of MATR3-mediated toxicity *in vivo*. We found that decreasing levels of endogenous rump strongly suppresses the lethality phenotype. HnRNP M has been identified as a direct interactor of MATR3 in multiple proteomic screens, and they are also known to be part of a complex that regulates alternative splicing, further indicating a role for dysregulated RNA metabolism in MATR3-mediated degeneration. Collectively, our results establish the MATR3 *Drosophila* model as a promising *in vivo* model to study the mechanism of neuromuscular degeneration and screen for genetic modifiers of MATR3 toxicity.

Disclosures: I. Casci: None. **U.B. Pandey:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: 472.11/P3

Topic: C.06. Neuromuscular Diseases

Support: ALS Finding A Cure
ALS Associtaion

Title: Genetic modifiers of stress-induced neurodegeneration in a *C. elegans* sod-1 knock-in model

Authors: *K. S. YANAGI[1], J. J. LINS[1], L. A. STINSON[1], M. B. WALSH[2], A. MAHAPATRA[2], S. N. BASKOYLU[1], J. YERSAK[4], A. C. HART[3]
[1]Neurosci., [3]Dept. of Neurosci., [2]Brown Univ., Providence, RI; [4]Neurosci., The ALS Assn., Washington, DC

Abstract: Amyotrophic lateral sclerosis (ALS) is a degenerative disorder that typically results in the death of a patient within 3-5 years after symptom onset. One of the classical hallmarks of ALS is the selective degeneration of motor neurons. Over a hundred mutations in superoxide dismutase 1 (SOD1), a gene that encodes an enzyme that catalyzes the breakdown of superoxide radicals, have been linked ALS. One of the patient alleles in SOD1 is G85R, which converts a glycine to arginine at position 85 in the SOD1 protein. Decades of research have advanced our understanding of the role of SOD1 in fALS. Genetic modifiers may provide insight into the molecular mechanisms behind the degeneration of motor neurons. We have undertaken a classical forward genetic screen in *Caenorhabditis elegans* to identify suppressors of glutamatergic neuron degeneration observed in a knock-in SOD-1G85R model. The SOD-1G85R knock-in animals exhibit glutamatergic neuron degeneration after exposure to oxidative stress. Using EMS, we mutagenized SOD-1G85R animals, and then screened for suppression of glutamatergic neuron degeneration. We identified suppressor lines and are using whole genome

sequencing to identify candidate genes. We will determine if the suppressors ameliorate cholinergic motor neuron death and survival defects observed in the SOD-1G85R knock-in model. Further, to determine if common pathways underlie neurodegeneration in ALS, we will test candidate and established ALS suppressor genes in other SOD1 and ALS models. Understanding genetic modifiers of ALS will facilitate treatment development and illuminate molecular mechanisms behind ALS.

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Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

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Topic: C.06. Neuromuscular Diseases

Support: Medical Faculty at Umeå University
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Integrative Medical Biology at Umeå University

Title: Structural CNS changes at presymptomatic stages in the G93A^{HSOD1} ALS model

Authors: *T. MEDIAVILLA, S. PARWEEN, D. J. MARCELLINO, F. SULTAN
Integrative Med. Biol. (IMB), Umea Univ., Umea, Sweden

Abstract: Insertion of human SOD1 G93A copies in transgenic mice has proven to be a useful model to replicate late stages of human amyotrophic lateral sclerosis (ALS). The typical severe phenotype of this model presents spinal motoneuron degeneration together with hind limb paralysis and weight loss. Few studies so far have attempted to look at and characterize early stages of disease to better understand disease onset and progression and to define early therapeutic windows for the evaluation of disease modifying treatments. We used a delayed onset G93A mouse model with a severe phenotype appearing at 7-8 months to allow for an extended pre-onset monitoring of preclinical symptoms. We combined behavioral testing with *in vivo* MRI to correlate behavior with structural imaging of CNS integrity to allow for a better system-level approach. Behavioral testing included measuring the time to fall from an inverted wire screen to monitor muscle strength and the pole test to evaluate motor coordination by measuring the time to reorient and to climb down the pole. We performed in vivo diffusion tensor imaging (DTI) to detect any alterations in CNS white matter tracts. DTI was performed with 4-segment EPI, TE/TR 22.9/3000ms, isotropic spatial resolution of 128µm, 10 A0 scans and 60 different diffusion directions. B-values of 900/1150/1400 s/mm2 were applied and the total scan duration was 38 minutes. DTI data postprocessing was performed with FSL and

included DWI denoising, eddy current and Gibbs ringing removal. We extracted fractional anisotropy, mean and radial diffusivity. Data analysis was carried-out on individually defined ROIs of some of the major fiber tracts of the forebrain. Our preliminary findings indicate that a preclinical phase of motor dysfunction is observed between 3 and 5 months of age before moderate or severe stages of disease are appreciable. This preclinical phase is associated with structural CNS changes detected by DTI.

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Poster

472. Studies of ALS in Animal Models

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Program #/Poster #: 472.13/P5

Topic: C.06. Neuromuscular Diseases

Support: ODPRT grant

Title: Deletion of C9orf72 induces an age-dependent decline in reversal learning and olfactory memory

Authors: *Y.-C. YEN[1], W. HO[1], S.-C. LING[1,2,3]
[1]Dept. of Physiol., [2]Neurobiology/Ageing Programme, Natl. Univ. of Singapore, Singapore, Singapore; [3]Program in Neurosci. and Behavioural Disorders, Duke-NUS Med. Sch., Singapore, Singapore

Abstract: Hexanucleotide (GGGGCC) repeat expansions in the noncoding region of *C9ORF72* gene are the most common genetic cause for amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). In addition to gain-of-toxic mechanisms that result from the aberrant translation of hexanucleotide repeats and trapping of RNA-binding proteins, reduced expression of *C9orf72* has also been proposed to contribute to the ALS-FTD pathogenesis. We and others have previously shown that mice with *C9orf72* ablation develop fetal autoimmune disease and exhibit reduced survival without motor neuron degeneration and overt motor deficits. Here, we examined the effect of *C9orf72* deletion on hippocampus-dependent cognitive functions. While *C9orf72*-knockout mice were normal in general locomotor activity, working memory, and contextual fear conditioning, they exhibited superior performance to wildtype mice in reversal learning and olfactory memory that showed an accelerated age-dependent decline. Taken together, our data suggest that deletion of *C9orf72* induces an age-dependent decline in some aspects of hippocampus-dependent cognition.

Disclosures: Y. Yen: None. **W. Ho:** None. **S. Ling:** None.

Poster

472. Studies of ALS in Animal Models

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FONDECYT 1150933 (LVN)
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Conicyt 21151265 (SA)

Title: Characterization of epigenetic and behavioral alterations in ALS and FTD mouse model

Authors: *N. JURY[1,2], S. ABARZUA[1,2,3], I. DIAZ[1,2], M. V. GUERRA[1], P. CUBILLOS[1,2], E. AMPUERO[1,2], P. MARTINEZ[1,2], M. MONTECINO[1,3], L. VARELA-NALLAR[1], B. ZAN ZUNDERT[1,2]
[1]Univ. Andrés Bello, Santiago, Chile; [2]Ctr. for Aging and Regeneration (CARE-UC), Santiago, Chile; [3]FONDAP Ctr. for Genome Regulation, Santiago, Chile

Abstract: Mutations in *SOD1* cause motoneuron pathology in amyotrophic lateral sclerosis (ALS) disease, while *C9ORF72* repeat expansions (RE) are implicated in both ALS and frontotemporal dementia (FTD). We evaluated if critical epigenetic modifications are altered in hSOD1^{G93A} and C9orf72-RE transgenic mice. Primary astrocyte cultures (P2) and brain tissue obtained from C9orf72-RE (9 months) and hSOD1G93A (4 months) mice were analyzed by immunostaining and western blot with specific antibodies to detect specific histone marks and DNA damage. In cultured astrocytes from hSOD1^{G93A} and C9orf72-RE mice, we observed a similar depletion in the nuclear expression of specific histone marks. Similar alterations were detected in the ALS/FTD astrocytes and neurons in the spinal cord, motor cortex and hippocampus tissue. We determined if the epigenetic alterations were correlated with behavioral changes and we found that object location memory (OLM discrimination in mature C9orf72-RE animals was reduces OLM compared to controls. Our data suggest that a common loss of epigenetic control contributes to pathogenesis and disease development in ALS and FTD. The epigenetic dysregulation in the hippocampus parallels previous undetected cognitive deficits in the ALS and FTD models.

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Poster

472. Studies of ALS in Animal Models

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Program #/Poster #: 472.15/P7

Topic: C.06. Neuromuscular Diseases

Support: Indian Council of Medical Research, Govt. of India

Title: Structural and functional alteration of motor neurons leads to motor deficit in a rat model of Sporadic Amyotrophic Lateral Sclerosis

Authors: *S. DAS, K. SABITHA, L. T. RAO, T. R. RAJU
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Abstract: Introduction: Amyotrophic Lateral Sclerosis (ALS), a late onset neurodegenerative disease causes loss of both upper and lower motor neurons (MNs) in the motor cortex, brainstem and spinal cord. Degeneration of MNs occurs both at the structural and functional levels, which is reflected in the behaviour. **Aim:** The present study has investigated the morphology of MNs and their functional alteration leading to motor deficit in sporadic ALS model, generated by serial intrathecal infusion of CSF from ALS patients in rat pups at post natal (P) days 3, 9 and 14. Structure and function of the MNs and motor behaviour of the rats were tested at P16 and P22. **Methodology:** To evaluate the morphological changes in MNs of cervical and lumbar regions, Cresyl violet and Golgi-cox staining were performed. For functional studies, Multielectrode array recording was carried out from spinal cord slices at the cervical and lumbar levels. Motor function was tested by using rotarod. **Results:** Infusion of ALS-CSF into rat pups has significantly reduced the total number and density of MNs in both lumbar and cervical region of the spinal cord along with the hypertrophy of surviving MNs. Functional study also reveals alterations in spike activity. Further analysis using rotarod indicated infusion of ALS-CSF into rat pups induced motor deficits, with a significant increase in the number of falls when they fail to balance on the rotating rod. **Conclusion:** Accordingly, ALS-CSF, if infused serially into rat pups can cause motor deficits which could be related to structural and functional impairment of MNs.

Disclosures: S. Das: None. **K. Sabitha:** None. **L.T. Rao:** None. **T.R. Raju:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.16/P8

Topic: C.06. Neuromuscular Diseases

Support: ALS Finding a Cure Grant 5290189

Title: Motor neuron hypoexcitability in TDP-43 Q331K knock-in mouse model of ALS/FTD

Authors: *J. P. WHITT[1], L. A. STINSON[1], R. H. BROWN, Jr.[2], J. R. FALLON[1], J. SREEDHARAN[3], D. LIPSCOMBE[1]
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Abstract: Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are progressive, neurodegenerative disorders that overlap clinically and that have common molecular origins. Mislocalization and aggregation of the tar-DNA binding protein 43 (TDP-43) is a hallmark feature of both ALS and FTD, and mutations in the TDP-43 encoding gene (*TARDBP*) can cause both ALS and FTD. Mice homozygous for the Q331K mutation in *Tardbp* exhibit motor and FTD-like cognitive impairment from 3 months and older, even though neuromuscular junction transmission is unaffected (White et al., 2018). *In vivo*and slice studies of various ALS mouse models have shown changes in motor neuron excitability that precede neurodegeneration in both vertebrate and invertebrates. Consistently, we find that motor neurons of 6 month mice homozygous for TDP-43 Q331K have reduced excitability as compared to 2 month mutants, and 2 and 6 month wild-type mice. We used whole-cell patch clamp recording in acute transverse spinal cord slices, and recorded from TDP-43 Q331K knock-in mouse (Q331K) motor neurons projecting to either the tibialis anterior, ~90% fast twitch (type II) muscle fibers, or soleus muscle, ~50% slow twitch (type I) muscle. At 3 months, Q331K homozygous mice exhibit motor defects, so we compared 2 and 6 month old mice as pre- and post-symptomatic groups. We found a slight increase in the rheobase current for 6 month Q331K motor neurons projecting to TA compared to wild-type littermates. In addition, with larger 3x-rheobase current injections, motor neurons from 6 month Q331K mice were hypoexcitable compared to littermate controls, regardless of target muscle. The hypoexcitability phenotype in 6 mth Q331K mice was notcorrelated with intrinsic membrane properties such as input resistance and cellular capacitance. In conclusion, we find that motor neuron hypoexcitability occurs coincident with defects in motor coordination and without alterations in nerve muscle junction transmission. We find hypoexcitability in motor neurons that innervate both fast and mixed twitch muscle types and hypothesize that altered ion channel function underlies this disease phenotype.

Disclosures: J.P. Whitt: None. **L.A. Stinson:** None. **R.H. Brown:** None. **J.R. Fallon:** None. **J. Sreedharan:** None. **D. Lipscombe:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.17/P9

Topic: C.06. Neuromuscular Diseases

Title: Effects of Cu(II)ATSM on phenotype progression in mice with a familial ALS mutation

Authors: *L. M. HODGE, L. CHERRY, C. A. ZIFICSAK, L. D. AIMONE, D. POSAVEC, K. FREITAS, I. J. REYNOLDS, S. E. BROWNE
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Abstract: Cu(II)ATSM is in Phase 1 clinical trials for ALS, following reports of improved outcomes in mouse lines expressing familial ALS Cu,Zn-superoxide dismutase (SOD1) mutations. To test the reproducibility of Cu(II)ATSM effects in an independent laboratory, we undertook a preliminary efficacy study in mutant SOD1 G93A/1Gur mice (Jackson Labs line 2726). Replicating a published approach (Williams et. al., 2016, Neurobiol. Dis. 89:1-9) we tested twice daily dermal application of Cu(II)ATSM in male G93A mice, dosed from 6 wks of age. Groups were powered to detect a 20% difference in rotarod score (30/group). Following acclimation, mice were pseudo-randomly ascribed to groups balanced by birthdate, litter, sire, weight, rotarod activity, and coat color. Cu(II)ATSM (50, 100 mg/kg/dose) or vehicle (DMSO, 6.7 ml/kg) was applied by pipette to animals' backs. Littermate wildtype mice received vehicle. Body weight and hind-limb neurological score were tracked twice weekly. Accelerating rotarod and wire hang were assayed from 6 to 16 wks of age. All experimenters were blinded to genotype and groups, and testing order was randomized. After 3 wks of dosing, twice daily administration of 100 mg/kg was poorly tolerated by mice, resulting in premature deaths. 100 mg/kg dosing was modified to alternate days, and then terminated 3 wks later. After 10 wks the 50 mg/kg regimen was modified to alternate days for the remainder of the study. The remaining mice were followed until the IACUC-approved endpoint (no righting response after 10s or 20% weight loss). Within these animals, average life-span of G93A mice receiving Cu(II)ATSM was increased significantly compared to vehicle treatment, by 18 +/- 2 d (13%) and 9 +/- 2 d (7%) after 50 and 100 mg/kg, respectively (mean +/- SEM; ANOVA, post-hoc t-test). G93A mice receiving 50 mg/kg/dose Cu(II)ATSM spent a significantly longer time in early symptomatic stages, gained weight longer, and reached significantly higher weights compared to their untreated counterparts. Rotarod ability was preserved in both 50 and 100 mg/kg groups at 16 wks. Wire hang was not improved by either dose.
These preliminary data suggest that further analyses of Cu(II)ATSM are warranted if an

appropriate dosing paradigm can be achieved. Our observation of tolerability problems underscores the need to understand the optimum dose, route, and frequency. These are fundamental requirements for any *in vivo* study, but in the case of Cu(II)ATSM are confounded by lack of a discrete CNS target engagement measure for Cu(II)ATSM. Understanding target engagement is essential to guide appropriate dose selection with which to interrogate the therapeutic window for Cu(II)ATSM.

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Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.18/P10

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R01 NS094678

Title: Building a plausible model for tdp-43 driven als/ftd pathology

Authors: *J. L. MARTINEZ[1], B. FLORES[2], X. LI[2], S. BARMADA[3], A. BEG[1]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that destroys neurons in the brain and spinal cord leading to the loss of muscle control. Frontotemporal dementia (FTD) is a clinically distinct disorder, characterized by progressive behavioral, language and memory deficits. Although the signs and symptoms of ALS and FTD are unique, ALS and FTD share key pathologic and genetic features, suggesting disease pathogenesis may arise from conserved aberrant mechanisms. The majority of individuals with ALS and FTD exhibit neuronal cytoplasmic inclusions rich in the RNA binding protein TDP43, and changes in TDP43 localization and levels are strongly predictive of neuron loss in ALS/FTD. Over 40 different mutations in the gene encoding TDP43 are responsible for familial ALS and FTD, further supporting the integral contribution of TDP43 to disease. However, the link between TDP43 RNA binding properties and neuronal survival are unclear in an endogenously expressed context. Specifically, the majority of studies rely on overexpression of WT or mutant forms of TDP43 to drive disease pathogenesis, yet there is no data indicating that actual TDP-43 related pathologies are caused by or related to protein overexpression.
TDP-43 is a nuclear RNA-binding protein that participates in transcriptional and translational regulation, pre-mRNA splicing, and neuronal RNA stability. TDP43 binds thousands of UG-rich RNA sequences, and TDP43-dependent toxicity is tightly tied to its ability to recognize RNA.

Intramolecular interactions between the RNA binding domains of TDP43, mediated by a salt bridge, are necessary for maintaining specificity for UG sequences; in the absence of the salt bridge, TDP43 inappropriately recognizes GC-rich sequences. Here, we demonstrate that mutations that eliminate the salt bridge enhance TDP43 mislocalization, decrease UG-rich RNA binding, and abrogate TDP43-dependent toxicity. Using a modified CRISPR-Cas9 targeting strategy we have generated mutations in *tdp-1*, the *C. elegans* ortholog of TDP43. We show that *tdp-1*(R219A) mutants phenocopy loss-of-function alleles in *C. elegans*. In ongoing work, we are investigating the effects that TDP43 salt bridge disruption has on RNA splicing and expression via RNA-sequencing in both mammalian cell lines and in *C. elegans*. These studies highlight previously uncharacterized properties of TDP43 that may serve as targets for therapy development.

Disclosures: J.L. Martinez: None. **B. Flores:** None. **X. Li:** None. **S. Barmada:** None. **A. Beg:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.19/P11

Topic: C.06. Neuromuscular Diseases

Support: NIH (R01NS060926)
Muscular Dystrophy Association (MDA418685)
Cure SMA (DID1718)

Title: Investigating p53 and p21 as mediators of spinal motor neuron degeneration in the $Smn^{2B/-}$ mouse model of spinal muscular atrophy

Authors: *E. REEDICH[1,2], G. COX[3], C. DIDONATO[1,2]
[1]Stanley Manne Children's Res. Inst., Chicago, IL; [2]Pediatrics, Northwestern Univ., Chicago, IL; [3]Genet., The Jackson Lab., Bar Harbor, ME

Abstract: Spinal muscular atrophy (SMA) is a pediatric neuromuscular disease caused by deficiency of the survival motor neuron (SMN) protein. The pathological hallmarks of SMA are spinal motor neuron loss and skeletal muscle atrophy. While the molecular mechanisms of spinal motor neuron degeneration in SMA remain unclear, recent transcriptional profiling and mechanistic studies identify increased activation of the p53 signaling pathway in motor neurons and spinal cord tissue of severe SMA mice and implicate phosphorylated p53 as a mediator of spinal motor neuron death. p53 pathway activation is associated with the increased expression of several p53 transcriptional targets such as the cyclin-dependent kinase inhibitor p21, whose upregulation in skeletal muscle promotes atrophy. To determine whether genetic ablation of p53

or p21 mitigates the SMA phenotype of $Smn^{2B/-}$ mice, we crossed *Trp53* and *P21* knockout alleles onto the $Smn^{2B/-}$ background and performed molecular, phenotypic, immunohistochemical, and electrophysiological studies. We find that p53 ablation impairs survival of $Smn^{2B/-}$ mice while ablation of p21 enhances survival. Notably, neither knockout modulates the timing of motor neuron loss in $Smn^{2B/-}$ mice as determined using the neurophysiological method of motor unit number estimation (MUNE). We will be presenting the results of p53 and p21 ablation on motor neuron morphology as determined using immunohistological approaches. Overall, these results demonstrate that neither p53 nor p21 signaling are the primary drivers of spinal motor neuron loss in SMA, as motor neuron death proceeds in their absence. The negative effect of *Trp53* knockout on survival of $Smn^{2B/-}$ mice is likely caused by consequences of p53 depletion in other organ systems. Interestingly, p21 depletion yielded a significant survival benefit; this may be due to mitigation of p21-driven pathology in other tissues, such as atrophy of skeletal muscle.

Disclosures: E. Reedich: None. **G. Cox:** None. **C. DiDonato:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: 472.20/P12

Topic: C.06. Neuromuscular Diseases

Support: CONACYT, México, project 240817
DGAPA, UNAM, project IN204516

Title: Neurotoxic effects of the acute and chronic administration of glutamate decarboxylase inhibitors in the rat spinal cord *in vivo*

Authors: E. COLIN[1], *R. TAPIA[2]
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Abstract: Alterations in the function of GABAergic inhibitory circuits in the spinal cord have been involved in experimental motor neuron (MN) degeneration and in MN diseases (Neuropharmacology 82;101, 2014; ACS Chem. Neurosci. 9:211, 2018; Neuropharmacology 117:85, 2017), but no studies have been carried out on the role of GABA metabolism in the spinal cord. GABA synthesis depends on the activity of glutamate decarboxylase (GAD), which can be pharmacologically inhibited in vivo by the competitive inhibitor 3-mercaptopropionic acid (MPA), by thiosemicarbazide (TSC) and by pyridoxal γ-glutamyl hidrazone (PLPGH), which impede the coenzymatic function of pyridoxal phosphate (Epilepsy Res. 116:27, 2015). In this work these inhibitors were administered directly in the adult rat spinal cord through microdialysis (acute treatment during 62 min) or by means of osmotic minipumps (continuous

chronic infusion during 10 days) (J. Neuropathol. Exp. Neurol. 66:913, 2007). Acute administration of the three drugs, separately, did not cause any significant effect on motor behavior or MN morphology, 24 h after surgery. In contrast, chronic infusion of 3, 10 and 20 mM MPA, as well as 15 mM TSC or 25 mM PLPGH, triggered frequent myoclonies of the ipsilateral rearlimb at the second or third day after pump implantation. The rotarod test showed that control rats did not fall during 120 s, whereas the animals treated with the three concentrations of MPA used or with TSC or PLPGH fell in about 75-100 s, since the first day after implantation, and this performance persisted during the 10 days-test period. Rats were fixed for histology at day 10 and the number of MNs in the infused lumbar spinal cord was counted. As compared with control vehicle-treated rats, in the ipsilateral ventral horn the number of MNs was significantly decreased 35%-50% after 3, 10 or 20 mM MPA, 45% after TSC and 40% after PLPGH. The number of MNs in the contralateral horn was also decreased but only about 10%. These results suggest that chronic inhibition of GABA synthesis results in a decreased GABA inhibitory action and that the consequent deficient function of inhibitory GABAergic circuits in the ventral horn is enough to cause MN degeneration, probably mediated by hyperexcitation. Work supported by CONACYT, México, project 240817, and DGAPA, UNAM, project IN204516. E.C. is recipient of a CONACYT scholarship for studies in the Programa de Posgrado en Ciencias Bioquímicas, UNAM.

Disclosures: E. Colin: None. **R. Tapia:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.21/P13

Topic: C.06. Neuromuscular Diseases

Support: Packard center for ALS at Johns Hopkins University

Title: Cell type specific exosomes signaling in disease spreading of ALS

Authors: *S. JIN, Y. TIAN, J. M. YELICK, Y. MEN, R. JARVIS, Y. YANG
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Abstract: Exosomes are generated from endosomal membranes and known be released by most cell types including neurons and glia cells in the CNS. These vesicles are involved with the clearance and cell-to-cell spreading of toxic molecules. Recent research suggested that the majority of pathogenic proteins of neurodegenerative diseases such as amyloid beta, mutant SOD1, TDP43, phosphor-Tau are detected in exosomes fraction of patients CSF or in vitro cell model of disease. However, the role of cell type-specific exosomes in the spreading of neurodegenerative disease is still unclear. In the current study, we developed a cell-type specific

exosome reporter mouse line (hCD63-GFP conditional knock-in, CD63-CKI) in which a GFP-fused CD63, an exosome surface marker, can be induced in a particular cell type when bred with the cell-type specific Cre driver mice or stereotaxic injection of viral vectors expressing Cre recombinase. By employing this mouse tool, we found that both neuronal and astrocyte-derived exosomes are widely present in the CNS. We performed stereotaxic injection AAV-CamkII-Cre and AAV-GFAP-Cre virus to ventral horn of lumber spinal cord in $CD63^{f/+}$ or $CD63^{f/+}$G93A SOD1 transgenic mice in disease on set (day90~100). We observed migration of astrocyte migration is significantly decreased in the direction of thoracic (1345±256um) and sacral (3130±632um) in SOD1 transgenic (Tg) mice compare to non-Tg mice. Neuronal secreted exosomes's migration is not changed in SOD1 Tg mice compare to non-Tg mice. We also performed spinal cord stereotaxic injection in $CD63^{f/+}$ mice treated with PLX3397 (selective CSF1R inhibitor) to deplete microglia. The migration distance of astrocyte secreted exosomes is decreased in the direction of sacral (1360±379um), while neuronal exosomes migration is sigenificantly longer without microglia. In summary, we demonstrated that exosomes are widely present in the CNS and astrocyte secreted exosomes are significant changed in SOD1 (G93A) mouse model of ALS. Microglia is implicated in both neuronal and astrocyte secreted exosomes miglation.

Disclosures: S. Jin: None. **Y. Tian:** None. **J.M. Yelick:** None. **Y. Men:** None. **R. Jarvis:** None. **Y. Yang:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.22/P14

Topic: C.06. Neuromuscular Diseases

Support: ALS finding a cure foundation

Title: Automated continuous behavioral monitoring and traditional behavioral testing reveal early phenotypes in a novel SOD1-G85R knock-in mouse model of ALS

Authors: *L. A. MADIGAN[1], J. PAGE[1], V. VEERABADRAN[1], T. SHARMA[1], J. DOMINOV[2], T. SERRE[1], R. H. BROWN[2], J. R. FALLON[1]
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Abstract: Dominant mutations in the gene encoding Superoxide dismutase 1 (SOD1) are a major cause of familial amyotrophic lateral sclerosis (fALS). Mouse models are a vital tool in revealing fALS pathogenic mechanisms and developing therapeutics for sporadic ALS. Until recently, models have been limited to transgenic mice overexpressing mutant human SOD1 alleles. While valuable, such transgenic lines rely on overexpression and do not reflect

endogenous expression patterns and regulation of these alleles. In particular, it is not clear to what extent these models are useful for delineating early abnormalities. To address these gaps we created a knock-in mouse model harboring the SOD1^{G85R} fALS mutation on the murine ortholog of the human SOD1 gene. We have characterized these animals using Automated Continuous Behavioral Monitoring (ACBM, Jhuang et al., 2010; White et al. 2018). During ACBM mice are video recorded at 30 frames/second for five days (total of ~1.3 x 10^7 frames/mouse/session). Behavioral assessment is then performed using a supervised, machine learning-based, computer algorithm to assign 1 of 8 designated behaviors to each frame. We assessed walking, hanging, rearing, drinking, eating from hopper, eating by hand, grooming and resting in male homozygous and heterozygous SOD1^{G85R} mice in three sessions over 1-6 months of age. In parallel, we have characterized the mice using traditional behavioral assessments including weight monitoring, wire hang, open field, grip strength, and rotorod. We find that homozygous SOD1^{G85R} mice exhibit robust weight and behavioral deficits as early as one month of age—much earlier than those reported for the transgenic SOD1^{G85R} lines. Notably, SOD1^{G85R} heterozygous mice also display these similar deficits, albeit to a lesser extent and/or at later times. We have also observed and characterized a core strength deficit that appears at one month of age and a tremor phenotype that appears at 6 months of age in homozygous animals. In summary, the combined use of ACBM and traditional behavioral measures has revealed behavioral abnormalities at early time in this novel SOD1^{G85R} knock-in model. We propose that the knock-in SOD1^{G85R} ALS disease model will be useful for characterizing early defects that could be important for predicting conversion in human fALS patients as well as revealing biomarkers useful for detecting presymptomatic changes and developing treatments for sporadic ALS.

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Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: 472.23/P15

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant AG051470
NIH Grant HD090216

Title: Effects of sex and amphetamine on orolingual motor function in the SOD1-G93A rat model of ALS

Authors: *J. A. STANFORD[1], L. GAN[2], K. STANFORD[3], Y. HONG[4], J. HARRIS[4]
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Affiliated Hosp. of Nanchang Univ., Nanchang, China; [3]Mol. & Integrative Physiol., [4]Univ. of Kansas Med. Ctr., Kansas City, KS

Abstract: The symptoms of Amyotrophic Lateral Sclerosis (ALS) include muscle weakness and atrophy that progress rapidly to paralysis and eventual death. Symptom onset can occur in the limbs (spinal onset) or in the muscles of the face (bulbar onset). These symptoms result from degeneration of motor neurons in the spinal cord and brainstem motor neurons, as well as in the corticospinal and corticobulbar neurons that innervate them. While bulbar symptoms are associated with a poorer prognosis, most preclinical studies focus on spinal deficits. We have found that the SOD1-G93A rat model of ALS exhibit both spinal and bulbar motor deficits. Bulbar deficits were manifested primarily as decreased tongue motility as disease progressed. As in human ALS, the presence of bulbar deficits in SOD1-G93A rats was associated with poorer survival. The goal of the current study was to determine the extent to which bulbar deficits were expressed differentially in male vs female SOD1-G93A rats, and whether d-amphetamine is able to normalize these deficits. Age-matched male and female SOD1-G93A rats and wildtype littermates were tested for tongue force and tongue motility throughout their lifespan. Rats were administered acute doses of d-amphetamine (1.0 and 2.0 mg/kg). In a separate group of rats, we measured motor cortical neurochemistry using ^{1}H-MRS in presymptomatic SOD1-G93A and age-matched wildtype rats. Results will be discussed in the context of sex differences in disease phenotype and potential non-invasive motor cortical neurochemical biomarkers for ALS.

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Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.24/Q1

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant NS087104

Title: Enhanced neurite outgrowth and regeneration in ALS resistant motor neurons from SOD1 mutant mouse models

Authors: *Z. OSKING[1], J. I. AYERS[2], R. HILDEBRANDT[3], K. SKRUBER[1], H. BROWN[2], D. RYU[2], A. R. EUKOVICH[1], T. E. GOLDE[2], D. R. BORCHELT[2], T.-A. READ[1], E. A. VITRIOL[1]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease characterized by motor neuron cell death and subsequent paralysis of voluntary muscles. Although ALS specifically affects motor neurons, some cells are resistant to disease progression. Most ALS studies have focused on the cellular mechanisms that cause loss of motor neuron viability. Less is known about the surviving neurons, and most of that information has come from gene expression profiling. In this study, we functionally characterize the surviving spinal motor neurons by culturing them from SOD1 ALS mouse models at various stages of disease progression. Surprisingly, we found that in comparison to non-transgenic controls, ALS resistant motor neurons from $SOD1^{G93A}$ mice have enhanced axonal outgrowth and dendritic branching. They also display an increase in the number and size of actin-based structures such as growth cones and filopodia. Increased outgrowth occurs independently of SOD1 enzymatic activity, is cell autonomous, and can be induced in motor neurons from non-transgenic mice by exogenous expression of $SOD1^{G93A}$. Further, the enhanced outgrowth occurs before the mice become symptomatic, but increases with disease progression. These results indicate that ALS resistant motor neurons are primed for regeneration significantly before ALS symptoms are present. Understanding this mechanism of cellular resistance and increased axonal outgrowth could uncover new therapeutic targets for the treatment of ALS

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Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: 472.25/Q2

Topic: C.06. Neuromuscular Diseases

Support: Gilliam Fellowship
NIH T32: 2T32GM008659-16A1
MDA255293

Title: Increasing glycolysis is neuroprotective in a *Drosophila* model of ALS

Authors: *E. MANZO[1], D. BARRAMEDA[2], A. G. O'CONNER[2], J. M. BARROWS[2], I. LORENZINI[3], R. G. SATTLER[4], D. C. ZARNESCU[2]
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Abstract: Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's Disease, is a fatal neurodegenerative disorder affecting upper and lower motor neurons. TAR DNA-binding protein

43 (TDP-43) is found in cytoplasmic inclusions in almost all non-SOD1 mediated ALS cases and is thought to play a major role in pathogenesis of the disease. Our lab has previously shown that overexpression of either wild type or mutant human TDP-43 in motor neurons of Drosophila melanogaster induces motor deficits and reduces lifespan. Using this model we have performed global metabolomics profiling and identified several significant changes consistent with alterations in glucose metabolism. Additionally, we have identified transcriptional alterations in the carnitine shuttle pathway within mitochondria leading defects in long chained fatty acid import. Based on our metabolomic data, we hypothesize that altering glucose metabolism through genetic and dietary intervention can bypass mitochondrial defects and provide protection against neurodegeneration. Our data indicate that a high sugar diet, or the genetic expression of either the human glucose transporters 3 or 4 (GLUT3 or GLUT4) in the CNS, suppresses toxic effects caused by TDP-43. Neuromuscular defects caused by neuronal TDP-43 expression are rescued by GLUT3 expression. Pfk mRNA, a key indicator of glycolytic activity, is significantly upregulated in TDP-43 expressing flies and iPSC motor neurons with TDP-43 pathology. Moreover, over-expression of Pfk is sufficient to rescue TDP-43 induced locomotor toxicity in Drosophila, while the knockdown of Pfk aggravates TDP-43 induced impairments. Taken together, our findings indicate specific metabolic alterations in ALS and highlight the predictive power of Drosophila as a model organism.

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Poster

472. Studies of ALS in Animal Models

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Program #/Poster #: 472.26/Q3

Topic: C.06. Neuromuscular Diseases

Support: F31 NS098764-01A1

Title: SMA-specific differences in the axonal and somato-dendritic translatome of motor neurons *in vivo*

Authors: *P. PRICE[1], C.-W. TSAI[2], C. DIDONATO[4], G. J. BASSELL[1], W. ROSSOLL[3]
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Abstract: Spinal muscular atrophy (SMA) is a neuromuscular disease caused by insufficient levels of the survival of motor neuron (SMN) protein, yet the molecular mechanisms by which reduced levels of SMN influence pathogenesis remain elusive. In addition to facilitating the assembly of core splicing machinery, SMN acts as a chaperone for the assembly of mRNAs and

mRNA-binding proteins into mRNPs and their axonal localization. As motor neurons are most severely affected in SMA, several studies have identified differences in global and compartmentalized mRNA expression in motor neurons *in vitro,* yet evidence for mRNA processing and localization defects in mature axons *in vivo* remains scarce. By combining motor neuron-specific transgene expression with affinity purification of translating ribosomes, we have performed a comprehensive RNA-seq study to establish the profile of ribosome-bound mRNAs in motor neuron cell bodies and axons at pivotal time points in a mouse model of SMA. Our results show disease-specific differences in the axonal and somato-dendritic transcriptome of motor neurons.

Disclosures: P. Price: None. **C. Tsai:** None. **C. DiDonato:** None. **G.J. Bassell:** None. **W. Rossoll:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.27/Q4

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant NS064224
MDA Grant 4209

Title: ZPR1 regulates expression of the Hox genes in the spinal cord motor neurons

Authors: *L. D. GANGWANI, N. GENABAI, A. KANNAN, S. AHMAD, X. JIANG
Biomed. Sci., Texas Tech. Univ. Hlth. Sci. Ctr., El Paso, TX

Abstract: The zinc finger proteinZPR1is a modifier of spinal muscular atrophy (SMA) andinteracts with SMN. ZPR1 is down regulated in SMA patients. Reduced expression of ZPR1 causes neurodegeneration in mice. However, the function of ZPR1 in motor neuron survival is unclear. To gain insight into the function of ZPR1 in motor neurons, we examined the effect of deficiency of ZPR1 in motor neurons using *Zpr1* conditional knockout mice that we have created. *Zpr1* gene was inactivated in motor neurons using Hlxb9 (Hb9)-Cre mice that resulted in developmental defects and perinatal lethality. Developmental defects are caused by aberrant expression of *homeobox*(*Hox*) genes during embryogenesis. Therefore, we examined levels of expression of different groups of *Hox*genes 5-13 that mainly express in the spinal cord during embryonic development. We show that selective *Hox*genes are significantly down regulated in the cervical, thoracic and lumbar regions of the spinal cord. Deregulation of *Hox*genes in different regions of the spinal cord show defects in the development of mouse embryo, including defects in the innervation of diaphragm, reduced ossification of sternum and absence of tail. We found that ZPR1 binds to promoter region of the human *HoxA5*gene and the levels of ZPR1

directly correlate with expression of HoxA5 levels. We also show that the ZPR1 deficiency causes down regulation of HoxA5 in the cervical region and results in degeneration of phrenic motor neurons and respiratory failure. In conclusion, ZPR1 is a transcription factor that regulates expression of *Hox*gene in the spinal cord motor neurons. Because death in SMA is caused by respiratory failure, our data suggest that reduced levels of ZPR1 in SMA patients may result in down regulation of Hox A5 leading to respiratory distress in SMA. ZPR1 may represent a potential therapeutic target to prevent neurodegeneration and reduce respiratory distress in SMA.

Disclosures: L.D. Gangwani: None. **N. Genabai:** None. **A. Kannan:** None. **S. Ahmad:** None. **X. Jiang:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.28/Q5

Topic: C.06. Neuromuscular Diseases

Support: NIG Grant GM103554

Title: Overexpression of UCHL1 in neurons extends survival of UCHL1 mutant mice

Authors: *T. W. GOULD, C.-Y. FENG, E. AIYUK, O. REID, D. J. HEREDIA
Physiol. and Cell Biol., Univ. of Nevada Sch. of Med., Reno, NV

Abstract: Loss-of-function mutations in ubiquitin C-terminal hydrolase L1 (UCH-L1) cause motor neuron (MN) disease in mice and neurodegeneration in humans. In contrast to other mouse models of MN disease, UCH-L1 mutants exhibit a selective loss of peripheral innervation without the degeneration of MN cell bodies in the spinal cord. Whether this distinction reflects a preferential role of UCH-L1 in the presynaptic terminals of MNs or not is unclear. In order to begin to address this issue, we generated transgenic mice overexpressing epitope-tagged UCH-L1 in neurons under the Thy1.2 promoter. Transgenic UCH-L1 was observed throughout MNs in UCH-L1 overexpressing mice. When crossed to UCH-L1 mutants, UCH-L1 overexpressing mice prevented paralysis and death and greatly reduced muscle weakness. Ongoing studies are examining the effect of UCH-L1 overexpression on MN disease in other models, as well as whether restricted transgenic overexpression of UCH-L1 to different regions of the neuron are as neuroprotective as overexpression targeted throughout the neuron.

Disclosures: T.W. Gould: None. **C. Feng:** None. **E. Aiyuk:** None. **O. Reid:** None. **D.J. Heredia:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.29/Q6

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant NS091546

Title: Investigating synaptic aging and neurodegeneration in developmentally arrested *Drosophila* larvae

Authors: *S. PERRY, P. GOEL, D. DICKMAN
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Abstract: The *Drosophila* larval neuromuscular junction (NMJ) has been established as a powerful model system for studying synaptic growth, structure, function, and plasticity. However, because of the short duration of the larval stage, this system is suboptimal for resolving processes that require longer time scales to manifest, such as aging and neurodegeneration. To more establish a more tractable model to probe these processes, we have terminally extended the larval stage. Utilizing recent insights into the developmental signals required for transition to pupal stages, we have fully arrested late-stage larval development in *Drosophila*, leading to arrested third instars (ATI). While wild-type larvae spend ~72 hours (3 days) in the third instar larval stage before transitioning to pupae, ATI larvae persist for over 700 hours (35 days) before dying, never reaching the pupal or adult stage. We have leveraged this system to characterize synaptic structure and function as NMJs grow, age, and degrade over the 700 hours as ATIs. We find that at day 5, ATI animals resemble wild-type controls in terms of muscle size, and synaptic growth, structure, function, and plasticity. However, by day 17, ATI larvae exhibit enhanced muscle size and a corresponding increase in synaptic growth and active zone number. In contrast, by terminal day 33, active zones are reduced in number and size and reduced presynaptic neurotransmitter release is observed. Interestingly, overall synaptic strength is maintained through a compensatory increase in postsynaptic neurotransmitter receptor levels, suggesting a novel form of homeostatic plasticity is expressed as ATIs reach the terminal life stage. Further, ATI synapses can express a homeostatic enhancement in presynaptic neurotransmitter release throughout larval lifespan, underscoring the robust homeostatic plasticity mechanisms with which these synapses are endowed. Finally, current efforts are focused on characterizing synaptic degeneration using the ATI model. In particular, we are investigating several models of neurodegenerative diseases and testing where neuroprotective mechanisms can counteract NMJ degradation. Together, this work will establish a robust model for interrogating synaptic aging and neurodegeneration in an accessible and genetically tractable system.

Disclosures: P. Goel: None. **D. Dickman:** None.

Poster

472. Studies of ALS in Animal Models

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 472.30/Q7

Topic: C.06. Neuromuscular Diseases

Support: MDA 255293
RO1 NS091299
Arnold and Mabel Beckman Foundation
Undergraduate Biological Research Program

Title: TDP43 interacts with translational machinery in a *Drosophila* model of amyotrophic lateral sclerosis

Authors: *R. BEAR, B. ZAEPFEL, S. YAMADA, L. PHAM, D. ZARNESCU
Mol. and Cell. Biol., Univ. of Arizona, Tucson, AZ

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a fatal disease that causes progressive neurodegeneration of motor neurons. TAR DNA Binding Protein (TDP-43) has been implicated in the progression of ALS, as well as at the level of pathology. TDP-43 is an RNA-binding protein that is known to regulate many steps of RNA processing, and in ALS it delocalizes to the cytoplasm. However, little is known of TDP-43's role in the dysregulation of translation and its translational targets. Several eukaryotic initiation factors (eIFs) have been identified in TDP-43-positive stress granules. Here we show that changing expression levels of several eIFs to modulate translation is neuroprotective in a Drosophila model of ALS. Specifically, when various eIFs are co-altered in the context of human TDP-43 overexpression in motor neurons of Drosophila, locomotor deficits and retinal neurodegeneration are suppressed. We are working to establish the mechanisms of this functional interaction and determine how TDP-43 physically interacts with translational machinery. We are further exploring the interaction between TDP-43 and the translational machinery in patient-derived lymphoblastoid cells. As we identify specific translational mechanisms that are dysregulated by the presence of cytoplasmic TDP-43, new targets may emerge for the development of novel therapies for ALS.

Disclosures: R. Bear: None. **B. Zaepfel:** None. **S. Yamada:** None. **L. Pham:** None. **D. Zarnescu:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.01/Q8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: PAPIIT-UNAM (IN214117) to Jorge Guevara
VIEP-BUAP grant (TEMS-NAT17-I) to Samuel Treviño
VIEP-BUAP grant (DIFA-NAT17-I) to Alfonso Díaz

Title: The administration of cadmium for 2, 3 and 4 months causes a loss of recognition memory, promotes neuronal hypotrophy and reactivity to caspase-3 and 9 in the hippocampus of rats

Authors: *G. PULIDO-FERNANDEZ[1], S. TREVIÑO, 72540[2], E. BRAMBILA, 72540[2], R. VAZQUEZ-ROQUE, 72540[2], G. FLORES[4], J. MORAN PERALES, 72540[5], A. HANDAL-SILVA, 72540[6], J. GUEVARA, 72540[7], P. AGUILAR-ALONSO[3], A. D. DIAZ[8]
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Abstract: Cadmium (Cd) is a toxic metal and classified as a carcinogen whose exposure could affect the function of the Central Nervous System. There are studies that suggest that Cd promotes neurodegeneration in different regions of the brain, particularly the hippocampus. It is proposed that its mechanism of toxicity maybe by an oxidative stress pathway, which modifies neuronal morphology and causes the death of neurons, and consequently affecting cognitive tasks. However, this mechanism is not yet clear. The aim of the present work was to study the effect of Cd administration on recognition memory for 2, 3 and 4 months, neuronal morphology and immunoreactivity for caspase-3 and 9 in rat hippocampi. For this work, one-month old male Wistar rats with an approximate weight of 80 to 100 g were used. Animals were randomly divided into two groups (n=45/ group): 1) control (drinking water) and 2) treatment with Cd. 32.5 ppm of Cd was added to the water in the form of cadmium chloride ($CdCl_2$) for the treatment group, while the control group received only purified water to, provided daily "ad libitum". Each group was subdivided into three (n = 15), with the purpose of evaluating the effect of Cd-exposure over two, three and four-month periods. The data were reported as the mean ± standard error (SE). A Two-Way ANOVA followed by a Bonferroni post-test was used to analyze the novel object recognition, dentritic length, branch order and spine density. The number of cells immunoreactive to Caspase-3 was analyzed by a Student's t-test. The results

show that the administration of Cd decreased recognition memory. Likewise, it caused the dendritic morphology of the CA1, CA3 and dentate gyrus regions of the hippocampus to decrease with respect to the time of administration of this heavy metal. In addition, we observed a reduction in the density of dendritic spines as well as an increase in the immunoreactivity of caspase-3 and 9 in the same hippocampal regions of the animals treated with Cd. These results suggest that Cd affects the structure and function of the neurons of the hippocampus, which contribute to the deterioration of recognition memory. Our results suggest that the exposure to Cd represents a critical health problem, which if not addressed quickly, could cause much more serious problems in the quality of life of the human population, as well as in the environment in which they develop.

Disclosures: G. Pulido-fernandez: None. **S. Treviño:** None. **E. Brambila:** None. **R. Vazquez-roque:** None. **G. Flores:** None. **J. Moran perales:** None. **A. Handal-silva:** None. **J. Guevara:** None. **P. Aguilar-Alonso:** None. **A.D. Diaz:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.02/Q9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Protective effect of calcium ions on prostaglandin E_2-induced apoptosis in rat cortical cells

Authors: *T. TAKADERA, S. UEMA
Hokuriku Univ., Kanazawa-Shi, Japan

Abstract: Calcium ions mediate a variety of neuron physiological responses, including cell death and survival. The purpose of this study was to examine the effect of calcium influx through the L-type calcium channel (LTCC) or the NMDA receptor on prostaglandin E_2 (PGE_2)-induced apoptosis in rat cortical cells.
Cultures of rat cortical cells were prepared from an embryonic day 18 rat neocortex. Apoptosis was quantified by scoring the percentage of cells that exhibited apoptotic nuclear morphology at the single cell level. Intracellular calcium levels were measured using the Ca^{2+}-reactive fluorescent probe Fluo4/AM.
After culture for 2 or 8 days in vitro (DIV), the rat cortical cells were subjected to PGE_2 treatment for 48 h, which induced caspase-dependent apoptotic cell death through activation of EP2 receptors. LTCC agonists such as FPL64176 protected the cells at 2 and 8 DIV from PGE_2-induced apoptosis. The EP2 receptors, Cav1.2 and Cav1.3 channels were expressed in the cells at 2 and 8 DIV. On the other hand, *N*-methyl-D-aspartate (NMDA), an agonist of the NMDA receptor, protected the cells at 8 DIV, but not at 2 DIV, from PGE_2-induced apoptosis.

FPL64176 increased the cortical cell calcium levels at 2 and 8 DIV, while NMDA increased the calcium levels at 8 DIV, but not at 2 DIV.
Treatment of cells with LY294002, an inhibitor of phosphatidylinositol-3 kinase (PI-3K), also induced apoptosis. Addition of FPL64176 to the cells at 2 and 8 DIV protected neurons from LY294002-induced apoptosis. NMDA protected the cells at 8 DIV, but not at 2 DIV, from LY294002-induced apoptosis. In addition, caspase-dependent apoptosis induced by PGE_2 and LY294002 was prevented by glycogen synthase kinase-3 inhibitors.
Our results suggest that LTCC modulates the cell death of cortical neurons induced by EP2 receptor activation in a PI-3K-independent manner.

Disclosures: T. Takadera: None. **S. Uema:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.03/Q10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Fondecyt 1150200
Conicyt 21140438
PMI PUC 1566

Title: Phosphorylation of neuroLSD1 modulates Nur77 expression

Authors: M. OLIVARES COSTA[1], *M. E. ANDRES[2]
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Abstract: Nur77 (NR4A1) is a transcription factor encoded by an immediate early gene (IEG) that belongs to the nuclear receptor superfamily. The expression of Nur77 is highly regulated by dopaminergic projections from the mesencephalon to the striatum and the prefrontal cortex. Drugs of abuse, stress and other stimuli modify the expression of Nur77 in these nuclei, although the mechanisms that regulate this expression have not yet been elucidated. Lysine-specific histone demethylase 1A (LSD1) is an epigenetic modifier that regulates the expression of IEGs in the brain. LSD1 has four splice variants, two of them with exclusive expression in neurons (neuroLSD1). NeuroLSD1 isoforms differ from the ubiquitous LSD1 only in the retention of a phosphorylatable four amino acid microexon (exon 8a). Here, we show that the phosphorylation of neuroLSD1 regulates the expression of Nur77. Also, both increment and decrease of Nur77 expression are associated with a change of neuroLSD1/LSD1 ratio. In a reporter gene assay in HEK293T cells, LSD1 and neuroLSD1 induced the expression of Nur77. A similar effect was observed with the phospho-deficient neuroLSD1, while phosphomimetic neuroLSD1 did not

modify the reporter. Additionally, in vivo experiments show that acute treatment with the dopamine D2 receptor antagonist haloperidol increased neuroLSD1 and concomitantly induced the expression of Nur77 in adult male and female mice striatum. Conversely, chronic amphetamine administration induced a significant increase of neuroLSD1, but a decrease of Nur77 in the striatum. Together, these data suggest that neuroLSD1 phosphorylation limits its function as an IEG inductor and that Nur77 expression results from neuroLSD1 phosphorylation rather than neuroLSD1/LSD1 ratio.

Disclosures: M. Olivares Costa: None. **M.E. Andres:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.04/Q11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Taurine supplementation during gestation increases oxidative and nitrosative stresses, impairs motor skills, and causes tissue damage in the brain of neonate rats

Authors: *V. VARGAS-CASTRO[1], A. GONZALEZ-VAZQUEZ[1], C. TOMAS-SANCHEZ[1], A. K. AGUILAR-PERALTA[1], V. M. BLANCO-ALVAREZ[1], J. R. EGUIBAR[1], A. UGARTE[1], D. MARTINEZ-FONG[2], G. SOTO-RODRIGUEZ[1], B. A. LEON-CHAVEZ[1]
[1]Benemerita Univ. Autonoma De Puebla, Puebla, Mexico; [2]Fisiologia, Biofisica y Neurociencias, Ctr. de Investigaciones y Estudios Avanzados del IPN, Ciudad de Mexico, Mexico

Abstract: In the CNS, taurine acts in the osmotic regulation, cellular membrane stabilization, ionic transportation, immune system regulation and, it also increases mitochondrial efficiency. It is well known that taurine has an essential role in neonatal brain development, even though the endogenous taurine concentrations tend to diminish over time. Furthermore, taurine supplementation during gestation has been reported to have significant benefits on injury models, such as intrauterine growth restriction, traumatic brain injury, and cerebral ischemia. Nevertheless, the effects of taurine supplementation on growth and development of healthy subjects have not yet been reported. This work aimed to determine whether the taurine supplementation in both gestational and postnatal periods may affect motor skills, nitric oxide levels, lipid peroxidation, and causes tissue damage. Healthy gestational Sprague Dawley rats were supplemented with taurine at a 50-ppm dose, in drinking water, from gestational day 15 and continued for the first month of life. We evaluated the neonate rats with a set of motor tests, which included ambulation, hind limb foot angle, surface righting, and negative geotaxis, fore limb and hind limb suspension, grip strength, and cliff aversion. We dissected out cerebral

cortex, subcortical nuclei, cerebellum, brainstem, and spinal cord from one-month-old specimens. We assessed nitrites levels of these regions by Griess methods and lipid peroxidation by Gerard-Monnier technique, in the supernatant of the homogenized tissue. We also determined brain cellular viability by Triphenyltetrazolium chloride (TTC) staining. The results showed that the taurine supplementation decreased the latency of front limb suspension, and increased the latency of cliff aversion, suggesting a motor injury. The taurine supplementation also increased lipid peroxidation in both frontal and occipital cortex and the cerebellum. Overall, these results allow us to conclude that the taurine supplementation in gestational stage can cause motor deficits and encephalopathy in healthy rats.

Disclosures: V. Vargas-Castro: None. **A. Gonzalez-Vazquez:** None. **C. Tomas-Sanchez:** None. **A.K. Aguilar-Peralta:** None. **V.M. Blanco-Alvarez:** None. **J.R. Eguibar:** None. **A. Ugarte:** None. **D. Martinez-Fong:** None. **G. Soto-Rodriguez:** None. **B.A. Leon-Chavez:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.05/Q12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: Vassar College ERI grant

Title: Behavior, growth and gene expression changes following exposure to pesticides and environmental stressors using *Caenorhabditis elegans* as a model

Authors: *K. M. RALEY-SUSMAN, E. WHIDDEN, M. RODMAN, C. HARDMAN
Biol., Vassar Col., Poughkeepsie, NY

Abstract: *C. elegans*, a powerful model organism for nervous system development and behavior, is an important soil nematode and, as such, is frequently exposed to a host of environmental stressors like thermal stress. In addition, a growing combination of pesticides in a variety of commercial formulations contaminate most soil and aquatic environments, creating a risk for non-target organisms including nematodes. We examined the effects of thermal stress alone and together with pesticide exposure on *C. elegans* growth, lifespan, behaviors and gene expression of the stress gene, *hsf-1*. We evaluated responses to imidacloprid, alone and in a commercial formulation called “Tree and Shrub.” Imidacloprid is a neonicotinoid insecticide directed at the insect acetylcholine receptor. It acts as an agonist, specific for the insect isoform of the nicotinic ACh receptor, leading to CNS dysfunction that results in disruption of behaviors like navigation that might be involved in honey bee colony collapse. Recent work has

demonstrated unexpected toxic effects on non-target organisms, including nematodes. We also examined the interactions between pesticide exposure and avocado oil as a possible mitigator of pesticide damage. Neither imidacloprid nor the commercial formulation was lethal to *C. elegans*. However, growth was reduced and *C. elegans* exposed to the oxidative stressor paraquat exhibited dysfunction in behaviors like pharyngeal pumping, which is crucial for feeding and survival. Paraquat is an herbicide with known effects in non-target organisms, causing substantial lethality in *C. elegans* after a 48 hr exposure in young adulthood. Aging nematodes exposed as young adults to paraquat exhibited a greater age-dependent reduction in pharyngeal pumping rate. Surprisingly, our results suggest that avocado oil significantly enhanced the pharyngeal pumping deficit in day 7 and day 10 nematodes, particularly in conjunction with paraquat exposure. Our results provide additional support for the enhanced vulnerability to environmental stressors resulting from even short duration exposure to pesticides.

Disclosures: E. Whidden: None. **M. Rodman:** None. **C. Hardman:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.06/Q13

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIEHS RO1ES022936

Title: Deciphering the ASK1 phosphorylation code used to trigger downstream signaling cascades

Authors: *A. M. PALUBINSKY[1], B. N. LIZAMA[1], D. SZYMKIEWICZ[2], M. V. GARRETT[2], J. W. MCLAUGHLIN[3], B. A. MCLAUGHLIN[2]
[1]Vanderbilt Brain Inst., [2]Neurol., [3]Marino Fndn. Summer Scholar, Vanderbilt Univ. Med. Ctr., Nashville, TN

Abstract: Apoptosis signal regulating kinase 1 (ASK1) is an essential mediator of cell survival in response to oxidative, environmental and inflammatory stress. Given the large size (155kDa) and ubiquitous expression, we hypothesized that ASK1s ability to effect changes in viability, proliferation, transcription and signaling was dependent upon novel protein partners and phosphorylation status. Identifying protein interactions and post-translational modifications provides a unique opportunity to understand how this redox-activated protein kinase affects cell survival in a discrete and systematic manner. Using shotgun and targeted mass spectrometry to catalogue ASK1 protein-protein interactions, we previously identified 14 proteins that undergo dynamic shifts in ASK1 association when exposed to the proteotypic lipid electrophile, HNE.

This data demonstrates that ASK1 signalosomes are much smaller and more exclusive than previously thought. Moreover, it suggests that the dozens of putative phosphorylation sites within the protein may play a greater role than expected. Only three ASK1 phosphorylation sites have been tied to functional outcome. Our screens revealed 12 previously unknown phosphorylation sites that are dynamically regulated by stress. We generated phospho-specific antibodies to four of these sites (Tyr140, Ser966, Ser1004 and Ser1059). Here, we present data demonstrating activation of ASK1 based on phosphorylation events at these novel sites in primary neuronal cultures and cell lines. Cells were exposed to short periods of oxidative or electrophilic stress and phosphomapping was performed for ASK1 as well as the downstream effector molecules p38, JNK and ERK. Using immunocytochemistry, we also present data characterizing the cellular localization of phospho-specific pools of ASK1 at baseline and in response to stress. Taken together, our data reveal an ASK1 phosphorylation code that may provide a targeted approach for generating therapeutics to promote cell survival over cell death in response to environmental stress.

Disclosures: A.M. Palubinsky: None. **B.N. Lizama:** None. **D. Szymkiewicz:** None. **M.V. Garrett:** None. **J.W. McLaughlin:** None. **B.A. McLaughlin:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.07/Q14

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: BARDA

Title: Gene expression profiling of multiple brain as well peripheral regions in rodent model of soman exposure

Authors: A. GAUTAM[1], L. S. NAIDU[2], D. GETNET[1], S. MILLER[2], D. DONOHUE[3], *J. L. MEYERHOFF[4], F. ROSSETTI[5], C. SCHULTZ[6], R. HAMMAMIEH[1], L. A. LUMLEY[7], M. JETT[8]
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Abstract: Soman (GD) is a potent organophosphate acetylcholinesterase (AChE) inhibitor that increases levels of acetylcholine and can lead to cholinergic crisis, including seizures and convulsions which, if left untreated, can lead to death. This issue is of increasing concern for both military and civilian populations Developing methods for detection and treatment requires understanding the acute and chronic effects of GD. Accordingly, we assessed the changes in patterns of gene expression associated with soman exposure and resultant seizure activity in rats. Adult male Sprague-Dawley rats were exposed to subcutaneously adminsistered soman, with or without medical countermeasures (atropine, HI-6, diazepam). Seventy-two hours after exposure, samples were collected from heart, kidney, liver, lung, spleen, and brain regions, (amygdala, hippocampus, hypothalamus, piriform cortex, medial prefrontal cortex, parietal cortex, and thalamus). RNA was extracted from each tissue and quantified on whole genome microarrays. Expression patterns demonstrated significant differences between animals that seized vs those that did not. The magnitude of gene expression changes across tissue types mapped closely to previously characterized patterns of histopathological damage, with the most significant changes occurring in the piriform cortex. Those dysregulated genes associated with seizure activity exhibited enrichment in several cellular functions including protein binding, cell division, phosphorylation, and the immune/inflammatory response. These patterns were generally well conserved across those tissues that exhibited robust histopathologic effects of seizure activity, namely amygdala, hippocampus, and piriform. In the liver, seizing animals showed significant downregulation of genes involved in the oxygen reduction process. Ongoing work will fully characterize the genes and pathways altered by soman exposure, especially those associated with soman-induced seizure responses across different organs to identify genes and pathways which might have diagnostic, prognostic, or exposure surveillance utilities. Disclaimers: Research was conducted in compliance with the Animal Welfare Act, and all other Federal requirements. The views expressed are those of the authors and do not constitute endorsement by the U.S. Army.

Disclosures: A. Gautam: None. **L.S. Naidu:** None. **D. Getnet:** None. **S. Miller:** None. **D. Donohue:** None. **J.L. Meyerhoff:** None. **F. Rossetti:** None. **C. Schultz:** None. **R. Hammamieh:** None. **L.A. Lumley:** None. **M. Jett:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.08/R1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CONACyT Grant 241655

Title: Nrf2 activation in the striatum after quinolinic acid administration is an oxidative stress independent process. Participation of p62 and DPP3 proteins

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Abstract: Nrf2 is a transcription factor involved in the defense against oxidative stress in homeostatic cells, Keap1 mainly regulates Nrf2 levels by its sequestering, ubiquitination and proteosomal degradation; however in non-homeostatic conditions, Nrf2 is activated by different stimuli increasing its nuclear translocation and inducing the expression of antioxidant enzymes and detoxified proteins. There are two mechanisms involved in Nrf2 activation, the canonical and non-canonical pathway. In the canonical pathway electrophilic compounds induce Nrf2 activation by oxidation of some cysteine residues in Keap1. On the other hand in the non-canonical pathway the Keap1-Nrf2 interaction is disrupted by direct interaction of Keap1 with some proteins such as p62, DPP3, WTX and others, inducing Nrf2 stabilization and activation. It has been reported that DPP3 and p62 are able to induce Nrf2 activation in IMR-32 human neroblastoma cells; however, in an *in vivo* model this has not been studied, for this reason we evaluated the participation of DPP3 and p62 on the Nrf2 activation though the non-canonical pathway in the quinolinic acid (QUIN) model, an excitotoxic molecule associated with the pathophysiology of neurodegenerative disorders, as a possible pharmacological target. We administrated 1 µL of isotonic saline solution or QUIN at different doses (15, 30, 60, 120 and 240 nmol) in the right striatum of male Wistar rats (260-300 g), and the striatum were extracted 30 min after injection. We evaluated Nrf2 activity by ELISA assay, and the oxidative stress by GSH/GSSG ratio, DHE assay and activity of antioxidant enzymes. Nrf2, Keap1, p62 and DPP3 levels were measured using western blot and cellular localization of Nrf2 and p62 by immunofluorescence. Finally we evaluated Keap1-DPP3 and Keap1-p62 interaction by immunoprecipitation. QUIN administration increased Nrf2 activation in striatum at 30 min, without increasing ROS production or modifying the redox cellular state. An increase in p62, Nrf2 and Keap1 nuclear levels were observed. Additionally the interaction between Keap1 and DPP3, and Keap1 and p62 increased 30 min after QUIN administration. Finally we found that this process is carried out in striatal neurons. Our results show that *in vivo*, p62 and DPP3 activate the Nrf2 pathway through the non-canonical pathway in striatal neurons.

Disclosures: C.A. Silva: None. **M.E. Chánez-Cárdenas:** None. **D. Barrera-Oviedo:** None. **M.E. Ibarra-Rubio:** None. **P.D. Maldonado-Jiménez:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.09/R2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH

Title: Excitotoxic cell death inducing megachannel within the ATP synthase: Mitochondrial permeability transition pore?

Authors: *N. MNATSAKANYAN[1], H.-A. PARK[2], J. WU[1], B. MURTISHI[1], P. MIRANDA[3], E. A. JONAS[1]
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Abstract: Mitochondrial permeability transition (mPT) is one of the main causes of necrotic and apoptotic cell death during neurodegenerative diseases and stroke. The opening of the mitochondrial permeability transition pore (mPTP) leads to mitochondrial inner membrane permeabilization and dissipation of membrane potential, followed rapidly by cell death. Despite the vital importance of mPTP in controlling cell life and death pathways, the molecular structure and identity of mPTP is not yet fully understood. We have growing evidence that F_1F_o ATP synthase c-subunit ring forms a large conductance ion channel the gating of which is performed by the F_1 hydrophilic portion of ATP synthase. We observed significant decrease in ATP synthase F_1 subunit levels under glutamate-induced excitotoxic conditions, which is prevented by the mPTP inhibitor cyclosporine A. This suggests that structural disassembly of ATP synthase subdomains unmasks the c-subunit channel, placing mitochondria at increased risk for permeability transition. We have now generated a mutant c-subunit channel with a markedly reduced conductance that we find protects from excitotoxic death of hippocampal neurons. In addition, in our recent studies we have successfully overexpressed and purified human ATP synthase c-subunit from *E. coli*, free of any potential contamination by other mitochondrial proteins. When human c-subunit purified from *E. coli* is reconstituted into artificial lipid bilayers, recordings reveal a large multi-conductance channel with the biophysical characteristics of mPTP. We are currently studying the role of c-subunit leak channel in mPT by using ATP synthase c-subunit CRISPR knockdown and knockout mouse embryonic stem cells. We find that ATP synthase c-subunit CRISPR knockdown cells have significantly smaller conductance channel activity compared with the wild type cells. These findings will provide us with an increased understanding of the molecular composition and structure of mPTP.

Disclosures: N. Mnatsakanyan: None. **H. Park:** None. **J. Wu:** None. **B. Murtishi:** None. **P. Miranda:** None. **E.A. Jonas:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.10/R3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Methylmercury (MeHg)-induced neuronal cell death via unfolded protein response

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Abstract: [Background]
MeHg known as a causative factor of Minamata disease induces neuronal cell death and damage the central nervous system, but the mechanism is poorly understood. Previously, we reported that MeHg induces S-mercuration at cysteine 383 or 386 in protein disulfide isomerase (PDI), and this modification induces the loss of enzymatic activity. Because PDI is a key enzyme for the maturation of nascent protein harboring a disulfide bond, the disruption in PDI function by MeHg results in endoplasmic reticulum (ER) stress via the accumulation of misfolded proteins. However, the effects of MeHg on unfolded protein response (UPR) sensors remain unclear. In the present study, we examined whether UPR is regulated by MeHg.
[Methods]
To investigate the activations of UPR sensors and downstream signaling by MeHg stimulation, we used western blot analysis and RT-PCR. To measure apoptosis cells induced by MeHg, we assessed the chromosomal condensation using the fluorescent dye Hoechst 33342.
[Results]
We found that MeHg activates protein kinase RNA-like endoplasmic reticulum kinase (PERK) and activating transcriptional factor 6 (ATF6) branches. Although phosphorylated inositol-requiring enzyme 1α (IRE1α) was detected, MeHg did not induce the cytosolic splicing of immature x-box binding protein 1 (XBP1) mRNA (a selective substrate of IRE1α). Then, the IRE1α-null MEFs were transfected with vectors encoding wild-type hemagglutinin (HA)-tagged IRE1α or cysteine mutants. MeHg-induced inhibition of IRE1α endonuclease activity was significantly ameliorated in the MEFs that expressed IRE1α cysteine-to-serine mutant (C931S). These results suggested that cysteine 931 in IRE1α could be a predominant target of MeHg. A

previous study has shown that the IRE1α-XBP1 branch functions as an anti-apoptotic pathway. In contrast, the PERK/ATF6 branches are involved in the induction of cell death. Therefore, these signals may be implicated in the MeHg-induced loss of cell viability. Indeed, treatment with GSK2606414, a specific PERK inhibitor, significantly attenuated MeHg-induced cell death. [Conclusions]
We demonstrated that MeHg disrupts anti-apoptotic signaling based on the IRE1α-XBP1 branch and simultaneously promotes pro-apoptotic signaling via the PERK/ATF6 branches. These findings may be utilized in the development of novel therapeutic approaches for MeHg-induced neurotoxicity.

Disclosures: H. Hiraoka: None. **K. Nakahara:** None. **M. Fujimura:** None. **Y. Kumagai:** None. **T. Uehara:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.11/R4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF-2015R1D1A1A01061219
18-BR-02-01

Title: O-GlcNAc modification of CHFR modulates neuronal survival by controlling its ubiquitin ligase activity

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Abstract: O-GlcNAc modification (also known as O-GlcNAcylation) is a dynamic posttranslational modification which is associated with neurodegenerative diseases and implicated in neuronal death. However, it still remains elusive how O-GlcNAcylation contributes to neurodegeneration. Here, we employed CHFR (Checkpoint with FHA and RING finger domains) ubiquitin ligase as a model protein to unveil the effect of O-GlcNAcylation on the protein function and neuronal survival. CHFR is a checkpoint protein and a tumor suppressor that plays an important role in cell cycle progression and is known to regulate protein deacetylases which are crucial for neural development and neuronal health. We have shown that CHFR interacts with and destabilizes SIRT1 by ubiquitylation and subsequent proteolysis. We found that CHFR is modified with O-linked N-acetylglucosamine (O-GlcNAc) by OGT (O-GlcNAc transferase) at the N-terminal region and this was further validated by mass

spectrometric analysis. Since CHFR protein levels are controlled by its auto-ubiquitination activity, we examined the half-life of CHFR wild-type (WT) and O-GlcNAcylation-defective mutant to investigate the effect of O-GlcNAcylation on its activity. The O-GlcNAcylation-defective mutant of CHFR was less stable than CHFR WT, suggesting that O-GlcNAcylation of CHFR may decrease its Ub-ligase activity. Upon oxidative stress, CHFR was destabilized and neuronal apoptotic death was prominent. Taken together, our results indicate that O-GlcNAcylation modulates its Ub-ligase function of CHFR and play important roles in neuronal stress response pathway.

Disclosures: M. Kim: None. **J. Seo:** None. **J. Seol:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.12/R5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Function of novel S-nitrosylated proteins identified by biotin switch method with LC-MS/MS analysis

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Abstract: Nitric oxide (NO) is a key signaling molecule that exerts diverse physiological effects via S-nitrosylation, a reversible type of post-translational modification that affects activity, localization, and stability of proteins. Comparable to protein phosphorylation, S-nitrosylation is regulated precisely in time and space. To date, a number of targets of S-nitrosylation have been identified and linked to functional consequences. Many reports have demonstrated the dynamic regulation of protein function by reversible modification; they play a pivotal role in physiological and pathophysiological functions. Previously, we found some S-nitrosylated protein including protein disulfide isomerase and IRE1 that play a crucial role in the pathogenesis of neurodegenerative diseases, including Alzheimer's and Parkinson' diseases. In the present study, we attempted to isolate S-nitrosylated proteins by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS).
To identify novel S-nitrosylated proteins and the modification sites, we prepared extracts from cells treated with NO donor (S-nitrosocysteine, SNOC) and specifically labeled with biotin. Next, we pulled down the biotinylating proteins using streptavidine beads. Then, the trypsinized samples were subjected to LC-MS/MS.
We detected several known S-nitrosylated proteins such as glyceraldehyde-3-phosphate

dehydrogenase (GAPDH), peroxiredoxin-4 and peroxiredoxin-6. In addition, we succeeded to identify some novel S-nitrosylated proteins including inosine-5'-monophosphate dehydrogenase 2 (IMPDH2). We examined the effect of S-nitrosylation on IMPDH2 activity. Unfortunately, its enzymatic activity of IMPDH2 was not affected by SNOC treatment. This result indicates that IMPDH2 is not regulated by S-nitrosylation. We are now examining the role of S-nitrosylation in other target proteins.

Disclosures: K. Nakahara: None. **H. Hiraoka:** None. **A. Ito:** None. **T. Uehara:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.13/R6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Comprehensive gene expression analysis and neurotoxicity testing of human iPSC derived neural progenitor cells and neurons

Authors: *L. P. JACOB, H. DESAI, M. SPENCER, D. YIN
ATCC, Gaithersburg, MD

Abstract: Human induced pluripotent stem cells (iPSC)-derived neural progenitor cells (NPCs) and neurons are an attractive *in vitro* model to study neurological development, neurotoxicity and to model diseases. However, there is a lack of validated NPCs and media that support differentiation into multiple types of neurons for disease modeling, drug screening, and toxicity screening. Here, we investigated the expression of genes associated with the differentiation of NPCs during three weeks in dopaminergic differentiation media. Known early neuron markers, MAP2 and Tuj1 genes reached peak expression at two weeks while expression of dopaminergic neuronal genes (TH, Nurr1, VMAT2, AADC) was significantly increased in a time-dependent manner ($p < 0.05$) in two types of normal NPCs. Furthermore, expression of genes associated with GABAergic (GABRB3) and glutamatergic (vGLUT1, vGLUT2, GLS2) neurons was also induced and peaked at the end of three weeks. This shows that our NPCs and dopaminergic differentiation media are capable of producing GABAergic and glutamatergic neurons, in addition to dopaminergic neurons. To validate that our NPCs and dopaminergic neuron differentiation media are suitable for drug screening, we conducted neurotoxicity screenings in three types of NPCs (non-reporter NPCs, MAP2-NanoLuc-HaloTag reporter NPCs, and Parkinson's disease NPCs) and NPCs-derived neurons using Reliablue™ cell viability reagent assay and high content imaging analysis. We found that paclitaxel, a microtubule-stabilizing chemotherapeutic agent, significantly induced neurotoxicity ($p < 0.001$) in the three types of NPCs evaluated, but not in NPC-derived neurons. Vincristine, amiodarone, and chlorhexidine

significantly decreased viability of both NPCs and neurons, whereas piperine, cisplatin, and hydroxyurea did not induce any significant neurotoxicity in either NPCs or neurons. This study demonstrates that our iPSC-derived NPCs and dopaminergic differentiation media are suitable for studying neurological development and neurotoxicity screening.

Disclosures: L.P. Jacob: None. **H. Desai:** None. **M. Spencer:** None. **D. Yin:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.14/R7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: 1R21NS097899

Title: Cross talk between ER and mitochondria in hypoxia adaptation in Andeans

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Abstract: Chronic mountain sickness (CMS) is a disease that potentially threatens a large segment of high-altitude population (more than 100 million highlanders) that has been living at above 2500m for an extended period. Patients with CMS suffer from severe hypoxemia, excessive erythrocytosis and neurologic deficits including migraine, headache, and mental confusion. The mechanisms underlying CMS neuropathology remain unknown. Our previous studies have shown that iPSC-derived CMS neurons have fragmentated mitochondria, decreased ATP level and increased susceptibility to cell death under stress. Genome analysis from the same population identified several genes including C-Jun activation domain-binding protein 1 (JAB1, also called COPS5) and suggested that such genes play an important role in hypoxia adaptation. JAB1 is known to a) act as a modulator of intracellular signaling and to affect cellular proliferation and apoptosis and b) participate in unfolded protein responses by association and disassociation with IRE1, one of three major pathways under endoplasmic reticulum (ER) stress. Since the ER forms physical contacts with mitochondria through mitochondria-associated membranes (MAM) and several genes such as VDAC and MFN2 located in MAM were decreased in expression in CMS neurons, we hypothesized that 1) ER-mitochondrial contacts and signaling regulation may contribute to CMS phenotype; 2) altered binding activity between JAB1 and IRE1 may lead to an increased ER stress through activation of IRE1 pathway in CMS neurons. Our preliminary data showed that increased Grp78 and phos-PERK expression in CMS

neurons as compared to non-CMS neurons, suggesting an increased ER stress in CMS neurons. Further studies are ongoing to investigate which specific ER stress signaling pathway is involved and whether the binding activity between IRE1 and JAB1 is a contributing factor of ER stress in CMS neurons.

Disclosures: H. Zhao: None. **G.C. Sieck:** None. **G. Haddad:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.15/R8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: CONACyT, Mexico Grant 000000000261323

Title: Oxidative stress markers in brain rats exposed to KA and PTZ: An immunohistochemical study

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Abstract: Epilepsy is a neurological disorder characterized by recurrent spontaneous seizures due to an imbalance between cerebral excitability and inhibition, with a tendency towards uncontrolled excitability. Two main types of epilepsy are generally recognized, mesial temporal lobe epilepsy (MTLE) and lateral temporal lobe epilepsy (LTLE). Epilepsy has been associated with oxidative and nitrosative stress due to prolonged neuronal hyperexcitation and loss neurons during seizures. Experimental animals models report level ATP diminished, increase on lipid peroxidation, catalase and glutathione altered activity in brain. The aim of this study was examines the immunohistochemical expression of oxidative stress markers such as: 4-Hidroxynonenal (4-HNN) Catalase (CAT), Glutathione peroxidase (GPx) and Super Oxide Dismutase 1 (SOD1) in rat brains treated with KA and PTZ considered animal models of epileptic seizures. Evident immunoreactivity of GPx, SOD and CAT was observed mainly in astrocytes and neurons of hippocampal brain region in rats exposed at KA similar results was observed in rats treated with PTZ at the first hours, the quantitative analysis is in process. These preliminary results provide evidence supporting the role of activation of antioxidant systems pathway Nrf2 against oxidative stress effects in experimental models of epileptic seizures.

Disclosures: M. Mendez-Armenta: None. **M. Munguía-Martínez:** None. **C. Nava-Ruíz:** None. **A. Ruíz-Díaz:** None. **M. Díaz-Ruíz:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.16/R9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: FONDECYT 1181243
; CMA BIO BIO, PIA-CONICYT, ECM-12

Title: Neuronal necroptosis is induced by vitamin C oxidation

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Abstract: Vitamin C is found in two states: reduced ascorbic acid (AA) and oxidized dehydroascorbic acid (DHA). In pathophysiological conditions, such as cerebral ischemia and reperfusion (IR), AA is oxidized to DHA. Interestingly, IR induces a particular type of cell death called necroptosis, which is characterized by activation of RIPK1, RIPK3 and MLKL. DHA alters neuronal metabolism and induces cell death; however, the pathway is unknown. Here, we propose that vitamin C oxidation and intracellular DHA production induces neuronal death by activation of necroptosis in vitro. The neural lineage cells, N2a and HN33.11, were supplemented with 200µM AA for accumulation of vitamin C. *"Ischemic-like"* oxidative stress was induced by deprivation of glucose and 0.5mM H2O2 for 30 min. A *"reperfusion-like"* condition was induced by leaving cells in complete medium for 3h. Intracellular AA concentration was measured by FRASC method, cell viability by XTT and confocal real-time live-cell microscopy. In addition, 3D reconstructions were performed in Imaris software. Morphology was analyzed by elliptical parameters: oblate, prolate, spherical. Cellular size was analyzed by Bounding-Box tool. Necroptosis was evaluated using necrostain-1 (RIPK1 inhibitor), compound-1 (MLKL inhibitor) and zVAD.FMK (apoptosis control). Characteristics of cell disintegration were analyzed by 4D real-time live-cell confocal-spectral microscopy, using the following fluorescent probes: mitotracker CMXRos (mitochondrial activity), Cellmask (plasma membrane stain and morphology), Hoechst 33342 (integrity of nuclei) and Phalloindin-alexa-488 (integrity of plasma membrane). DHA production induces 50% neuronal death and necroptotic disintegration. Necroptosis inhibition with necrostatin-1 and compound-1 prevents neuronal death. However, apoptosis inhibition with zVAD does not. During necroptosis, live cell imaging shows bubbles formation prior to loss of plasma membrane integrity and cytoplasm

shedding. In conclusion we propose that DHA could regulates activation of necroptosis in neuronal cells *in vitro.*

Disclosures: L.E. Ferrada: None. **F.J. Nualart:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.17/R10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Institute of General Medical Sciences grant 2R01GM20818 to LS

Title: Opioid-induced accumulation of carbonylated protein aggregates in rat brain and blood

Authors: *N. KORNEEVA[1], R. FAN[2], L. SCHROTT[3], T. ARNOLD[4]
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Abstract: Opioids are the most effective drugs commonly prescribed to treat pain. Despite widespread abuse of opioids, we know little about the long-term consequences of chronic use. Recently, concern regarding the effect of chronic opioid exposure on neuronal degeneration has emerged. Toxic effect of opioids has been documented not only for heroin abusers but also for patients with a history of long-term use of prescription opioids. Currently, there is no inexpensive, minimally invasive method to monitor neuronal degeneration. Recently, an increase in protein carbonyl content was found to be associated with the development of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, as well as with cancer and aging. We have developed a method to detect the carbonyl content in protein aggregates in rat blood plasma. Using this method we demonstrated that prolonged oxycodone administration causes an increase in carbonylated protein levels in both rat brain and blood plasma, which correlates with the appearance of biomarkers for neuronal degeneration. We hypothesize that opioid-induced toxicity is associated with the accumulation of insoluble carbonylated protein aggregates in the brain and blood, allowing the level of carbonylated protein aggregates in blood to serve as a biomarker for opioid-induced neuronal degeneration. We also demonstrated that the integrated stress response (ISR) is activated in the brain and blood of animals chronically treated with oxycodone or morphine. The key event in the ISR is phosphorylation of translation initiation factor 2 alpha (eIF2α), which modulates the expression and translation of specific mRNAs important for adaptation to the stress. Activation of the ISR helps cells to cope with

stress and promotes their survival. However, under severe or prolonged stress, over-active ISR may lead to an increase in protein synthesis and accumulation of large molecular protein complexes and cell death. Elevated eIF2α phosphorylation is correlated with neuronal degeneration and has been observed in the brain samples of Alzheimer's disease patients. We hypothesize that over-activated ISR is responsible for the accumulation of toxic protein aggregates in the brain and blood of animals chronically treated with opioids. Detection of protein aggregates in whole blood may serve as a diagnostic tool to monitor drug-induced neuronal degeneration in research and clinical settings.

Disclosures: N. Korneeva: None. **R. Fan:** None. **L. Schrott:** None. **T. Arnold:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.18/R11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NEI RO1EY024481 (PAR)
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NINDS K12NS079414 (CME)
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IDDRC HD018655

Title: The oxidizing thiol reagent 2,2'-dithiodipyridine (DTDP) induces an increase in intracellular mobile zinc in oligodendrocytes, but toxicity is not blocked by zinc chelation

Authors: *C. M. ELITT[1,2], M. ROSS[1], N. W. HODGSON[3], C. J. FAHRNI[4], K. VAN LEYEN[5], E. AIZENMAN[6], P. A. ROSENBERG[1,2]
[1]Neurol., Boston Children's Hosp., Boston, MA; [2]Harvard Med. Sch., Boston, MA; [3]Boston Children's Hosp., Boston, MA; [4]Sch. of Chem. and Biochem. and Petit Inst. for Bioengineering and Biosci., Georgia Inst. of Technol., Atlanta, GA; [5]Massachusetts Gen. Hosp., Charlestown, MA; [6]Neurobiology/PIND, Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA

Abstract: Oxidative stress plays an important role in white matter injury in preterm infants, in stroke in adults, and in multiple sclerosis. We have previously demonstrated that mature oligodendrocytes (OLs) treated with peroxynitrite undergo a pathway of non-apoptotic cell death involving increase in intracellular free zinc, ERK1/2 phosphorylation, 12/15-lipoxygenase activation, and generation of reactive oxygen species (Zhang et al., *Journal of Biological Chemistry*, 2006). Similarly, the oxidizing thiol reagent 2,2'-dithiodipyridine (DTDP), which induces zinc release from metallothioneins, has been shown to induce a programmed cell death

pathway in neurons. DTDP has the advantage over peroxynitrite as an oxidative stress agent of being more stable and more specific in its actions. Therefore, we tested its effects in OLs. Developing OLs were prepared from P2 rat glial cultures using selective detachment and plating of isolated OLs. Stage-specific cultures were produced by using FGF and PDGF in serum free medium for developing OLs, and T3 and CNTF for mature cells, according to published methods. Using chromis-1, a recently published ratiometric zinc probe (Bourassa et al., *ACS Sensors*, 2018), we first confirmed that 100uM DTDP causes a robust increase in free zinc in both developing and mature OLs within minutes. We next assessed DTDP toxicity. Developing and mature OLs were treated with a brief 10 minute exposure to 100uM DTDP and survival was assessed after 20-24 hours using the Alamar Blue cell viability assay. In contrast to OL death following peroxynitrite exposure that can be blocked using the high-affinity zinc chelator N,N,N',N'-tetrakis (2-pyridylmethyl) ethylenediamine (TPEN), OL toxicity in response to DTDP could not be blocked by 10uM TPEN. Furthermore, inhibition of other targets in the cascade activated by peroxynitrite in OLs or DTDP in neurons, including ERK1/2 and 12/15-lipoxygenase, had no effect on OL survival in response to DTDP. Because the redox potential in OLs is highly dependent on glutathione, we hypothesized that there could be differential effects using DTDP compared to peroxynitrite as an explanation for the different types of cell death observed with these two agents. However, there was no significant change in GSH/GSSG ratio in response to DTDP or peroxynitrite . In summary, although peroxynitrite produces programmed cell death in OLs that can be interrupted at several downstream steps, DTDP appears to produce unregulated OL toxicity. Further studies into the mechanism by which OLs respond to oxidative stress induced by DTDP are warranted, as elucidating death pathways may provide a strategy to prevent white matter injury.

Disclosures: C.M. Elitt: None. **M. Ross:** None. **N.W. Hodgson:** None. **C.J. Fahrni:** None. **K. van Leyen:** None. **E. Aizenman:** None. **P.A. Rosenberg:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.19/R12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant EY027881
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NIH Grant HD018655

Title: Astrocytes determine pathway of cell death triggered by oxidative stress in neurons

Authors: *M. ROSS[1], C. M. ELITT[1], N. W. HODGSON[1], K. A. HARTNETT[2], K. VAN LEYEN[4], C. J. FAHRNI[5], E. AIZENMAN[3], P. A. ROSENBERG[1]
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Abstract: Understanding how oxidative stress contributes to the pathogenesis of chronic neurodegenerative diseases is of critical importance. One well-characterized neurodegenerative pathway studied in vitro involves increase in free zinc, p38 phosphorylation, enhancement of potassium channel-mediated currents, and caspase activation following exposure to the thiol oxidant 2,2'-dithiodipyridine (DTDP) . Previous studies left ambiguous the role of astrocytes in execution of this neuronal programmed death pathway. To investigate this issue, we compared the effect of DTDP on neurons grown in astrocyte rich (AR) and astrocyte poor (AP) cultures derived from embryonic rat forebrain. We used a ratiometric zinc sensor, chromis-1, to confirm that brief DTDP exposure causes a rapid increase in intracellular free zinc in AP neurons. Similar to previous studies, DTDP was toxic to neurons in both AR and AP cultures. A 10 minute exposure to 75 μM DTDP reduced neuronal survival in AR cultures to 14 ± 4%. Zinc chelation with the high-affinity zinc chelator N,N,N,N',N'-tetrakis (2-pyridylmethyl) ethylenediamine (TPEN; 3 μM) increased neuronal survival to 58 ± 1% ($p<0.0001$), confirming previously published results. We also newly identified 12/15-lipoxygenase as a target in the programmed death pathway activated by DTDP in AR cultures, providing additional evidence for the programmed nature of neuronal death in the presence of astrocytes. Inhibition of 12/15-lipoxygenase increased neuronal survival in AR cultures following DTDP exposure to 49 ± 4% compared to DTDP alone ($p<0.0001$). In contrast, TPEN, 12/15-LOX inhibitors, tetraethylammonium, and caspase inhibitors offered no protection in AP cultures exposed to DTDP. These results suggested that neuronal death in AP cultures is unprogrammed or follows a different program yet to be discovered. Interestingly, in contrast with these results obtained using DTDP in neuronal cultures, peroxynitrite has been reported to cause neuronal death in AP cultures that is programmed and involves elevation of free zinc, activation of 12/15-LOX, and p38 kinase activation. We considered and were able to exclude three possible mechanisms to explain astrocyte dependence for programmed neuronal death induced by DTDP: (1) excitotoxicity, since neurons in cultures without astrocytes are much more sensitive to glutamate excitotoxicity than in cultures with astrocytes, (2) astrocytic metabolism of DTDP, or (3) catastrophic collapse of intracellular GSH levels. Future studies will investigate other possible mechanisms by which astrocytes may influence the pathways of neurodegeneration in the setting of oxidative stress.

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Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.20/R13

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: EDCHP106007
EDAHI107004

Title: The effects of alcohol on neurons, glial cells and memory function in rats

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Abstract: Alcohol (EtOH) is considered to be one of the most commonly abused chemical. Excessive alcohol consumption induces damage to neurological function including change of neuroinflammatory response and impairment in normal learning and memory function. It is known that neuroinflammation is an important factor in neurodegeneration, and the activation of glial cells (including astrocytes and microglial cells) may play the key role. Alzheimer's disease (AD) is the most common neurodegenerative disorder. It is associated with neuroinflammatory response, too. Evidence indicated that ethanol exposure induced microglial abnormal activation to release TNF-α and nitric oxide (NO) and decreased the number of neurons in mice brain. However, some data indicated that the microglial activation was not equivalent to neuroinflammation in EtOH-induced neurodegeneration. Even though glial cells are very important constituents in the brain, but investigation of the effects on EtOH in glial cells are not clear. In this study, we wanted to estimate the role of glial cells and the changes of behavior following alcohol exposure in rats. Male SD rats fed with various concentration of alcohol for 1 week (Day 1 and 2: 1 %; Day 3 and 4: 5 %; Day 5, 6 and 7: 10 % alcohol). The diet of rats was restricted in order to decrease 20 % body weight. Then we started operating the behavioral experiment and estimated the memory functions by 8 arm maze. Rats were sacrificed after about 1 month and prepared brain section for immunocytostaining. Our data indicated that the latency time of alcohol group was longer at Day 3, 7 and 11 than control group. The memory task (total time) was significantly increased in alcohol group at Day 2, 3, 4 and 6. The total working memory error (WME) and working reference error (WRE) were increased in alcohol group, too. The results of immunocytostaining of brain revealed that the number of neuron and astrocyte were decreased significantly in prefrontal cortex and hippocampus (CA1); however, the activation of microglial cells and the expression of iNOS were increased significantly. We

suggested that alcohol will impair the normal memory function via induced the microglial cells activation.

Disclosures: J. Wang: None. **S. Chen:** None. **C. Chen:** None. **C. Yang:** None. **S. Yang:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.21/R14

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grants AG022550 and AG027956 from NIH/NIA, RR027093 from NIH/NCRR and EY022774 from NIH/NEI (PK)

Title: Chronic oxidative stress primes glial cells to generate exaggerated cytokine expression after secondary TLR4 activation

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Abstract: Objective: to determine whether exposure of C6 glioma cells to chronic oxidative stress enhances toll-like receptor 3 (TLR3)- and toll-like receptor 4 (TLR4)-mediated expression of inflammatory markers.
Background/Rationale: Oxidative stress occurs in many neurodegenerative diseases contributing to neuronal damage and death. Chronic oxidative stress in the CNS is associated with other pathophysiological events including excitotoxicity and glial-mediated neuroinflammation. The vulnerability of neurons to inflammatory mediators generated by TLRs, such as proinflammatory cytokines, makes targeting of cytokine-expressing glia a promising therapeutic strategy.
Hypothesis: We hypothesized that exposure of C6 cells to sublethal concentrations of the lipid peroxidizer, tert-butylhydroperoxide (tBHP), for 72 hours leads to a potentiation of TLR3- and TLR4- mediated nuclear factor kappa B (NFkB) and pro-inflammatory cytokine expression above that of control conditions.
Methods: C6 cells were grown on glass coverslips and exposed to 10μM tBHP for 72 hours to induce chronic sublethal oxidative stress. Cells not exposed to oxidant were used as controls. Cells in both the control and tBHP-exposed groups were treated for 2 – 6 hrs with the TLR3 ligand polyinosinic:polycytidylic acid (pI:C) or the TLR4 ligand lipopolysaccharide (LPS). Cells were fixed with paraformaldehyde and immunocytochemistry was carried out to label TLR3, TLR4, NFkB and interleukin-1 beta (IL-1β). Samples were imaged using a Leica SPX5 laser scanning confocal microscope. Image-J software was used to conduct microfluorimetric analysis.

Data are expressed as normalized integrated density.
Results: Exposure of cells to tBHP, itself, led to a 30% decrease in cell proliferation and a 2-fold and 5-fold increase in NFkB and IL-1beta immunoreactivity, respectively. Treatment of cells with LPS 72hr after onset of tBHP exposure led to a 60% decrease in cell number and an additional 2-fold increase in TLR4-induced NFkB expression and an additional 4-fold increase in IL-1beta expression. In addition, chronic tBHP exposure alone increased TLR3- and TLR4-induced TLR3/4 immunoreactivity, suggesting that oxidative stress causes a positive feedback loop for inflammatory signaling.
Conclusions: Chronic oxidative stress reduces C6 cell proliferation and potentiates TLR4-mediated NFkB and pro0inflammatory cytokine expression. Reducing oxidative stress may reduce subsequent neuroinflammation in the CNS. Furthermore, TLR4 inhibition may be a promising therapeutic strategy for combating neurodegenerative diseases where oxidative stress plays a major role.

Disclosures: R.S. Duncan: None. **P. Koulen:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.22/R15

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIAAA AA011605
NIAAA AA020024

Title: Ethanol induces interferon signaling in astrocyte and neuronal cell lines

Authors: *C. J. LAWRIMORE, L. G. COLEMAN, F. T. CREWS
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Abstract: I**ntroduction**: Excessive ethanol (EtOH) consumption causes innate immune signaling in brain that is linked to alcohol use disorders. Previously, we found that EtOH activates pro-inflammatory signaling in SH-SY5Y neurons and BV2 microglia, including toll-like receptor (TLR) 7, a key inducer of interferon signaling. We also previously found that EtOH increases release of let7b, an endogenous miRNA that activates TLR7, in hippocampal-entorrhinal slice culture. While interferons are also upregulated in post-mortem human alcoholic brain, the role of different cell types in brain in EtOH-induced interferon signaling has yet to be elucidated. **Methods**: SH-SY5Y neurons, U373 astrocytes, and BV2 microglia were treated with EtOH (100mM, 24hr) and cell lysates were analyzed for mRNA expression of various interferons, interferon receptors, and interferon stimulated genes. Data is represented at

%CON±SEM. **Results**: In SH-SY5Y neurons EtOH upregulated IFNβ (272±18%,p<0.001), IFNγ (504±75%,p<0.001), IFNAR1 (344±41%,p<0.001), IFNAR2 (297±21%,p<0.0001), IFNγR1 (461±84%,p<0.01), and IFNγR2 (328±29%,p<0.0001). In U373 astrocytes, EtOH upregulated IFNβ (293±54%,p<0.05), IFNγ (258±38%,p<0.01), IFNAR2 (157±16%,p<0.05), and IFNγR2 (137±10%,p<0.05), however there was no significant effect of EtOH on any interferons examined in BV2. Furthermore, EtOH increased let7b in the media of U373. EtOH-conditioned media from U373 also increased expression of IFNβ (236±32%,p<0.01), IFNγ (233±39%,p<0.01), IFNAR1 (222±24%,p<0.01), and IFNγR1 (186%±31,p<0.05) in SH-SY5Y. In addition, EtOH-conditioned media from U373 increased expression of interferon stimulated genes in SH-SY5Y, such as OASL (170±22%,p<0.05), NGFR (113±4%,p<0.01), and TRAIL (177±17%,p<0.05). TRAIL, which further activates death receptors (DRs) 4 and 5, was also released in the media of EtOH-treated U373. Both DR4 (163±12%,p<0.01) and DR5 (137±7%,p<0.05) were increased by EtOH in SH-SY5Y as well. **Conclusion**: EtOH upregulates interferon signaling in both U373 astrocytes and SH-SY5Y neurons, but not BV2 microglia, suggesting possible astrocyte-neuron interferon signaling. EtOH-conditioned media from U373 activated interferon signaling and interferon stimulated genes in SH-SY5Y, suggesting EtOH causes astrocytes to secrete an interferon-activating mediator. The increase in let7b and TRAIL by EtOH in U373, as well as the corresponding increase in receptors TLR7 and DR4/5 in SH-SY5Y, suggest possible let7b-TLR7 and TRAIL-DR4/5 signaling astrocytes and neurons. Further experiments will explore the roles of these respective pathways.

Disclosures: C.J. Lawrimore: None. **L.G. Coleman:** None. **F.T. Crews:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.23/R16

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant 1R01DA042737

Title: Alcohol produces inflammation to promote enhanced methamphetamine-induced neurotoxicity

Authors: *A. L. BLAKER[1,2], E. A. RODRIGUEZ[1], B. K. YAMAMOTO[1]
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Abstract: Alcohol and methamphetamine (Meth) are often co-abused but the neurochemical consequences of this co-abuse are unknown. Individually, both drugs cause inflammation which

can contribute to adverse effects in the brain. We tested the hypothesis that ethanol (EtOH) drinking would enhance Meth-induced neurotoxicity based on the known inflammatory properties of EtOH exposure. Male Sprague Dawley rats were allowed a 2 bottle choice with intermittent (24 hr on, 24 hr off) access to 10% EtOH or water for a total period of 28d. Twenty-four hr after the last day of drinking, an increase in lipopolysaccharide (LPS, a component of gram-negative bacteria) was detected in the serum and striatum of EtOH-drinking rats (*$p<0.05$ vs. Water). Likewise, EtOH rats displayed increases in the pro-inflammatory mediator COX-2 in the striatum (*$p<0.05$ vs. Water). To investigate the comorbid effects of Meth, a subset of EtOH-drinking rats was exposed to Meth in a binge-like regimen (10mg/kg x 4 inj) one day after the last day of drinking. Two hr after the last Meth injection, pro-inflammatory cytokines IL-1β and CNTF were elevated in the serum of EtOH+Meth rats compared to EtOH or Meth alone (*$p<0.05$ vs. EtOH+Saline and Water+Meth). Furthermore, microglia in the brains of EtOH+Meth rats displayed increased cell body size compared to controls 2h after Meth. Seven days after Meth, dopamine was depleted in the striatum compared to controls (*$p<0.05$ vs. Water+Saline). Interestingly, EtOH alone did not alter dopamine concentrations in the brain but rats that drank EtOH and were then challenged with Meth exhibited an exaggerated depletion of dopamine to 10% of controls (*$p<0.05$ vs. Water+Saline). The synergistic decreases in dopamine were paralleled by decreases in tyrosine hydroxylase immunoreactivity in the substantia nigra pars compacta and deficits in motor function. Finally, we tested the hypothesis that EtOH-mediated inflammation mediates this enhanced neurotoxicity by administering the COX inhibitor ketoprofen during EtOH drinking. COX inhibition blocked the upregulation of cytokines, enhanced dopamine depletions, and motor deficits. These findings show that EtOH drinking can exaggerate the neurotoxic effects of Meth on dopamine neurons and motor behavior through inflammation.

Disclosures: A.L. Blaker: None. **E.A. Rodriguez:** None. **B.K. Yamamoto:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.24/R17

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: (CONACYT Grant No: 219703)
DGAPA IN221417

Title: Effect of oxidative stress on energy metabolism and the expression of HIF-1 caused by ozone exposure

Authors: *A. E. RODRIGUEZ[1], S. L. RIVAS-ARANCIBIA[2]
[1]Univ. Nacional Autonoma de México, City, Mexico; [2]Facultad de Medicina, UNAM, 04510 Mexico DF, Mexico

Abstract: Environmental pollution is a global public health problem. It is known that chronic exposure to environmental pollutants such as ozone, causes a state of oxidative stress. This condition, plays an important role in the development of neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. On the other hand, the hypoxia inducible factor-1 alpha (HIF-1α) increases its expression in response to low oxygen conditions, activating cascades of inflammation through the activation of the nuclear factor *Kapa* B (NF*k*B), as well as its signaling on the proteasome. The objective of this work was to study the effect of chronic oxidative stress, caused by low doses of ozone, on the changes in mitochondrial metabolism, and its relation with the loss of the regulation of the inflammatory response, through the activation of HIF-1α. Ninety male Wistar rats, were divided into 5 groups randomly (n = 18), each group received one of the following treatments: exposed to air without ozone (control group), and groups exposed to ozone for 7, 15, 30 and 60 days respectively. Exposure to ozone was for 4 hours daily at 0.25 ppm. Two hours after the end of the ozone treatment, the animals of each group were divided into three subgroups, were deeply anesthetized and processed for immunohistochemistry techniques and western blot for HIF-1α, NF*k*B, IL-1β. IL-10, IL-17, as well as spectrophotometry technique to determine succinate dehydrogenase activity (SDH) and respiratory activity in isolated mitochondria of the hippocampus. The results indicate changes in the expression of HIF-1α from 7 days to 60 days of ozone exposure and a significant immunoreactivity increase in NF*k*B, IL-1β and IL-17 from 15 to 60 days compared to the control group ($p<0.05$), as well as a decrease in IL-10 ($p<0.05$), also western blot indicate a significant decrease in IL-10 and increases of NF*k*B, IL-1β and IL-17 versus control group ($p <0.05$). The activity of the SDH enzyme presents a decrease from 7 to 60 days of exposure ($p <0.05$), also we found a significant decrease in respiratory activity at 60 days of exposure to this gas versus control group ($p <0.05$). Conclusions: The state of oxidative stress caused by chronic exposure to low doses of ozone, produces deficit in mitochondrial metabolism, activation of HIF-1α, increment in NF*k*B, IL-1β, IL-17 and decrease in IL-10, these alterations explain in part, the loss of the regulation of the inflammatory response present in neurodegenerative diseases such as occurs in Alzheimer's Disease.

Disclosures: A.E. Rodriguez: None. **S.L. Rivas-Arancibia:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.25/R18

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: 2017M3C7A1028949
HI14C1913
HI15C0527
NRF-2016R1E1A1A01941212
2017-084

Title: Zinc dyshomeostasis plays a key role in inflammasome formation in cultured neurons and astrocytes following LPS or OGD exposure

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Abstract: Inflammasome is a protein complex that plays a key role in the initiation of inflammatory response in diverse pathological conditions. In the brain, following acute insults such as ischemia and seizures, neurons and astrocytes form inflammasomes and release cytokines such as IL-1β and IL-18, which trigger microglial activation and inflammation. If excessive, such inflammation may contribute to the expansion of brain lesions. In the present study, we examined the hypothesis that zinc dyshomeostasis, a key mechanism in acute brain injury, mediates inflammasome formation in mixed cell cultures containing neurons and astrocytes. In mouse cortical cell cultures, exposure to LPS induced inflammasome formation, as indicated by increases in the level of NLRP3, ASC, caspase-1, and IL-1β by Western blot assay and immunocytochemistry. At the same time, LPS increased levels of free zinc in neurons and astrocytes. Indicating that rises in zinc levels play a role in inflammasome formation, the membrane-permeant zinc chelator TPEN blocked the increase in levels of NLRP3 and caspase-1, as well as the release of inflammatory cytokines into the media. Conversely, addition of a zinc ionophore, clioquinol, markedly increased the inflammasome formation by LPS. Similar changes were observed in OGD in cortical cultures, a cell model for ischemia. OGD induced zinc dyshomeostasis and inflammasome formation. Modulation of zinc levels altered the extent of inflammasome formation. These results suggest that zinc dyshomeostasis plays a key role in LPS-induced inflammasome formation. The present study for the first time showed that zinc dyshomeostasis plays a role in inflammasome formation in neurons and astrocytes induced by LPS and OGD. In light of evidence that inflammasome formation may contribute to the expansion of brain injury in ischemia, understanding the mechanism of zinc dyshomeostasis and its suppression may help reduce inflammation-related secondary brain injury.

Disclosures: H. Park: None. **J. Koh:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.26/S1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH
UCR Seed Grant
NSF Fellowship

Title: Inhalation allergen exposure decreases basal expression of innate immune molecules in murine brainstem

Authors: *M. J. CARSON[1], J. M. VALDEZ[2], X. PENZ[2], A. MADANY[2], A. BURR[1], J. C. JANG[1], Y. Y. GRINBERG[1], T. M. NORDGREN[1], M. G. NAIR[1], D. COCKER[1], D. D. LO[1]
[1]Div. of Biomed. Sci., [2]Univ. of California Riverside, Riverside, CA

Abstract: Continuous exposure to aerosolized fine (particle size $\leq$ 2.5 μm) and ultrafine (particle size $\leq$ 0.1 μm) particulates can trigger innate inflammatory responses in the lung and brain depending on particle composition. Most studies of manmade toxicants use inhalation exposure routes while most studies of allergens use soluble solutions administered via intranasal or injection routes. Here, we tested whether continuous inhalation exposure to aerosolized *Alternaria alternata* particulates (a common fungal allergen associated with asthma), would induce innate inflammatory responses in the lung and brain. By designing a new environmental chamber able to control particle size distribution and mass concentration, we continuously exposed adult mice to aerosolized ultrafine *Alternaria* particulates for 96 hours. Despite induction of innate immune responses in the lung, induction of innate immune responses in whole brain samples was not detected by qPCR or flow cytometry. However, exposure did trigger decreases in Arginase 1, INOS, and TNFα mRNA in the brainstem-only samples containing the CNS respiratory circuit (the dorsal and ventral respiratory groups, the pre-Botzinger and Botzinger complexes). Additionally, a significant decrease in the percentage of TLR2-expressing brainstem microglia was detected by flow cytometry. Histologic analysis revealed a significant decrease in Iba1 but not GFAP immunoreactivity in both the brainstem and the hippocampus. Together these data indicate that inhalation exposure to a natural fungal allergen under conditions sufficient to induce lung inflammation, surprisingly causes reductions in baseline expression of select innate immune molecules (similar to that observed during endotoxin tolerance) in the region of the CNS controlling respiration.

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Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.27/S2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: MOST 105-2320-B-002 -060 -MY3

Title: The roles of ZNRF1 in neuronal development and neuroinflammation

Authors: *Y.-C. CHANG[1], S.-J. CHOU[2], L.-C. HSU[1]
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Abstract: Neuroinflammation, the inflammatory responses in the nervous system, has emerged as a critical factor in shaping synaptic structure and function. Dysregulation of neuroinflammation has been shown to link to neurodegenerative diseases such as Alzheimer's disease, multiple sclerosis and Parkinson's disease. However, how neuroinflammation contributes to neuronal development and neurodegenerative diseases is still not clear. ZNRF1, a zinc finger/RING finger type E3 ubiquitin ligase, was reported to play an important role in inflammation as it promotes caveolin-1 ubiquitination and degradation to modulate TLR4-triggered inflammation in *in vitro* and *in vivo.* The expression ZNRF1 was found in rat embryonic, adult cerebral cortex and hippocampus, and it was shown to be up-regulated in Schwann cells after peripheral nerve injury to promote Wallerian degeneration and neuronal/axonal degeneration. Based on its expression pattern, and its role in inflammation, we hypothesize that ZNRF1 functions in the central nervous system to regulate neuronal development and neuroinflammation. To test this hypothesis, we generated several *Znrf1* conditional knockout (cKO) mice by crossing *Znrf1* floxed mice with several Cre recombinase-expressing lines to delete *Znrf1* in the nervous system or immune cells. We compared the brain morphology in control and cKO animals at early postnatal stages and found no significant anatomical defects in the *Znrf1* cKO, suggesting that ZNRF1 is not required for the early brain development. To further examine the function of ZNRF1 in neuroinflammation, we employed the experimental autoimmune encephalomyelitis (EAE), a mouse model of human neuroinflammatory disease multiple sclerosis, in control and cKO mice. Our results showed that depletion of ZNRF1 in myeloid cells attenuates EAE development in mice. Our findings indicate

that ZNRF1 may not regulate murine brain development but the function of ZNRF1 in myeloid cell is involved in the development of neuroinflammation.

Disclosures: Y. Chang: None. **S. Chou:** None. **L. Hsu:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.28/S3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DTRA CB3943

Title: Effects of pro-inflammatory pathway inhibition on seizure dynamics in mice exposed to the acetylcholinesterase inhibitor soman

Authors: *E. A. JOHNSON[1], K. LAITIPAYA[1], J. K. CHANDLER[1], D. D. PALMER[1], B. C. LAGER[1], T. M. FERRARA-BOWENS[1], C. L. HONNOLD[2]
[1]Pharmacol., [2]Comparative Pathlogy, US Army Med. Res. Inst. of Chem. Def., Aberdeen Proving Ground, MD

Abstract: Exposure to acetylcholinesterase inhibitors such as soman (GD) can initiate status epilepticus (SE) that can lead to progressive brain damage and behavioral impairment. Current treatments targeting the GABA system can ameliorate GD-induced SE, though treatment effectiveness diminishes rapidly following exposure. Therefore, new treatment strategies that do not rely on the GABA system are needed to reduce seizure activity, tissue loss and cognitive deficits. One strategy involves modulation of the pro-neuroinflammatory response, a prominent feature in GD-induced brain injury, which can exacerbate seizure susceptibility, generation and frequency. We have previously shown that reducing interleukin -1 receptor 1 (IL-1R1), tumor necrosis factor receptor 1A (TNFR1A) signaling or inhibition of both pathways can reduce deleterious physiological effects such as mortality and brain damage after SE. This study focused on whether these changes were related to anticonvulsant, seizure activity modulation or neuroprotective mechanisms. Using knockout mouse strains for IL1R1, TNFR1A and a double IL-1R1/ TNFR1A KO and wild type control strains (C57BL/6J and B6129SF/J), seizure incidence, seizure power and progression, neuropathology, mortality, and other relevant physiological responses were compared. Changes in seizure initiation, seizure incidence and seizure latency were noted between the strains and were most pronounced in strains lacking a functional TNFR1A signaling pathway. Seizure progression and power, however, were similar between all strains tested. Reduced neuropathology was also observed in strains lacking a

functional IL1R1 signaling system. These data suggest that inhibition of specific pro-inflammatory pathways may be a useful addition to standard therapies to treat SE.

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Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.29/S4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: DTRA Grant CB3943

Title: The role of IL-1 signaling in neuroinflammation after soman-induced convulsions and anakinra treatment in mice

Authors: *T. M. FERRARA-BOWENS[1], J. K. CHANDLER[1], C. L. HONNOLD[2], K. LAITIPAYA[1], B. C. LAGER[1], D. D. PALMER[1], M. D. WEGNER[3], E. A. JOHNSON[1,3]
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Abstract: Brain injury resulting from status epilepticus (SE) induced by soman (GD) stimulates peripheral macrophages and leukocytes, and microglia and astrocytes to overexpress neurotoxic cytokines, including interleukin-1 (IL-1), resulting in a neuroinflammatory response. IL-1 binds to the IL-1 receptor (IL-1R1) to initiate IL-1 signaling by activating various kinase pathways, including NFκB, which signals the release of IL-6 and TNFα. The IL-1R1 is inhibited by the IL-1 receptor antagonist (IL-1Ra), which competes with IL-1 for binding to the IL-1R1. Although the presence of IL-1, IL-6, and TNFα has been reported after GD-induced SE, the role of IL-1 signaling in the neuroinflammatory response has not been investigated post exposure in knockout (KO) mice. The purpose of these studies was to determine cytokine expression levels of IL-1, IL-6, and TNFα after GD-induced convulsions in wild type (WT), IL-1R1 KO, and IL-1Ra KO mice, and anakinra treatment in exposed WT mice. Results showed early upregulation of IL-1 followed by later downregulation in the KO strains, as well as IL-1 signaling early and later after anakinra treatment. Additionally, IL-6 upregulation was found between 3 and 12 hours in KO mice, whereas TNFα expression was prominent later in WT mice. These results show the regulatory function of IL-1 regarding neuroinflammation after GD-induced convulsions. Additionally, targeting the IL-1 signaling pathway with anakinra changes cytokine expression, and therefore, the neuroinflammatory response.

Disclosures: T.M. Ferrara-Bowens: None. **J.K. Chandler:** None. **C.L. Honnold:** None. **K. Laitipaya:** None. **B.C. Lager:** None. **D.D. Palmer:** None. **M.D. Wegner:** None. **E.A. Johnson:** None.

Poster

473. Neurotoxicity, Inflammation, and Neuroprotection: Cellular Stress and Death Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 473.30/S5

Topic: C.08. Ischemia

Support: K111923
BO/00327/14/5, to EF
GINOP-2.3.2-15-2016-00060
EFOP-3.6.1-16- 2016-00008

Title: The dihydropyridine derivative LA1011 does not alter the cerebral blood flow response to somatosensory stimulation and spreading depolarization in the intact and ischemic rat cerebral cortex

Authors: *Í. SZABÓ[1], D. P. VARGA[1], Á. MENYHÁRT[1], F. BARI[1], E. FARKAS[1], I. HORVÁTH[2], Z. TÖRÖK[2], L. VIGH[2]
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Abstract: The dihydropyridine derivative LA1011 has been shown to be neuroprotective via modulating cellular stress response in a transgenic mouse model of Alzheimer's disease. In contrast with other well-known dihydropiridines such as nimodipine or nifedipine, LA1011 has no L-type calcium channel antagonistic effect. Here we set out to explore whether LA1011 achieves neuroprotection by improving the efficacy of neurovascular coupling in the intact or ischemic rat cerebral cortex.
Two open cranial windows were prepared over the parietal cortex of isoflurane-anesthetized, adult, male Sprague-Dawley rats (n=44). Local field potential (LFP) and cerebral blood flow (CBF) were recorded from the rostral craniotomy, with the aid of a glass capillary microelectrode and laser Doppler flowmetry. CBF variation was assessed in response to repeated whisker stimulation, and subsequent spreading depolarization (SD) events triggered by 1 M KCl applied in the caudal craniotomy. Experiments were repeated under global forebrain ischemia induced by bilateral common carotid artery occlusion (2-vessel occlusion, 2VO). In the first set of experiments, LA1011 or its vehicle were injected i.p. (n=12, 2x1mg/kg/day/2 weeks). In the second set of experiments, LA1011 or its vehicle were administered topically to the cortical surface (n=32, 100 μM).

LA1011 had no significant impact on baseline CBF, and did not alter the amplitude of hyperemia in response to whisker stimulation (8.0±3.8 pp vs. 6.2±2.9 pp, LA1011 vs. vehicle in 2VO group) or SD (110.9±30.4 pp vs. 150.7±96.5 pp, LA1011 vs. vehicle 2VO group). Yet, LA1011 significantly increased the amplitude of SD in all LA1011 treated groups (19.0±1.9 mV vs. 15.1±2.1 mV, LA1011 vs. vehicle, intact, acute group).
The data suggest that LA1011 exerts no direct effect on neurovascular coupling, but it augments the elicited SDs under all experimental conditions tested. We propose that LA1011 possesses a potential anti-inflammatory effect, which would be consistent with the previously reported reduction of SD amplitude by tumor necrosis factor-alpha.

Disclosures: Í. Szabó: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gedeon Richter Plc. (H-1103 Budapest, Gyömrői út 19-21.). **D.P. Varga:** None. **Á. Menyhárt:** None. **F. Bari:** None. **E. Farkas:** None. **I. Horváth:** None. **Z. Török:** None. **L. Vigh:** None.

Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.01/S6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: EPA Grant 83543401 Project 3
NIEHS P01 ES002848-Project 3
JW partially supported by Brain and Behavior Research Foundation NARSAD Young Investigator Grant

Title: Disruption of developmental neurogenesis and apoptosis by perinatal phthalates in the rat medial prefrontal cortex

Authors: *E. P. SELLINGER[1], C. DRZEWIECKI[2], J. WILLING[3], J. M. JURASKA[3]
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Abstract: The perinatal period is a time when the developing brain is especially vulnerable to environmental insult. One such environmental concern is exposure to phthalates, a class of endocrine-disrupting chemicals used as plasticizers, solvents, and emulsifiers in a variety of products, which results in ubiquitous human exposure. As phthalates can readily cross the placenta and are transferred to offspring through lactation, exposure can occur during early development. Previous work indicates that exposure to an environmentally relevant mixture of phthalates composed of 35.35% DEP, 21.12% DEHP, 15.12% DiNP, 15.10% DBP, 8.16% DiBP, and 5.15% BBP during early development leads to a decrease in neuron number in the

adult rat medial prefrontal cortex (mPFC). Here, we investigate whether phthalate exposure disrupts neurogenesis or apoptosis. Pregnant and lactating rats consumed a cookie with a dose of 0mg/kg, 1mg/kg, or 5mg/kg of the same phthalate mixture from embryonic day 2 through postnatal day (P)10. Brains were collected at P10 to analyze levels of apoptosis through TUNEL labelling. In order to directly observed the impact of prenatal phthalate exposure on neurogenesis, a second group of pregnant rats received a dose of 0mg/kg, 1mg/kg, or 5mg/kg from embryonic day 2 through parturition. The dams were injected with BrdU, a thymidine analog and marker of cell proliferation, at embryonic days 16 and 17, and the brains of the offspring were collected at P5. Exposure to the 5mg/kg phthalate dose during early development resulted in increased apoptosis across sexes at P10 as assessed through density of TUNEL labelled cells. Prenatal phthalate exposure at both doses significantly reduced BrdU labelling in the mPFC at P5. These results demonstrate a two-hit model in that phthalate exposure dysregulates early neuronal proliferation as well as apoptosis in the mPFC during development, leading to lasting changes in neuron number.

Disclosures: E.P. Sellinger: None. **C. Drzewiecki:** None. **J. Willing:** None. **J.M. Juraska:** None.

Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.02/S7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH grant NIMH R21 ES026896

Title: Acute effects of perinatal bisphenol A exposure on cortical apoptosis in rodents

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Abstract: Cell death during development, or apoptosis, is critical for the proper refinement of the nervous system. Apoptosis occurs in region- and sex-specific patterns, and can be influenced by genetic, hormonal as well as environmental factors. One potential environmental threat to apoptosis is bisphenol A (BPA), a nearly ubiquitous endocrine disruptor which acts as both an agonist and antagonist at the estrogen receptor. Previous work from our laboratory has shown that perinatal BPA exposure in males, but not in females, is associated with increased numbers of neurons in the medial prefrontal cortex (mPFC) in adulthood, which may be indicative of an autism-like phenotype (Sadowski et al., 2014). We hypothesize that BPA exposure may prevent

perinatal apoptosis, leading to increased cell numbers later in life. While previous work examined long-term BPA exposure from gestation through the perinatal period, the current study examines the effects of short-term BPA exposure on apoptosis. In the developing mPFC, the number of pyknotic cells per live neurons is highest at P8 and P12 in males and females, respectively, indicating brief windows of development where rapid cell death is occurring (Willing et al., unpublished data). In this study, Long Evans rodent pups were dosed orally with a 0 (control), 40 or 400 μg/kg/day BPA solution across a 3-day window on P6, P7, and P8 (early dose) or P10, P11, and P12 (late dose). All subjects were sacrificed four hours after their last BPA dose, and the brains were collected and stained for TUNEL, a marker of apoptotic cells. A Nissl stain was performed on adjacent tissue slices to quantify the density of live neurons. We found a significant effect of BPA treatment, such that males dosed from P6-P8 with 400 μg/kg of BPA had significantly fewer TUNEL cells per live neurons in the mPFC than controls, suggesting that BPA exposure during this brief window prevented cell death. These results provide evidence that BPA acts in a sex-specific manner to disrupt normal apoptosis, which could result in increased neuron numbers in adulthood. Further work is needed to determine the behavioral implications of these outcomes.

Disclosures: C. Drzewiecki: None. **E.P. Sellinger:** None. **J. Willing:** None. **S. Rhoads:** None. **J.M. Juraska:** None.

Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.03/S8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Institutes of Health/National Institute on Drug Abuse Grant DA000266.

Title: Cocaine elicits autophagic cytotoxicity via a nitric oxide-GAPDH signaling cascade

Authors: *P. P. GUHA
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Abstract: Cocaine exerts its behavioral stimulant effects by facilitating synaptic actions of neurotransmitters such as dopamine and serotonin. It is also neurotoxic and broadly cytotoxic, leading to overdose deaths. We demonstrate that the cytotoxic actions of cocaine reflect selective enhancement of autophagy, a process that physiologically degrades metabolites and cellular organelles, and that uncontrolled autophagy can also lead to cell death. In brain cultures, cocaine markedly increases levels of LC3-II and depletes p62, both actions characteristic of autophagy. By contrast, cocaine fails to stimulate cell death processes reflecting parthanatos, monitored by cleavage of poly(ADP ribose)polymerase-1 (PARP-1), or necroptosis, assessed by levels of

phosphorylated mixed lineage kinase domain-like protein. Pharmacologic inhibition of autophagy protects neurons against cocaine-induced cell death. On the other hand, inhibition of parthanatos, necroptosis, or apoptosis did not change cocaine cytotoxicity. Depletion of ATG5 or beclin-1, major mediators of autophagy, prevents cocaine-induced cell death. By contrast, depleting caspase-3, whose cleavage reflects apoptosis, fails to alter cocaine cytotoxicity, and cocaine does not alter caspase-3 cleavage. Moreover, depleting PARP-1 or RIPK1, key mediators of parthanatos and necroptosis, respectively, did not prevent cocaine-induced cell death. Autophagic actions of cocaine are mediated by the nitric oxide-glyceraldehyde-3-phosphate dehydrogenase signaling pathway. Thus, cocaine-associated autophagy is abolished by depleting GAPDH via shRNA; by the drug CGP3466B, which prevents GAPDH nitrosylation; and by mutating cysteine-150 of GAPDH, its site of nitrosylation. Treatments that selectively influence cocaine-associated autophagy may afford therapeutic benefit.

Disclosures: P.P. Guha: None.

Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.04/S9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Evaluation of hiPSC-derived neuronal cultures for safety assessment of potential therapeutic compounds against zika virus

Authors: *F. ZANELLA[1], I. SLAVIN[2], S. DEA[3], S. MONTEFUSCO[4], J. SIQUEIRA-NETO[4], C. CARROMEU[1]
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Abstract: The recent global threat of Zika Virus epidemic has highlighted the need for sophisticated screening systems capable of detecting unintended toxicity of candidate compounds against this serious infection. Toxicity to the Central Nervous System (CNS) is a key aspect in safety pharmacology evaluation of drugs under development. The characterization of the toxicological profiles of new chemicals to the CNS involves extensive investigation using *in vitro* and *in vivo* models. Currently, primary cultures and animal models are popular platforms for those studies. In spite of their importance, those platforms typically are not amenable to larger scale toxicity screens. Human induced pluripotent stem cell (hiPSC) technology has enabled the ready availability of large and consistent batches of neural cells and tissues for wider toxicity screens, having the potential to change the current paradigm in pharmacological research. Through hiPSCs and state-of-the-art differentiation protocols, researchers now have available unlimited source of neural cells, able to mimic early and late stage of human CNS

development. These sophisticated cellular models hold great potential in reducing the time to assess toxicity of developing drugs. Here we investigate the toxicological profile of 29 compounds recently described in the literature as potential therapeutic compounds against Zika Virus infection. hiPSCs-derived neural cells at different developmental stages were challenged with this library of compounds in two-dimensional cultures as well as three-dimensional mini-brain organoids. We observed greater susceptibility of the neural tissues to compound toxicity at early stages of development, and decreasing toxicity as the neuronal cultures mature *in vitro*. Compounds with the safest profiles were further evaluated in high throughput calcium flux and multi-electrode array assays for assessment of potential functional side effects on the normal function of the CNS. In summary, our work highlights the power of a human CNS model in predicting toxicological profiles of proposed drugs against Zika Virus. Moreover, this system can be applied to investigate the safety profiles on new chemical entities, improving predictivity of clinical outcome and reducing overall drug development costs.

Disclosures: **F. Zanella:** A. Employment/Salary (full or part-time):; StemoniX. **I. Slavin:** A. Employment/Salary (full or part-time):; Vertex. **S. Dea:** A. Employment/Salary (full or part-time):; StemoniX. **S. Montefusco:** None. **J. Siqueira-Neto:** None. **C. Carromeu:** A. Employment/Salary (full or part-time):; StemoniX.

Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.05/DP05/S10

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/NIEHS Grant R43ES026268 Assay of chemicals for Parkinson's toxicity in human iPSC-derived neurons

Title: Increased spontaneous activity of hiPSC-dopaminergic neurons harboring an early-onset Parkinson's disease mutation (A53T-α-Syn) quantified via kinetic image cytometry

Authors: ***P. MCDONOUGH**, R. C. B. BASA[1], W. LASSOUED[1], J. V. KARPIAK[1], J. H. PRICE[1,2]
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Abstract: Parkinson's Disease (PD) afflicts ~1% of humans and prevalence increases with age. Initial symptoms include tremors in extremities due to loss of dopaminergic neurons in the substantia nigra. Familial PD (fPD, with a family history of PD) accounts for ~10% of cases and is often early-onset (e.g., <60 yrs), whereas sporadic cases (sPD, no family history) make up ~90%. Mutations responsible for fPD occur in protein-coding genes including *SNCA* (encodes α-synuclein [α-Syn]), *LRRK2*, *PARK2*, *PINK1*, *PARK7* and *GBA*. Of these, the A53T mutation in

α-Syn (A53T-α-Syn) has the highest penetrance (~90%, with early onset). The goal of our study was to quantify neuronal function relevant to PD in dopaminergic neurons derived from human induced pluripotent stem cells (iCell Dopa Neurons, Cellular Dynamics International). We studied an isogenic pair of cell lines (hiPSC-wt-α-Syn-DNs, and hiPSC-A53T-α-Syn-DNs) in which the A53T mutation was introduced into hiPSCs derived from a normal donor. Neurons were seeded into either 96- or 384-well dishes, loaded with fluo-4 (for calcium) or FluoVolt (for voltage) and activity was recorded with a Kinetic Image Cytometer^{TM} (KIC), an automated digital microscopy workstation that collects images at up to 1200 frames per second (fps). The digital movies were quantified with CyteSeer^{TM}, which quantifies activity on a cell-by-cell basis. The hiPSC-A53T-α-Syn-DNs exhibited greater spontaneous and synchronized calcium transients vs. wt-α-Syn, and exhibited greater sensitivity to rotenone, a pesticide linked to PD. hiPSC-A53T-α-Syn-DNs also displayed more spontaneous voltage activity (action potentials and more prolonged depolarizations, recorded at 400 fps) and were more responsive to electrical stimulation delivered by the KIC. The results suggest that A53T-α-Syn induces hyperactivity in dopaminergic neurons, likely increasing susceptibility to cytotoxic-stresses. The methods developed in this study will enable high throughput screening of compounds or genetic constructs to identify those with potential toxic or beneficial effects relevant to PD.

Disclosures: P. McDonough: A. Employment/Salary (full or part-time):; Vala Sciences Inc. **R.C.B. Basa:** A. Employment/Salary (full or part-time):; Vala Sciences Inc.. **W. Lassoued:** None. **J.V. Karpiak:** A. Employment/Salary (full or part-time):; Vala Sciences Inc. **J.H. Price:** A. Employment/Salary (full or part-time):; Vala Sciences Inc..

Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.06/S11

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: An automated high content screening platform detects changes in iPSC-neuron calcium activity and morphology

Authors: *K. L. GORDON, R. C. B. BASA, J. V. KARPIAK, S. FENG, S. ANKAM, B. AZIMI, R. INGERMANSON, J. HILTON, J. PRICE, P. MCDONOUGH, D. RINES
Vala Sci. Inc., San Diego, CA

Abstract: Calcium regulation is very important for neuronal health, and dysregulation of calcium is linked to multiple neurodegenerative disorders. For example, alpha-synuclein and amyloid β-peptide fragments, associated with Parkinson's Disease and Alzheimer's Disease, respectively, disrupt calcium homeostasis of neurons, in vitro. Human induced pluripotent stem cell (hIPSC) derived neurons are a powerful tool for high-throughput screening of drugs that may

modulate changes in calcium regulation or affect neurite outgrowth and synapse formation. We have developed the IC200 Kinetic Image Cytometer™ (KIC) and with it can perform high-throughput, cell-by-cell analysis allowing us to investigate the effect of drugs on calcium regulation in living neurons cultured in 384-well dishes. Additionally, our IC200 can perform automated scans on fixed neurons that have been immunolabeled to visualize relevant biomarkers and structures, to assess morphological changes. With our CyteSeer Analysis software, we developed algorithms that quantify beta III tubulin expression and localization to assess neurite outgrowth and algorithms to quantify puncta of pre- and post-synaptic markers to access synaptic density. In the current study, we performed experiments to test the capability of our platform to detect changes in calcium activity, neurite morphology, or synapse number using compounds that have been demonstrated to induce changes in cultured neurons. We plated commercially available cortical neurons differentiated from hiPSCs, allowed them to recover from plating and mature, then treated the cells with compounds or DMSO (control). Neuronal activity analysis was performed on live neurons using our KIC technology, and we found that forskolin, which increases c-AMP, reduced calcium transient activity, whereas 4-aminopyridine (4-AP), a K+ channel inhibitor that has epileptic effects, increased calcium transients. Blebbistatin, a myosin inhibitor, was also found to increase neurite outgrowth. Thus, our platform detects changes in iPSC-neuron activity and morphology providing proof of concept for use in future high content screening studies.

Disclosures: K.L. Gordon: A. Employment/Salary (full or part-time):; Vala Sciences, Inc. **R.C.B. Basa:** A. Employment/Salary (full or part-time):; Vala Sciences, Inc. **J.V. Karpiak:** A. Employment/Salary (full or part-time):; Vala Sciences, Inc. **S. Feng:** A. Employment/Salary (full or part-time):; Vala Sciences, Inc. **S. Ankam:** A. Employment/Salary (full or part-time):; Vala Sciences, Inc. **B. Azimi:** A. Employment/Salary (full or part-time):; Vala Sciences, Inc. **R. Ingermanson:** A. Employment/Salary (full or part-time):; Vala Sciences, Inc. **J. Hilton:** A. Employment/Salary (full or part-time):; Vala Sciences, Inc. **J. Price:** A. Employment/Salary (full or part-time):; Vala Sciences, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vala Sciences, Inc. **P. McDonough:** A. Employment/Salary (full or part-time):; Vala Sciences, Inc. **D. Rines:** A. Employment/Salary (full or part-time):; Vala Sciences, Inc..

Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.07/S12

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIGMS R01GM118197
NIGMS R01GM118197-11S1

Title: Neonatal sevoflurane exposure up regulates cation-chloride cotransporter KCC2 in mouse thalamus

Authors: *O. H. CABRERA, V. TESIC, Q. L. E. TAT, N. QUILLINAN, S. E. CHASTAIN, V. JEVTOVIC-TODOROVIC
Anesthesiol., Univ. of Colorado Anschutz Med. Campus, Aurora, CO

Abstract: Sedative/anesthetic drugs (SADs) are used pervasively in neonatal medicine despite being neurotoxic to developing mammalian brain and linked to neurodevelopmental impairment in children treated with SADs as infants. In neonatal rodents and non-human primates, SADs cause acute neuroapoptosis, but impairments persist into adulthood in animal models and at least early childhood in humans, suggesting long-term perturbation of surviving neurons. Indeed, we have observed altered GABA neurotransmission in sensory and cognition networks of adult rodents exposed to SADs as neonates.

The cation-chloride cotransporters regulate neurotransmission by controlling intracellular chloride concentration $[Cl^-]_i$ and, therefore, polarity of neuronal responses to GABA. During early neurodevelopment, NKCC1 maintains high $[Cl^-]_i$ in immature neurons, and GABA binding causes chloride efflux and neuronal depolarization. As development proceeds, neurons predominantly express KCC2, which maintains low $[Cl^-]_i$. Thus, GABA binding mediates neuroinhibition via chloride influx. These findings led us to hypothesize that SAD-induced dysregulation of cation-chloride cotransporters may be partially responsible for altered GABA neurotransmission observed in our previous studies.

We treated litters of postnatal day (PND) 7 mice with sevoflurane (SEVO) for 6h (3% for 2h; 2.4% for 4h). To prevent hypoxia, we supplemented SEVO with a mixture of 30% O_2 and compressed air. The littermates randomly assigned to control group received only carrier gases. We maintained body temperature of all pups at 35 °C and monitored vitals of SEVO pups. We collected cortex, hippocampus, and thalamus at 6h and 24h after initial exposure, then probed changes in NKCC1 and KCC2 protein expression via Western Blot. SEVO increased KCC2 protein expression in thalamus at 24h, $p = 0.002$, but not at 6h. Cortical and hippocampal KCC2 was unchanged at 6h and 24h in SEVO pups. SEVO challenge did not alter NKCC1 protein expression in brain regions of interest at 6h or 24h. Next, we histologically identified specific thalamic nuclei at the 24h time point as putative targets of KCC2 dysregulation. We observed a statistically significant increase in KCC2 immunoreactivity in ventrobasal (VB) thalamus of SEVO pups versus controls, $p = 0.01$.

The VB participates in thalamocortical oscillations important for normal sensory processing and attention, as well as neuropathological disorders such as epilepsy. In future studies, we will test the possibility that SEVO-induced upregulation of KCC2 in VB may interfere with GABA neurotransmission and thalamocortical oscillations.

Disclosures: O.H. Cabrera: None. **V. Tesic:** None. **Q.L.E. Tat:** None. **N. Quillinan:** None. **S.E. Chastain:** None. **V. Jevtovic-Todorovic:** None.

Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.08/S13

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: R0144517
R01 GM118197
R21 HD080281

Title: Alphaxalone has broader therapeutic index than propofol and shows no neurotoxic effects to developing rat brain

Authors: *V. TESIC[1], S. CHASTAIN[3], Q. TAT[4], O. H. CABRERA[5], N. QUILLINAN[6], K. KATHIRESAN[7], D. F. COVEY[7], S. M. TODOROVIC[5], V. JEVTOVIC-TODOROVIC[2]
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Abstract: Recent studies have raised awareness that exposure to GA during childhood may be associated with an increased risk for subsequent deficits in learning, memory and cognition. Thus, there is an urgent need to develop safer GAs.
Alphaxalone (3α-hydroxy-5 α-pregnane-11, 20-dione) is a neuroactive steroid with anesthetic properties. It modulates neurotransmission through interaction with a steroid recognition site on the $GABA_A$ receptor complex causing a positive allosteric modulation of the ligand-gated chloride channel, thus inhibiting neuronal excitability. In addition, alphaxalone inhibits neuronal T-type calcium channels. Propofol, a commonly used GABAergic general anesthetic (GA) which has very little effects on T-type calcium channels, was shown to be neurotoxic to developing brain of both rodents and non-human primates at clinically-relevant doses.
We investigated the hypnotic properties of alphaxalone in comparison with propofol by testing the loss of righting reflex (LORR) in post-natal day 7 Sprague Dawley rats. Alphaxalone and propofol caused dose-dependent hypnosis with higher therapeutic index for alphaxalone (32.1 for alphaxalone and 23.1 for propofol). In terms of LORR, the 50% effective doses (ED_{50}) for alphaxalone and propofol were 1.57 mg/kg and 2.36 mg/kg, respectively. LD_{50} (dose that caused 50% of mortality) was 50.41 mg/kg and 54.55 mg/kg for alphaxalone and propofol, respectively. Next, we compared the number of activated caspase 3 (AC3) positive cells after exposure to alphaxalone and propofol, as AC3 is considered to be the marker of GA-induced neurotoxicity. We exposed the pups to equipotent doses of anesthetics that cause a LORR for 40 min (10 mg/kg

of alphaxalone and 20 mg/kg of propofol every hour for total of 6 i.p. injections). Brains were collected 2h after exposure and immunohistochemical staining was performed. In order to determine neurotoxicity levels, we focused on counting of AC3 positive cells in the subiculum, output structure of hippocampus that is highly sensitive to GA-induced neuroapoptosis. We found that alphaxalone treatment did not cause a statistically significant increase in AC3-positive cells in subiculum when compared to sham-treated group, while propofol caused a ~5-fold increase in neurotoxicity compared to controls.
Our data suggest that alphaxalone is safer than propofol since it has broader therapeutic index. Importantly, we show that alphaxalone does not induce developmental neuroapoptosis. Thus, neuroactive steroid analogues with anesthetic properties, such as alphaxalone may warrant further investigation as new class of anesthetics potentially safe for use in infants and children.

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Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.09/S14

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIGMS R01 GM118197

Title: Early postnatal exposure to sevoflurane causes long-lasting changes in expression of synaptic plasticity related genes in rat subiculum

Authors: *S. E. CHASTAIN[1], V. TESIC[2], Q. TAT[3], O. H. CABRERA[1], N. QUILLINAN[4], V. JEVTOVIC-TODOROVIC[1]
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Abstract: Multiple and prolonged prenatal and neonatal exposure to sevoflurane has been shown to cause neurobehavioral and developmental abnormalities, but the mechanisms are incompletely understood. DNA methylation is crucial to normal development and differentiation by acting as a suppressor of gene expression and is found in the promoter region of critical genes. Once formed DNA methylation is extremely stable and possesses a self-perpetuating capacity. For demethylation to occur it requires a prohibitively high degree of energy. 5-hmC is hypothesized to be a potential key intermediate in an active DNA demethylation process. We aimed to elucidate the role of DNA methylation by examining long-lasting 5-mC and 5-hmC

modifications of DNA resulting from postnatal exposure to sevoflurane.
Postnatal day (PND) 7 Sprague-Dawley rats of equal gender were exposed to sevoflurane at 3% for 2h followed by 2.4% for 4h in 30% oxygen, with vehicle group exposed to 30% oxygen for 6h. Brains were collected at PND28 for analysis of methylation in subiculum, the region of the hippocampus known to be highly sensitive to anesthetics. Intensity of 5-mC and 5-hmC were determined in subicular neuronal-nuclei. A single postnatal exposure to sevoflurane resulted in 33.4%$\pm$5.9 reduction of 5-mC DNA methylation and a 29.7%$\pm$6.9 increase in 5-hmC DNA methylation.
Due to the resulting changes in DNA methylation and known neurobehavioral abnormalities we hypothesized that expression of specific genes involved in synaptic plasticity would change. Employing a synaptic plasticity PCR assay we revealed that 21 out of 84 investigated targets were changed by $\geq$30% when exposed to sevoflurane. Of these genes Arc, Cebpb, Junb, Ntf3, Ntf4, Mmp9 and Tnf were examined in more depth due to their function as transcription factors and involvement in neuronal survival and proliferation. Of these genes ARC, Junb, NTF3 were upregulated by $\geq$70%; Cebpb, Mmp9, Ntf4 and Tnf were downregulated by $\geq$50%.
Since we observed a decrease in the 5-mC and sequential increase in 5-hmC DNA methylation we propose it to be, at least in part, responsible for changes in gene expression. Sevoflurane exposures results in a shift in global subicular methylation, inferring altered gene expression, as shown by change in crucial synaptic plasticity gene expression. These genes play vital role in the neurobehavior and development and their changes could contribute to abnormalities seen after exposure to sevoflurane.

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Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.10/S15

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01AG051521
R21 AG-040753
R01AG053982-01
RF1AG053982-01A1
R01AG057912-01
R00AG052604-02
Cure Alzheimer's Fund

Title: Environmental toxicants, ApoE and sex interaction in human cognitive aging and in mice transgenic for Alzheimer-associated genes

Authors: *A. HAGHANI[1], M. CACCIOTTOLO[1], K. R. DOTY[3], C. SIOUTAS[2], T. C. TOWN[3], T. E. MORGAN[1], M. LEVINE[4], C. E. FINCH[1]
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Abstract: Cigarette smoke and air pollution are strong risk factors of Alzheimer's disease (AD) and other age-associated chronic diseases. While many effects of these environmental toxicants are well documented, less is known about their interactions with sex and *ApoE* alleles (Cacciottolo et al. 2017, PMID:28140404). This study investigates the pathways of interactions of sex, *ApoE* genotype, and environmental toxicants that contribute to cognitive decline and neurodegenerative diseases. We evaluate correlations of human genomic and phenomic data from the Health Retirement Survey (HRS, U.S. sample) with transcriptomic data from male and female *ApoE* transgenic mice exposed to air pollution. Results from the HRS cohort show *ApoE4* and smoking are risk factors of accelerated cognitive aging (Method from Levine et al. 2018 under review) with stronger trends in women. To complement these human studies, we applied Weighted Gene Co-Expression Network Analysis (WGCNA) to identify gene networks differentially expressed in the mouse cerebral cortex as a function of sex, *ApoE*, and environmental toxins. One WGCNA module enriched for nervous system-associated signaling pathways showed significant interactions among sex, *ApoE* and air pollution. These genes had high overlap with 215 previously-defined polygenic genes for predicting long-lived human smoking survivors. This suggests cigarette smoke and air pollution have convergent molecular toxicities that mediate gene environment interactions in cognitive aging. We further analyzed AD associated genes for susceptibility to each factor and possible genotype-environment interaction. These findings suggest influences of *ApoE4* allele in sex difference of cognitive aging vulnerability to environmental toxins.

Disclosures: A. Haghani: None. **M. Cacciottolo:** None. **K.R. Doty:** None. **C. Sioutas:** None. **T.C. Town:** None. **T.E. Morgan:** None. **M. Levine:** None. **C.E. Finch:** None.

Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.11/S16

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: R21 AG05020

Title: Effects of a novel gamma secretase modulator on traffic-related air pollution exposure: Implication in the amyloidogenic processing of APP and cognitive impairment

Authors: *C. D'AGOSTINO[1], M. CACCIOTTOLO[1], F. SHIRMOHAMMADI[2], C. SIOUTAS[2], S. L. WAGNER[3,4], R. E. TANZI[5], T. E. MORGAN[1], C. E. FINCH[1]
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Abstract: Traffic-related air pollution (TRAP) is increasingly documented as a risk factor for Alzheimer Disease (AD) onset and for accelerated cognitive decline (Cacciotttolo et al 2017). TRAP exposure increases the levels of endogenous amyloid beta (Aβ) peptides in rodents after chronic exposure (Levesque et al. 2011). Multiple evidences suggest that accumulation or overproduction of Aβ peptides is one of the main cause of Alzheimer disease (AD) (Zhang et al. 2011). Amyloid-β peptides are generated following a proteolytic processing of the amyloid precursor protein (APP) by β- and γ-secretases. γ-secretases generates the most abundant Aβ40 and Aβ42 isoforms and the latest is considered to be the key pathogenic species in AD. γ-secretase modulators (GSMs) are the last generation drugs that target Amyloid peptides (Kounnas MZ et al. 2010). Among them a novel soluble γ-secretase modulator (BPN-15606) has been shown to strongly and selectively decrease Aβ42 levels (Wagner SL et al 2017). To evaluate whether pharmacological inhibition of Aβ production during exposure to a nano-scale subfraction of TRAP (nPM) attenuates the amyloidogenic processing of APP and has impact on pathological AD hallmarks, we treated C57BL/6JN mice with the γ-secretase modulator BPN-15606. 3 months old male mice were exposed to nPM for 8 weeks, 3day/w, 5hr/d and fed with regular diet or 10 mg/kg GSM in the chow for 1 week before and during exposure to air pollution. Cerebral cortices were collected and analyzed by MSD multiplex ELISA for the quantification of Aβ40 and Aβ42 peptides. Mice exposed to nPM had elevated levels of Aβ40 and 42 peptides, which were reduced by 35% and 45%, in mice exposed to both nPM and GSM. Moreover, nPM induction of the microglial marker Iba1, in hippocampal subfields by nPM was significantly attenuated by the GSM. The strong connection between microglia inflammatory responses due to nano-particulate exposure and Aβ peptides confirm the possible role of endogenous Aβ levels in cognitive changes. Our data suggest that cognitive impairment due to air pollution exposure might be ameliorated through the manipulation of the APP processing and the novel γ-secretase modulator drugs could be the lead on this path.

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Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.12/S17

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: the Cure Alzheimer's Fund
R21 AG-040753
R01AG051521
R01AG050201

Title: Lipid rafts as novel target of traffic related air pollutant exposure: Evidence from *in vivo* and *in vitro* models

Authors: *M. CACCIOTTOLO[1], T. E. MORGAN[1], A. C. SAFFARI[3], F. SHIRMOHAMMADI[3], H. J. FORMAN[1], C. SIOUTAS[3], C. E. FINCH[2]
[2]USC Col., [1]USC Leonard Davis Sch. of Gerontology, Los Angeles, CA; [3]USC Viterbi Sch. of Engin., Los Angeles, CA

Abstract: Traffic-related air pollution (TRAP) is increasingly documented as a risk factor for Alzheimer Disease (AD) onset and for accelerated cognitive decline. Mouse models exposed to a nano-scale subfraction of TRAP (nPM) showed increased brain amyloid levels, concurrently with oxidative damage, as possible mechanism of neurotoxicity (Cacciotttolo et al 2017). Additionally, cell production of Aβ is also increased by oxidative stress. Brain cell oxidative responses to nPM are also shown in *in vitro* models of hippocampal slices and primary brain cell cultures with increased NO (nitric oxide) production and lipid oxidation (4-HNE) (Davis et al 2013; Cheng et al 2016). Air pollutants may affect multiple steps in APP processing. In neurons, APP undergoes an endoproteolytic cleavage mediated by the 'secretases' in which the initial cleavage by α- or β-secretase determines the level of Aβ production. Subsequently, the γ-secretase yields soluble APP fragments (sAPPα and sAPPβ), then processed for Aβ peptides of 38-43 residues. We investigated subcellular lipid rafts, which are the main site of pro-amyloidogenic processing of APP by BACE 1 and γ-secretase catalytic subunit PS1 with J20 mice and N2a cells transgenic for hAPP/Swe (familial AD). Exposure of J20 mice for 150 hours to nPM increased lipid oxidation (4-HNE) and increased proamyloidogenic processing of APP on lipid raft subcellular fractions. The lipid raft responses to nPM were regionally selective, arising in cerebral cortex, but not in cerebellum, which parallels the regionality of Aβ deposits in transgenic mice and humans. *In vitro,* N2a-APP/Swe cells modeled brain responses to nPM, with dose-dependent production of NO, oxidative damage (4-HNE, 3-NT), and lipid raft alterations of APP that increased Aβ peptides. The anti-oxidant n-acetyl-cysteine (NAC) attenuated oxidative

damage and lipid raft alterations of APP processing. These novel findings identify neuronal lipid rafts as targets of oxidative damage in the proamylodogenic effects of air pollution.

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Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.13/S18

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: AG040683
AG051521
ES023780

Title: Glutamatergic mechanisms in depressive responses to prenatal exposure to traffic-related air pollution

Authors: *R. G. JOHNSON, III[1], A. HAGHANI[1], V. COUSSA[1], F. SHIRMOHAMMADI[2], C. SIOUTAS[2], C. E. FINCH[1], T. E. MORGAN[1]
[1]Leonard Davis Sch. of Gerontology, [2]Viterbi Sch. of Engin., USC, Los Angeles, CA

Abstract: Prenatal exposure to nano-sized particulate matter (nPM), a subset of traffic-related air pollution particulate matter$_{0.2}$ (TRAP-PM$_{0.2}$), causes depressive-like symptoms in rodents (Davis et al 2013; Woodward et al 2017). Based on the collection methods, the nPM used in those studies were devoid of water-insoluble organic materials, such as polyaromatic hydrocarbons, which are known to cause deleterious neurodevelopmental and behavioral effects in children. Here, we used a novel method of collecting TRAP-PM$_{0.2}$ in a slurry (sPM) which retains the water-insoluble organics for mouse exposure. Pregnant mice were exposed to sPM at 340 ug/m^3 or filtered air for five hours a day for three days a week from conception to birth. At sixteen weeks of age mice underwent the forced swim behavioral test to screen for depressive-like symptoms. Male mice exposed to sPM showed a 22% increase in total time immobile and a 16% decrease in latency to first time immobile, compared to filtered air exposed males. Supporting the nPM study (Davis et al 2013), exposed female mice did not show depressive-like symptoms. The forced swim test was repeated 8 days later, after the mice were injected (i.p.) with the NMDA antagonist, MK-801, 0.06mg/kg, or saline. MK-801 reduced the total time immobile of sPM exposed mice back to control levels. We are further exploring the role of glutamatergic pathways by measuring glutamatergic receptor mRNA and protein levels. These results suggest that the glutamatergic pathway may play a critical role in the mechanism by which prenatal exposure to TRAP-PM$_{0.2}$ causes neurodevelopmental and behavioral effects.

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Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.14/T1

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: Exploring the hormetic effect of dietary polyphenols in fruit flies - The dose makes the poison

Authors: *L. S. VILLALPANDO, J. M. NAPAN, A. M. BRISENO, C. B. BARCENAS, W. L. HARDEMAN, B. TOLAN, A. D. TROFIMOVA, D. PATEL, R. E. HARTMAN
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Abstract: Polyphenols are phytochemicals produced by plants that protect them from environmental insults such as insects and ultraviolet irradiation, and consuming them can induce beneficial effects by altering various inflammatory pathways and redox mechanisms. Previous research from our laboratory has shown that dietary supplementation with low doses of pomegranate polyphenols can have beneficial effects in Drosophila melanogaster fruit flies (reduced seizure-like activity), mice (radioprotection, cognition and motor improvements, reduced Alzheimer's-like neuropathology, increased neurogenesis), and humans (amelioration of cardiovascular / stroke-related deficits). However, evidence suggests that these same compounds may become toxic at higher doses. The term hormesis refers to a biphasic dose response curve, in which low doses of a substance may have beneficial effects, but higher doses of the same substance become toxic and induce detrimental effects.
The aim of this study was to characterize the dose response curve of dietary polyphenols in Drosophila melanogaster fruit flies with regard to longevity and behavioral functions, and to determine the range at which the dose changes from protective to adverse. We hypothesized that longevity and behavioral performance would be improved by exposure to low levels of dietary polyphenols, but that increasingly larger doses would ultimately become detrimental. Therefore, Drosophila melanogaster were exposed to varying levels of polyphenols in their diet media following eclosion. The flies were put through a behavioral test battery that assessed learning/memory and locomotor activity, and lifespan was recorded. Preliminary data suggest that high levels of dietary polyphenols reduced longevity and may have had detrimental effects on behavior. Identifying the point at which the anti-inflammatory pathways and redox mechanisms affected by dietary polyphenols become harmful, rather than helpful, will illuminate targets that can be specifically manipulated pharmacologically or via lifestyle changes to improve longevity and maintain high function throughout life.

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Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.15/T2

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH T32 ES007051

Title: Dopaminergic dysfunction in Sprague-Dawley rats as a potential mechanism for deficits in egocentric and allocentric learning and memory following developmental manganese overexposure

Authors: *R. A. BAILEY[1,2,3], A. GUTIERREZ[1,2,3], J. R. HUFGARD[1,2], C. V. VORHEES[1,2,3], M. T. WILLIAMS[1,2,3]
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Abstract: Manganese (Mn) is a crucial cofactor in many functions, such as growth, metabolism, antioxidation, and nervous system function, however, Mn overexposure (MnOE) causes cognitive deficits as well as motor dysfunction in severe cases. Mn deposits in the globus pallidus, leading to dysfunction in the nigrostriatal pathway. The mechanisms of this toxicity are poorly understood especially in developmental exposure models. Sprague Dawley rats were gavaged with Mn or saline every other day from postnatal day (P)4 to P28, and cognitive function was assessed beginning in adulthood (P60). In another cohort of rats, dopaminergic function was assessed on P29, P60, or P111. We found that MnOE impaired egocentric and allocentric learning and memory, indicating striatal and hippocampal deficits respectively. No effects were found for conditioned freezing in MnOE rats. Control procedures to ensure motor deficits were not a factor in the cognitive deficits demonstrated that the MnOE rats only had a transient decrease in motor function that resolved over time. Dopamine and its metabolites in the neostriatum were not affected by MnOE. However, the expression of dopamine receptors, Drd1, Drd2, and σR1, changed in neostriatum from MnOE. MnOE increased Drd1 and Drd2 expression and decreased σR1 at P29. In adult rats, both Drd2 and σR1 were decreased after MnOE with no long-term effect on Drd1. How these changes relate to the egocentric deficits remains to be determined. To test whether MnOE alters dopamine release, fast scan cyclic voltammetry (FSCV) will be used. We hypothesize that MnOE reduces phasic dopamine release without affecting tonic release. (Supported by NIH T32 ES007051.)

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Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.16/T3

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: UNAM-DGAPA-PAPIIT IN203916
CONACYT 251510

Title: Chronic atrazine exposure alters striatal glutamatergic neurotransmission and behavior in the male rat

Authors: D. REYES-BRAVO[1], M. CHÁVEZ-PICHARDO[2], M. MENDOZA-TREJO[2], A. MARÍN-LÓPEZ[2], N. HERNÁNDEZ-CHAN[1], K. DOMINGUEZ-MARCHAN[2], L. ORTEGA-ROSALES[2], J. ZEPEDA-ALMONTE[2], M. GIORDANO[2], *V. RODRIGUEZ CORDOVA[2]
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Abstract: Several studies in rodents, have shown that exposure to the widely used herbicide atrazine (ATR; 2-chloro-4-ethylamino-6-isopropylamino-s-triazine) causes deficits in the nigrostriatal pathway such as alterations in locomotor activity, decreased striatal dopamine levels, and diminished counts of tyrosine hydroxylase positive cells in substantia nigra pars compacta. However, the effects of ATR on other neurotransmitters such as GABA and glutamate have been scarcely studied. To test if ATR also affects other neurotransmitter systems in this study we evaluated the effects of chronic exposure (one year) to 1 or 10 mg ATR/kg of body weight, on behavior and striatal levels of GABA, glutamine and glutamate and the striatal release of glutamate. Behavioral results showed that chronic ATR exposure to 10 mg ATR/kg causes hyperactivity, and increased anxiety in both groups exposed to ATR. The striatal levels of glutamine were increased in the group exposed to 10 mg ATR/kg, and the levels of striatal glutamate were decreased in the group exposed to 1 mg ATR/kg. Striatal extracellular basal levels of glutamate were increased in the group exposed to 10 mg ATR/kg, in contrast to the control group, none of the ATR exposed groups responded to the high potassium challenge. These data show that chronic ATR exposure causes alterations not only on dopaminergic markers but also on glutamine and glutamate levels and glutamate release in striatum, which in combination could generate the behavioral changes observed.

Disclosures: D. Reyes-Bravo: None. **M. Chávez-Pichardo:** None. **M. Mendoza-Trejo:** None. **A. Marín-López:** None. **N. Hernández-Chan:** None. **K. Dominguez-Marchan:**

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Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.17/T4

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01A193504

Title: Characterization of the functional recovery of diaphragmatic muscle fiber populations in a novel sublethal model of botulism

Authors: *J. MACHAMER, E. VAZQUEZ-CINTRON, M. STENSLIK, C. ONDECK, K. PAGARIGAN, A. BRADFORD, P. MCNUTT
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Abstract: Botulinum neurotoxins (BoNTs) cleave SNARE molecules required for exocytosis of synaptic vesicles containing acetylcholine, thereby silencing motor neurons and paralyzing muscles. Severe intoxication results in death by asphyxiation due to the paralysis of the diaphragm and accessory respiratory muscles. As no treatments exist to prevent respiratory collapse or accelerate recovery of muscle paralysis, survival in severe cases depends on the use of artificial ventilation until respiratory muscles recover. Therefore, new treatments need to be discovered that promote the recovery of respiratory muscles. Although many studies have modeled recovery from botulism in locally paralyzed limb muscles, these muscle are structurally and functionally distinct from respiratory muscles, and local delivery of BoNT does not model clinical cases of botulism. Therefore, developing a systemic sublethal model of botulism that targets respiratory muscles would facilitate 1) investigation of the cellular and molecular mechanisms underlying the recovery of diaphragmatic function and 2) testing of potential therapies to promote recovery of respiratory muscle function. Here we describe a novel sublethal model of botulism resulting in ~75% of exposed animals developing symptomatic botulism that peaks at 3 d post-exposure. In surviving animals (~60%), clinical manifestations subside between 7-14 d post-exposure. In contrast, by measuring voluntary running wheel activity in recovering mice, we find that motor activity recovers between 14-21 d. Consistent with running behavior, ex vivo diaphragm contraction strength measurements indicate that aggregate diaphragm function remains impaired at 14 d and does not recover until 21 d post-exposure. To further understand how the diaphragm recovers from systemic intoxication, we used intracellular electrophysiology to measure synaptic transmission at diaphragm endplates. By sampling a large number of diaphragmatic muscle fibers, we found that severity of intoxication and recovery from intoxication were endplate-specific. Additionally in recovering diaphragms we identified

multiple secondary changes in neuromuscular physiology that both act to both promote and inhibit muscle contraction. Moving forward, this model will be useful for both characterizing the molecular mechanisms of endogenous compensatory and inhibitory changes in neuromuscular function that could serve as potential physiological targets for therapeutic intervention as well as testing novel treatments to enhance respiratory recovery relevant to clinical botulism.

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Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.18/T5

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Title: High-content imaging of iPSC-derived human neurons for toxicity screening

Authors: *M. L. HENDRICKSON[1], L. ZHANG[2], M. XIA[2], Z.-W. DU[1]
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Abstract: There is a significant need for in vitro systems that more closely model the human nervous system and its response to environmental toxins. Such a platform would have greater predictive power to indicate which compounds pose a risk. Toward this goal, we have developed a platform centered on the use of iPSC-derived human neurons. First, iPSCs were gene-edited to ubiquitously express eGFP. We then patterned these iPSCs to a neuroepithelial fate and next to neuronal progenitors before finally differentiating them into neurons. Spinal motor neurons were generated in this manner and used for this proof-of-concept project. They were plated in 384-well format for high-content imaging. Optimizing imaging in this manner required attention to the source of cells, plate surface coating, medium composition, staining protocol, imaging parameters, and the timeline for neuron maturation and neurite outgrowth. Optimization of all parameters yielded a sensitive and robust system with a Z-prime value greater than 0.5.

Disclosures: M.L. Hendrickson: A. Employment/Salary (full or part-time):; BrainXell, Inc.. **L. Zhang:** None. **M. Xia:** None. **Z. Du:** A. Employment/Salary (full or part-time):; BrainXell, Inc..

Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.19/T6

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Science Foundation (01A-1632881)

Title: Inorganic scintillators are biocompatible with neuronal and circuit function

Authors: *A. F. BARTLEY[1], K. ABIRAMAN[2], L. T. STEWART[2], M. K. BURDETTE[3], S. H. FOULGER[3], L. E. DOBRUNZ[1], L. L. MCMAHON[2]
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Abstract: In recent years, optogenetics has become a widely used technique for neuroscience research. However, the use of optogenetics in vivo is limited by the invasive nature of current methods to deliver light, which cause damage to delicate brain tissue. The creation of noninvasive optogenetic methods could transform the field of optogenetics, and multiple labs are in the process of developing novel noninvasive strategies for light delivery. One potential method could employ x-ray activation of radioluminescent particles (RLPs), enabling localized generation of light within the brain. RLPs can be made from inorganic scintillators, which emit light of different wavelengths depending upon their composition. Whether inorganic scintillators themselves impact neuronal processes and circuit function is unknown. Lutetium oxyorthosilicate (LSO:Ce), an inorganic scintillator that emits blue light in response to x-ray or UV stimulation, could potentially be used to activate channelrhodopsin-2 (ChR2). Here we used electrophysiology to investigate effects of LSO:Ce particles on neuronal health and circuit function in acute hippocampal slices. We find that LSO:Ce particles have no effect on cell health measurements, including resting membrane potential and input resistance. Basal synaptic excitatory field potentials are also unaltered, even with incubation times up to 3 hours. However, there is a trend for a decrease in the frequency of spontaneous EPSCs and IPSCs measured in CA1 pyramidal cells. Next, we tested for effects of LSO:Ce particles on long term potentiation, a more robust measurement of synaptic health and integrity, and found no effect. Together, these results indicate that neuronal function and synaptic plasticity are intact during exposure to LSO:Ce particles, demonstrating their biocompatibility. As proof of principle that light emitted from LSO:Ce particles can activate ChR2, we applied UV stimulation (315 nm) to LSO:Ce particles on slices from mice that expressed ChR2 in excitatory neurons (Emx-cre:ChR2 mice). This caused an increase in the frequency of spontaneous EPSCs. Therefore, the LSO:Ce inorganic scintillator is potentially a viable tool for use in noninvasive optogenetic methods.

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Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.20/T7

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIDA/IRP

Title: Activation of glutamatergic receptors promotes endoplasmic reticulum calcium depletion in primary cortical neurons

Authors: *A. M. DOSSAT[1], L. V. FORTUNO[2], B. K. HARVEY[2]
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Abstract: Glutamate is the most ubiquitously expressed excitatory neurotransmitter within the central nervous system. Glutamate acts upon many postsynaptic receptor subtypes to promote neuronal depolarization and cellular plasticity. Excitotoxicity results from elevated synaptic glutamate and hypersynchronous neuronal firing and has been documented in conditions like epilepsy. The contribution of extracellular calcium (Ca^{2+}) to the expression of seizure-like neuronal activity and excitotoxicity are well established. However, the role of endoplasmic reticulum (ER)-sourced Ca^{2+} in the pathophysiology of epilepsy remains to be elucidated. The ER maintains Ca^{2+} levels like that of the extracellular space, which is roughly 1000 times higher than what is found in the cytosol. This makes the ER a likely contributor to the pathophysiology of epilepsy.
Using a previously described secreted Gaussia luciferase reporter of ER calcium (GLuc-SERCaMP), and we compared the effects of a known ER calcium dysregulator, Thapsigargin (100 nM, Tg), to glutamate (100 µM) and kainic acid (100 µM). GLuc-SERCaMP activity was induced by AAV vector transduction using mixed-sex primary cortical neurons. Treatment with Tg, glutamate, and kainic acid induced GLuc-SERCaMP secretion, indicative of ER calcium depletion. Pre-treatment with antagonists for IP3 receptors (IP3R) and ryanodine receptors (RyR) significantly blunted the GLuc-SERCaMP secretion induced by Tg, glutamate, and kainic acid. Taken together, our findings indicate that in addition to promoting influx of Ca^{2+} from the extracellular space, glutamate and kainic acid also promote efflux of Ca^{2+} from the ER. Ongoing studies with the GLuc-SERCaMP reporter also support a change in the ER proteome in response to glutamate and kainic acid. The depleted ER calcium stores may contribute to the excitotoxicity observed in epilepsy and other conditions characterized by excessive neuronal

activity. Future studies will investigate the role of other ER calcium stabilizers to mitigate ER calcium dysregulation in conditions of excitotoxicity using *in vivo* models.

Disclosures: A.M. Dossat: None. **L.V. Fortuno:** None. **B.K. Harvey:** None.

Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.21/T8

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIGMS RISE Grant
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Vanderbilt CTSA

Title: Activation of proline synthesis pathway protects neurons from methamphetamine-induced toxicity

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Abstract: Methamphetamine (METH) is a highly addictive psychostimulant drug. METH induced neurotoxicity is known to cause long-lasting effects especially on the dopaminergic neurons in the CNS. Therefore, METH abuse has been linked to increased risk of developing several neurodegenerative diseases, such as Parkinson's disease, HIV-Associated Neurocognitive Disorder (HAND) and others. It has been suggested that METH increases extracellular concentrations of both dopamine (DA) and glutamate (GLU) in the striatum. Release of these neurotransmitters with repeated METH administration has been suggested to elicit oxidative stress and excitotoxicity to DA nerve terminals. Despite the well documented effects of METH on glutamate neurotoxicity, the molecular mechanisms remain poorly understood. In this study, we demonstrate an essential role of pyrroline-5-carboxylate reductase 2 (PYCR2), the enzyme that catalyzes the final step of proline biosynthesis in METH-induced glutamate neurotoxicity. We hypothesize that sequestration of excess glutamate for proline synthesis protects DA neurons from glutamate-induced neurotoxicity. To test this hypothesis, we used "SH-SY5Y" neuroblastoma cell line as a model to mimic DA neuronal phenotype. Acute METH exposure for 24 h did not induce cytotoxicity or increase levels of ROS, however, a marked induction in expression of PYCR2 was observed. To elucidate the role of the PYCR2 in METH-induced effects we knocked down PYCR2 in neurons. Interestingly, knockdown of PYCR2 increased

extracellular glutamate levels upon METH treatment suggesting that in the absence of PYCR2 excess glutamate cannot be converted into proline allowing its accumulation and release. Therefore, we believe that the induction of PYCR2 may be necessary for protecting neurons from METH-induced glutamate toxicity. These studies will help unravel a novel role of proline metabolism as stress response pathway in coping neurotoxicity.

Disclosures: B. Jones: None. **M. Balasubramaniam:** None. **C. Dash:** None. **J. Pandhare:** None.

Poster

474. Neurotoxicity, Inflammation, and Neuroprotection: Mechanisms of Neurotoxicity I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 474.22/T9

Topic: C.07. Neurotoxicity, Inflammation, and Neuroprotection

Support: NSF Phase I SBIR award 1549126
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Marcus Center for Therapeutic Cell Characterization and Manufacturing
The Georgia Tech Foundation
The Georgia Research Alliance

Title: A perfused three-dimensional culture model of human cortical tissue

Authors: *J. VUKASINOVIC[1], J. T. SHOEMAKER[1], M. C. LAPLACA[2]
[1]Lena Biosciences, Inc., Atlanta, GA; [2]Georgia Inst. of Technol., Atlanta, GA

Abstract: Human neural tissue can be exceedingly difficult to model in vitro. Issues of cellular survival and maintaining in vivo-like function pervade, often affecting study validity and translatability. Planar cultures have long been the standard method of growing cells in vitro, but they fail to capture the complexities of the in vivo environment. This is particularly applicable to the delicate balance of microglia-mediated inflammatory responses. Three-dimensional (3D) cultures have been shown to be more physiologically relevant models of in vivo tissue. However, even they fail to fully mimic living tissue and suffer from the lack of active oxygen and nutrient transport. Lena Biosciences has developed a groundbreaking in vitro system that facilitates long-term survival of 3D cultures and significantly improves cellular metabolic function. PerfusionPal offers a simple method for simultaneously perfusing twelve statistically independent 3D cultures using only a single tube and pump. Utilizing a unique blood substitute, cultures grown in SeedEZ 3D scaffolds receive superior oxygenation, resulting in significant functional improvements and allowing for growth of denser cultures with increased longevity. Using this system, Lena Biosciences has developed a human cortical model comprising iPSC-derived neurons (acquired from BrainXell), primary astrocytes, and cells from the HMC3 microglia cell line. Both

glutamatergic and GABAergic neurons were combined to generate a more accurate model. Exploratory studies assessing cell viability and function were carried out in PerfusionPal with and without active perfusion. These data were compared with 3D cultures grown in multi-well plates. The results showed that growth in PerfusionPal improved cellular viability after two weeks in culture as determined by live/dead assay and improved cellular respiration as measured by alamarBlue. The model is uniquely positioned to serve as a test-bed for inflammation-induced neurotoxicity. Preliminary studies in which the cultures were treated with pro-inflammatory reagents have confirmed they are inducible into a state of neuroinflammation. PerfusionPal will allow for study of the complex interplay between pro- and anti-inflammatory responses to insult and the long-term effects of activating these pathways.

Disclosures: J. Vukasinovic: A. Employment/Salary (full or part-time):; Lena Biosciences, Inc.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); BrainXell. **J.T. Shoemaker:** A. Employment/Salary (full or part-time):; Lena Biosciences, Inc.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); BrainXell. **M.C. LaPlaca:** None.

Poster

475. Ischemia III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.01/T10

Topic: C.08. Ischemia

Title: Long-term outcome of low-level light therapy in focal ischemic mouse model

Authors: *H. LEE[1,2], Y.-I. SHIN[1,2]
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Abstract: Low-level light therapy has a promising modality for a variety of wound healing, physical medicine and rehabilitation medicine. LLLT facilitates wound healing by proliferative effects on dividing cells, exerts potent inflammatory effects, products growth factor. However, its long-term
effect on functional recovery are unknown. In this study, we aimed to investigate the effects of long-term outcomes after cerebral ischemia, and the timing of initiation of LLLT affects functional recovery. We used focal cerebral ischemia following photothrombosis and LLLT treated to mice at different time point. Immediately after the infarct, the animals administrated Bromodeoxyuridine for 5 sequential days post-infarct. Proliferation of astrocyte, migroglia, immature and mature neuron, endothelial cells were examined at behaviroal, structural levels. Aucte, subacute LLLT-treated group significantly improved motor function, not brain atrophy at

28 days. Furthermore, the LLLT increased the survival proliferating GFAP, DCX, NeuN, CD31-positive cells, especially subacute LLLT-treated group, whereas decreased proliferating microglia. Furthermore, BDNF was significantly upregulated in Subacute LLLT. Our results suggest that Subacute LLLT may have long-term protective effect through proliferation of cell survival, concentrations at 28 days resulting in increased gliogenesis, neurogenesis, angiogenesis through releasing of promoting mBNDF.
These findings have important implications for timing of initiation of LLLT of focal cerebral ischemia, that appropriate subacute phase associated with neurovascular network and remodeling.

Disclosures: H. Lee: None. **Y. Shin:** None.

Poster

475. Ischemia III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.02/T11

Topic: C.08. Ischemia

Title: Time-course of the development of inflammation in a model of transient cerebral ischemia in the rat

Authors: *E. ESNEAULT[1,2], G. PEYON[1], F. SIMON[2], P. KITCHENER[2]
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Abstract: Inflammation plays an important role in the pathogenesis of ischemic stroke and is characterized by a rapid activation of resident cells (mainly astrocytes and microglia) followed by the infiltration of circulating inflammatory cells. Microglia activation involves caspase 1 activation through the NLRP3 inflammasome which controls the release of proinflammatory cytokines such as Il1beta. The aim of the present study was to determine the kinetics of inflammatory responses in a model of transient cerebral ischemia in the rat. In parallel, sensory-motor deficits were evaluated to identify the potential therapeutic window for targeting inflammatory pathways.
Cerebral ischemia was induced by an embolus placed at the origin of the middle cerebral artery (MCA). The filament was maintained during 90 minutes and was then removed to allow reperfusion. Rats were sacrificed at different time-points after cerebral ischemia, (24 hours, 72 hours and 7 days) and brain sections were stained with markers assessing neurons (NeuN), astrocytes (GFAP) and microglia (Iba1). NLRP3 and caspase-1 were also evaluated as actors of the inflammatory response. In parallel, the ischemic rats were evaluated with a battery of functional tests, and compared with sham-operated rats.
Neuronal/glial death, mainly localized in the cortex and in the striatum, increased over 72 hours following cerebral ischemia after which there was no further progression of the ischemic insult.

Recruitment of reactive astrocytes increased until Day 7 at the border of the infarct region. The number of active microglial cells started to increase from 72 hours after MCAo into the infarct region with a maximum at Day 7. In parallel, caspase 1 positive cells and caspase 1 expression increased in the infarct region from 24 hours to 7 days with a maximum observed at 7 days. Sensory-motor deficits appear from 24 hours in the neurological score and were confirmed at 72 hours in the adhesive removal test and the foot-fault test. A partial and spontaneous recovery was observed in the ischemic rats from Day 7.
These results show that the inflammatory response is progressively established over several days following transient MCA occlusion in the rat, as a reaction to the massive initial neuronal cell death, and is still highly present while rats are showing signs of functional recovery. Modulation of inflammation at an early stage may be of interest to improve sensory-motor impairment. A comprehensive understanding of the time-dependent recruitment of inflammatory cells is a prerequisite for developing new therapeutic strategies targeting inflammatory pathways for the treatment of acute ischemic stroke.

Disclosures: E. Esneault: None. **G. Peyon:** None. **F. Simon:** None. **P. Kitchener:** None.

Poster

475. Ischemia III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.03/T12

Topic: C.08. Ischemia

Support: Capes
CNPq
Fapergs

Title: Coumestrol administration attenuates cognitive deficits and reactive astroglyosis caused by neonatal hypoxia-ischemia in Wistar rats

Authors: *J. B. ANASTÁCIO, E. F. SANCHES, F. NICOLA, R. FABRES, C. A. NETTO
Univ. Federal do Rio Grande do Sul, Porto Alegre, Brazil

Abstract: Introduction: Neonatal Hypoxia-ischemia (HI) is one of the major causes of morbidity and death in neonates. HI is the result of impaired blood flow and oxygen delivery to the brain, and no effective therapies have been developed so far. Following HI injury, a robust glial response starts in the brain involving astrocytes and microglia that are important for a variety of physiological and pathological processes in the developing brain. Phytoestrogens are nonsteroidal plant substances that are structurally and functionally similar to estrogen. Here, we tested the effects of the phytoestrogen coumestrol, a potent isoflavonoid, for treating HI rats. Methods: At 7th postnatal day (PND), Wistar rats were submitted to the Levine-Rice model of

neonatal HI (permanent occlusion of the right common carotid artery with subsequent exposure to hypoxia - 8% O_2 and 92% N_2 for 60 min). Animals were randomly allocated into four groups: sham, HI+vehicle, HI+coumestrol pre-hypoxia and HI+coumestrol post hypoxia. Intraperitoneal injections of coumestrol (Sigma), in a dose of 20mg/kg, were administered immediately pre-hypoxia or 3 hours post-hypoxia. Sham animals were injected with vehicle (DMSO). Results: The Morris water maze task showed cognitive deficits induced by HI at PND60, both in reference and working spatial memory. Following behavioral analysis, histological assessment showed HI tissue loss of ipsilesional hemisphere and hippocampus, this effect was counteracted by coumestrol treatment. Moreover, reactive astroglyosis, a determining factor for severity of HI injury, was decreased in the CA1 region in coumestrol treated rats. This indicates that HI caused an increase in GFAP expression that was prevented by coumestrol administration. A negative correlation was found between performance in the last day of training in the reference memory protocol and GFAP expression, in which animals with better performance showed smaller astrocyte reactivity. Conclusions: It is shown that coumestrol is able to prevent behavioral and histological deleterious effects caused by HI, suggesting its possible use as a therapeutic strategy for neonatal hypoxia-ischemia in humans.

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Poster

475. Ischemia III

Location: SDCC Halls B-H

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Program #/Poster #: 475.04/T13

Topic: C.08. Ischemia

Support: NRF-2016R1A2B3009660, www.nrf.re.kr
CRI 13072-3, www.cnuh.com
GIST, 2017, www.gist.ac.kr

Title: Transcortical photothrombotic pyramidotomy model with persistent motor deficits

Authors: J.-Y. PARK[1], H. SONG[1], B.-M. CHOI[2], M.-S. KIM[3], W.-G. KIM[4], M.-C. LEE[5], *H.-I. KIM[1]
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Abstract: Introduction:Traditional pyramidotomy models have a high mortality rate from breathing difficulties and show early recovery from the induced motor deficits. This study

establishes a novel pyramidotomy technique that generates persistent motor deficits and has a reduced mortality rate. Material & method: We used viral neural tracing to identify the course and relative distribution of forelimb and hindlimb motor fibers (n = 9). On basis of the neural tracing data, the medullary pyramid was targeted dorsally from the cerebellar cortex for photothrombotic infarct lesioning (n = 20). Our target specifically included the medial portion of the medullary pyramid. Results: Neural tracing demonstrated that forelimb motor fibers(FMFs) and hindlimb motor fibers (HMFs) are intermingled and it is difficult to distinguish the relative location of the FMFs and HMFs. However, the density of FMFs is higher than that of HMFs in the medial portion of the pyramid, indicating that it is essential to destroy the medial portion of the pyramid during pyramidotomy. The photothrombotic technique selectively destroyed the corticospinal fibers in the medullary pyramid with relative preservation of neighboring grey-matter tissue because of the different degree of light scattering in the white and grey matter. There was a significant and persistent decrease in motor and sensory function in the contralateral limb following pyramidotomy, as demonstrated by performance in the single pellet reaching task, the foot-fault test, and the adhesive-removal test. There was no operative mortality or loss of respiratory function in this study. Conclusion: These results indicate that photothrombotic pyramidotomy with a dorsal transcortical approach is a safe technique for generating a reliable pyramidotomy model with persistent motor deficits.

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Poster

475. Ischemia III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.05/T14

Topic: C.08. Ischemia

Title: Evaluating estetrol as a neuroprotectant in cerebral ischemia

Authors: *S. MUKHERJEE, G. KUMAR, B. VERMANI, R. P. PATNAIK, 221005
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Abstract: RIPK1 is the molecular mediator of non-apoptotic DR-mediated cell death pathway, which has been termed as necroptosis, a pathway intrinsically involved in ischemic cell death. Several studies have suggested that RIPK1 inhibition ameliorates cerebral ischemic conditions *in-vivo*. Though Necrostatins has been designed as chemical inhibitors of RIPK1, their low pharmacokinetics property and lower metabolic stability causes the need of designing new RIPK1 inhibitors an absolute necessity. Neuroprotective ability of Estrogen molecules is long reported and Estetrol, which was thought to be the weakest among the Estrogen hormones, has been recently reported to successfully combat neonatal ischemic hypoxia. *In-silico* screening of

Estrogen molecules reveal that Estradiol and Estetrol bind to RIPK1 with affinity higher than Necrostatin-1 and Necrostatin-4. Also, analysis of hydrophobic interactions and hydrogen bonds between the enzyme and inhibitors represent Estetrol as possible strong inhibitor of RIPK-1. The *in-silico* study is supported by in-vivo experiments, where Estetrol shows neuroprotection in rat model, by ameliorating cerebral ischemia in rat models. The neuroprotective ability of Estetrol was evaluated by analyzing infarct volume of brain, blood-brain barrier permeability of Evan's Blue and Cerebral Blood Flow (CBF) measurement. The study suggests that neuroprotective ability of Estetrol might be further exploited and the molecule can be designed into neurotherapeutics.

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Poster

475. Ischemia III

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Program #/Poster #: 475.06/T15

Topic: C.08. Ischemia

Support: BioTime Inc.

Title: Intracerebral delivery of brain-derived neurotrophic factor using HyStem®-C hydrogel implants improves functional recovery and reduces neuroinflammation in a rat model of ischemic stroke

Authors: *D. BRIGGS[1], K. RAVINA[1], S. KISLAL[1], Z. WARRAICH[1], T. NGUYEN[1], R. LAM[1], T. ZAREMBINSKI[2], M. SHAMLOO[1]
[1]Stanford Univ., Palo Alto, CA; [2]BioTime Inc., Alameda, CA

Abstract: Ischemic stroke is a leading cause of death and disability worldwide. Potential therapeutics aimed at neural repair and functional recovery are limited in their ability to permeate the blood-brain barrier and may exert systemic or off-target effects. We examined the effects of brain-derived neurotrophic factor (BDNF), delivered via an extended release HyStem®-C hydrogel implant or vehicle, on sensorimotor function, infarct volume, and neuroinflammation, following permanent distal middle cerebral artery occlusion (dMCAo) in rats. Sprague Dawley rats aged 64-69 days received dMCAo lasting 60 min or sham surgery. Eight days later, treatments were implanted directly into the infarction site. Rats received either vehicle, BDNF-only (0.167 µg/µL), hydrogel-only, hydrogel impregnated with 0.057 µg/µL of BDNF (hydrogel+$BDNF_{LOW}$), or hydrogel impregnated with 0.167 µg/µL of BDNF (hydrogel+$BDNF_{HIGH}$). The 28-point Neuroscore (28-PN) and adhesive removal tests (ART) were used to evaluate sensorimotor function up to two months post-stroke. The hydrogel+$BDNF_{HIGH}$ group showed significant improvements on the ART 6-8 weeks following

treatment and their behavioral performance was consistently greater on the 28-PN. Infarct volume was reduced in rats treated with hydrogel+$BDNF_{HIGH}$ as were levels of Iba1, CD68, and GFAP in the corpus striatum. These data suggest that targeted intracerebral delivery of BDNF using hydrogels may mitigate ischemic brain injury and restore functional deficits by reducing neuroinflammation.

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Poster

475. Ischemia III

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Program #/Poster #: 475.07/T16

Topic: C.08. Ischemia

Support: National Natural Science Foundation of China(Nos. 81471339)

Title: Metformin improves neurological outcome via AMPK mediated autophagy activation in a rat model of cardiac arrest and resuscitation

Authors: *S. PAN[1], J. ZHU[2], Y. HU[2], K. HUANG[2], Z. JI[2], Y. GU[2], K. LIU[2]
[1]Dept. of Neurology, Nanfang Hospital, Souther, Guangdong, China; [2]Nanfang Hospital, Southern Med. Univ., Guangzhou, China

Abstract: Background: Sudden cardiac arrest (CA) often results in severe injury to the brain, and neuroprotection after CA has proven to be difficult to achieve. Here, we sought to investigate the effects of metformin pretreatment on brain injury secondary to CA and cardiopulmonary resuscitation (CPR).
Methods and Results: Rats were subjected to 9-minute asphyxia CA after receiving daily metformin treatment for 2 weeks. Survival rate, neurologic deficit scores, neuronal loss, AMPK and autophagy activation were assessed at indicated time points with the first 7 days after return of spontaneous circulation. Our results showed that metformin pretreatment elevated the 7-day survival rate from 55% to 85% and significantly reduced neurologic deficit scores. Moreover, metformin ameliorated CA-induced neuronal degeneration and glial activation in the hippocampal CA1 region, which was accompanied by augmented AMPK phosphorylation and autophagy activation in affected neuronal tissue. Of note, inhibition of AMPK or autophagy with pharmacological inhibitors abolished metformin-afforded neuroprotection, and augmented autophagy induction by metformin treatment appeared to downstream of AMPK activation.
Conclusions: Taken together, our data demonstrate for the first time that metformin confers

neuroprotection against ischemic brain injury after CA/CPR by augmenting AMPK-dependent autophagy activation.

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Poster

475. Ischemia III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.08/T17

Topic: C.08. Ischemia

Title: Quantitative susceptibility mapping (GSM) MRI in a collagenase rat model of intracerebral hemorrhage (ICH)

Authors: *K. LEHTIMÄKI, A. SHATILLO, E. LATONUMMI, A. J. NURMI
Charles River Discovery, Kuopio, Finland

Abstract: Intracerebral hemorrhage (ICH) is a significant cause of mortality throughout the world. Management of ICH in terms of clot lysis and iron scavenging after the initial insult is critical for the recovery and appropriate imaging methods to detect and follow the process are needed (Morgenstern et al., Stroke 2010). The objective of this study was to validate quantitative susceptibility mapping (QSM) methodology in a collagenase-induced ICH model in Wistar rats. Working hypothesis was that QSM could show window to observe the susceptibility changes both in the edematous processes and iron environment.
Male Wistar rats weighing 230-300 g were used for the experiment. Intracerebral hemorrhage was induced by intra-striatal infusion of collagenase IV (MacLellan et al., J Cereb Blood Flow Metab. 2008). In vivo T2 and diffusion mapping MRI were performed at sub-acute 6 hours, 1, 3 and 14 day time-points to characterize the lesion development. Subgroups of rats were perfused and fixed brains were subjected to QSM MRI at 1 and 3 days post-ICH.
In vivo T2 mapping showed large hypointense lesions corresponding to actual acute hemorrhage at 6 hours which developed progressively hyperintense lesions at later time points (1, 3 and 14 days). Diffusion values showed clear increase (while T2 remaining roughly at the same level) from day 1 to day 3, most likely reflecting reduced cytotoxic contribution in the lesion development. QSM revealed large collagenase-induced ICH lesions with low susceptibility core and high susceptibility outer rim (high iron contribution) surrounded again by low susceptibility region outside the actual lesion. This “rim-around-rim” is assumed to reflect ongoing cytotoxic edema process whereas the low susceptibility in the core of the lesion relates to vasogenic edema and cell death. Total lesion QSM results by histogram comparison show clear modulation of spread of susceptibility values from day 1 to day 3; namely, day 1 distribution contain significantly higher proportion of both oedema processes and iron content than day 3. Based on

these data, QSM method seems particularly suitable for the in vivo application in a rat model of ICH due to proper lesion size and the clear presence of iron. This combination of methodology and animal model may provide the window to study novel treatments of ICH.

Disclosures: A. Shatillo: None. **E. Latonummi:** None. **A.J. Nurmi:** None.

Poster

475. Ischemia III

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.09/T18

Topic: C.08. Ischemia

Title: Functional imaging of thromboembolic stroke in rats using PET, ultrasound and MRI

Authors: *E. LATONUMMI[1], J. RYTKÖNEN[1], A. SHATILLO[1], K. LEHTIMÄKI[1], P. POUTIAINEN[2], T. HUHTALA[1], D. MISZCZUK[1], A. J. NURMI[1]
[1]Charles River Discovery, Kuopio, Finland; [2]Kuopio Univ. Hosp., Kuopio, Finland

Abstract: Embolic stroke is a significant cause of mortality and neurological deficits e.g. paralysis, throughout the world. It is a devastating complication resulting from blood clots forming elsewhere in the body and traveling through the blood stream to the brain where it enters a blood vessel that is too small to allow it to pass and blocks the flow of blood to the brain area. It is associated with multiple risk factors including atrial fibrillation, atherosclerosis and hypertension. Fast diagnosis and early start of thrombolytic treatment is critical for limiting the ischemic damage and for the patient's well-being. The objective of this study was to visualize clot dissolving treatment during hypoxia PET scanning in a thromboembolic stroke (TBE) model in SHR rats. Further, the efficacy of treatment was assessed with ultrasound imaging (US) and magnetic resonance imaging (MRI).
Male SHR rats weighing 230-300 g were used for the experiment. TBE was induced injection of autologous blood clots in suspension into the internal carotid artery. Dynamic PET scan was performed 60-180 minutes after the stroke with hypoxia radiotracer ^{18}F-FMISO. Treatment with vehicle or tissue plasminogen activator (tPA, Alteplase) was performed during the PET scanning, 120-180 minutes after the stroke. On the following day animals were scanned with fUS and MRI for vascular map and lesion volume, respectively.
^{18}F-FMISO localization to hypoxic areas could be visualized from the PET images. Thrombolytic treatment with tPA was shown to correlate with reduced lesion size in individual animals. This combination of functional imaging and animal model may provide the tools to study novel treatments of ischemic stroke.

Disclosures: E. Latonummi: None. **J. Rytkönen:** None. **A. Shatillo:** None. **K. Lehtimäki:** None. **P. Poutiainen:** None. **T. Huhtala:** None. **D. Miszczuk:** None. **A.J. Nurmi:** None.

Poster

475. Ischemia III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.10/U1

Topic: C.08. Ischemia

Title: Longitudinal population characteristics of volume-behaviour measures in a non-human primate model of stroke

Authors: *K. A. HARRISON[1], G. RAMÍREZ-GARCÍA[4], J. FERNANDEZ-RUIZ[5], J. Y. NASHED[2], J. LECLERC[3], D. J. COOK[2]
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Abstract: Stroke is the second leading cause of death worldwide. Brain imaging data from rodent stroke models suggest size and location of ischemic lesions relate to behavioural outcome. However, such a relationship is not well established in Non-Human Primate (NHP) models. Thus, we evaluated size, location, and severity of stroke following controlled Middle Cerebral Artery Occlusion (MCAO) in NHP to neurological outcome. Cynomolgus macaques underwent structural T2 scans prior to, 48h, and 30-days post-MCAO. Neurological function was assessed with the Nonhuman Primate Stroke Scale (NHPSS). T2 whole lesion volume was calculated per subject. The longitudinal lesion volume evaluation showed a positive correlation with the NHPSS score, whereas the remaining brain volume negatively correlated with the NHPSS. Following ROI parcellation, NHPSS outcome correlated to lesion volume at 30- days of frontal, temporal, occipital, and middle white matter, as well as the internal capsule, and the superior temporal and middle temporal gyri, and the caudate nucleus. This supports the notion that stroke regionality and severity predicts outcome. The NHP model provides a fairly homogenous stroke in terms of regionality, and this outcome correlated with severity. This research represents an important step in stroke translational research by defining characteristics of the NHP stroke model; though to have greater similarities to the clinical population of interest.

Disclosures: K.A. Harrison: None. **G. Ramírez-García:** None. **J. Fernandez-Ruiz:** None. **J.Y. Nashed:** None. **J. LeClerc:** None. **D.J. Cook:** 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.; Revalesio Corp.

Poster

475. Ischemia III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.11/U2

Topic: C.08. Ischemia

Support: Intramural Research Program of the NIH, NINDS

Title: Generation of Notch3 mutations in marmoset using CRISPR/Cas9 system

Authors: *J. PARK[1], X. ZHANG[1], K. C. YOUNG[1], S. HA[2], A. C. SILVA[1]
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Abstract: Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited cerebral small vessel disease caused by the notch homolog protein 3 (NOTCH3) mutation. The molecular mechanisms underlying CADASIL remain poorly defined and studies in animal models of CADASIL will shed light on potential disease mechanisms. The common marmoset (Callithrix jacchus) is an important nonhuman primate model for studying human neurological disorders. Recent advances of genome editing in marmosets provide even wider opportunities for the development of new marmoset models of disease. The aim of this study was to generate Notch3 mutant marmosets using CRISPR/Cas9 system to model CADASIL. In group 1, specific CRISPR gRNAs for exon 8 regions of the marmoset notch3 gene were designed and gRNA/Cas9 protein complexes were microinjected into single cell stage marmoset embryos. In group 2, a single-stranded oligonucleotide donor template containing the desired point mutation was microinjected with gRNA/Cas9 protein complexes for more precise genome editing. The microinjected embryos were cultured in Sequential Cleav culture medium for 3 days and noninvasively transferred to recipient females. The presence of Notch3 gene mutation in microinjected embryos were confirmed by T7E1 assay and sanger sequencing of PCR amplicons spanning the targeted exon. In group 1, 164 embryos were transferred to 56 recipient females and 16 recipients (28.6%) were confirmed by ultrasonography to be at early stages of pregnancy. Four recipients took the pregnancy to term and 6 neonate were born alive. Of those, five neonates died within the first week of age, but one neonate survived and exhibits mutations of the Notch3 gene. In group 2, 40 embryos were transferred to 12 surrogate mothers and 4 recipients (33.3%) were confirmed to be at early stages of pregnancy. Among the pregnant recipients, one is currently in advanced stage of her gestation period. These results are important steps in establishing a marmoset model of CADASIL, the most prominent known cause of inherited stroke and neurovascular disorders in human. We are confident that these animals will bring about novel and exciting opportunities to investigate the pathogenesis of CADASIL and for developing innovative therapeutics.

Disclosures: J. Park: None. **X. Zhang:** None. **K.C. Young:** None. **S. Ha:** None. **A.C. Silva:** None.

Poster

475. Ischemia III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.12/U3

Topic: C.08. Ischemia

Support: Grants-in-Aid and by special coordination funds from Grants-in-Aid for Scientific Research (C) [grant number 16K10988] from the Ministry of Education, Culture, Sports, Science and Technology of Japan
Kobe Gakuin University joint research (C)

Title: Orexin-A suppresses the central post-stroke pain through the activation of the descending pain inhibitory system

Authors: *S. HARADA, W. MATSUURA, S. TOKUYAMA
Kobe Gakuin Univ., Kobe, Japan

Abstract: Central post-stroke pain (CPSP), an intractable secondary disease, is a serious problem that occurs following cerebral stroke. However, the detailed mechanisms underlying CPSP and standard treatments for it are not well established. That is, it is necessary to establish for new therapeutic strategy for CPSP. The orexin-A is a identified group of neuropeptides that are mainly expressed in the lateral hypothalamic area (LHA), perifornical area and posterior hypothalamus. They play roles in many physiological functions including arousal and energy metabolism such as glucose metabolism, feeding behavior, sleep and wakefulness. Recently, it was also reported that orexin-A regulates the several pain behavior. However, it is unknown about interaction of CPSP and orexin-A. The aim of the present study was to determine the involvement of orexin-A in the CPSP in an animal model of global cerebral ischemia.
Male ddY mice were subjected to 30 min of bilateral carotid artery occlusion (BCAO). The development of hind paw mechanical allodynia was measured using the von Frey test. On day 3 after BCAO, mice were intracerebroventricular (i.c.v.) injected orexin-A (50, 150 pmol/mouse), after then we performed the von Frey test. SB334867 (orexin-1 receptor antagonist) i.c.v. injected at 30 min, and yohimbine (α_2 receptor antagonist) or WAY1000635 (5-HT_{1A} receptor antagonist) intrathecal (i.t.) injected at 15 min before orexin-A i.c.v. injection.
The number of escape behaviors, called for mechanical allodynia, in response to the stimulation applied by the von Frey filament was significantly increased on day 3 after BCAO as compared with sham group. The BCAO-induced mechanical allodynia was significantly suppressed by i.c.v. injection of orexin-A. Orexin-A-induced suppressive effect was significantly despaired by i.c.v. injection of SB334867. In addition, that effect also canceled by i.t. injection of yohimbine,

a α_2 receptor antagonist, or WAY1000635, a 5-HT_{1A} receptor antagonist.
We conclude that orexin-A may involve in alleviation of CPSP. As one of its mechanism, it is possible that effect of orexin-A is mediated by activation of the descending pain inhibitory system.

Disclosures: S. Harada: None. **W. Matsuura:** None. **S. Tokuyama:** None.

Poster

475. Ischemia III

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Topic: C.08. Ischemia

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Title: Thalamic neurodegeneration following distal middle cerebral artery occlusion in rats is not associated with thermal or mechanical hypersensitivity

Authors: *J. E. ANTTILA, S. PÖYHÖNEN, M. AIRAVAARA
Inst. of Biotech., Univ. of Helsinki, Helsinki, Finland

Abstract: Introduction: Central post-stroke pain (CPSP) is a neuropathic pain syndrome that may develop after a stroke in the somatosensory pathways. Patients suffering from thalamic infarcts have a higher risk of developing CPSP as the thalamus has a prominent role in pain processing. The symptoms often include hyperalgesia, which has also been described in rodents after direct ischemic or hemorrhagic damage of the thalamus. A cortical infarct induces neuronal loss in the ipsilateral thalamus as a secondary effect due to connecting thalamocortical and corticothalamic pathways. However, the behavioral consequences of secondary neurodegeneration are unclear. By inducing a cortical ischemia-reperfusion injury, we investigated the amount of secondary neurodegeneration in the thalamus, and whether it is associated with hyperalgesia.
Methods: Unilateral cortical infarction was induced in adult male Sprague Dawley rats (n=9) by transiently ligating the distal branch of the right middle cerebral artery with a 10-0 suture and occluding both common carotid arteries for 90 minutes. Thermal hyperalgesia was examined with Hargreaves' test and mechanical hyperalgesia with modified Von Frey test. Sham-operated

(n=9) and naïve (n=10) rats were used as controls. At 4 weeks after the stroke/sham operation the number of neurons and phagocytic microglia/macrophages in the thalamus were quantified.
Results: At 4 weeks post-stroke, 38% of the neurons in the ipsilateral thalamus were lost ($p<0.0001$), and the number of phagocytic microglia/macrophages was over 30-fold greater compared to sham-operated and naïve rats ($p<0.0001$). There were no differences between the stroke and sham groups in thermal or mechanical sensitivity.
Conclusions: We observed extensive neuronal degeneration and microglial activation in the ipsilateral thalamus at 4 weeks post-stroke but found no hyperalgesia. Therefore, thalamic neurodegeneration and inflammation alone are not enough to trigger hyperalgesia after experimental stroke, but the development of hyperalgesia may require direct ischemic or hemorrhagic injury of the thalamus.

Disclosures: J.E. Anttila: None. **S. Pöyhönen:** None. **M. Airavaara:** None.

Poster

475. Ischemia III

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Program #/Poster #: 475.14/U5

Topic: C.08. Ischemia

Support: Qatar National Research Fund(QNRF)
Alberta Innovates Health Solutions(AIHS)
Li Ka Shing Sino-Canadian Exchange Program

Title: Accelerated collateral failure in aged rats during ischemic stroke

Authors: *J. MA[1,2], Y. MA[2], A. SHUAIB[1,3], I. R. WINSHIP[1,2]
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Abstract: Background and purposes: Cerebral collateral circulation and age are critical factors in determining outcome from acute ischemic stroke. Cerebral collaterals are recruited in the hyper acute phase of ischemia and are significant determinants of tissue outcome and response to therapy. Aging may lead to rarefaction of cerebral collaterals and thereby accelerate ischemic injury in brain tissues by reducing penumbral blood flow. However, dynamic changes in cerebral pial collaterals after onset of the cerebral ischemia in different ages of rats has not been well studied.
Methods and Results: In this study, two imaging methods, Laser speckle contrast imaging(LSCI) and two photon laser scanning microscopy(TPLSM) were combined to continuously monitor cerebral pial collaterals between the anterior cerebral artery (ACA) and the middle cerebral artery (MCA) in young (2 months) and aged (16 months) male Sprague Dawley

rats during distal middle cerebral artery occlusion (dMCAo). LSCI showed that both cerebral collateral perfusion declined over time after stroke ("collateral failure") in both aged and young rats. However, this decline was significantly accelerated in aged rats. TPLSM confirmed that pial arterioles narrowed faster after dMCAo in aged rats compared to young rats. Notably, while arteriole vessel narrowing was comparable by the experimental endpoint in aged and young rats, red blood cell velocity and the overall flux of blood through pial arterioles were significantly reduced at all time points in aged rats relative to young rats. Infarction measurement in Hemotoxylin-Eosin stained tissue showed aged rats had significantly ischemic damage than young rats.
Conclusions: Our findings show that cerebral pial collateral failure is accelerated in aged rats than young rats. Interestingly, while arteriole constriction was accelerated in aged rats, within 3hours vessel diameters were comparable between aged and young rats. However, blood flow velocity and flux remained significantly lower at all time points in aged rats.These findings confirm that aging has detrimental effects on pial collateral dynamics in rats in the hyper acute phase of stroke.

Disclosures: J. Ma: None. **Y. Ma:** None. **A. Shuaib:** None. **I.R. Winship:** None.

Poster

475. Ischemia III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.15/U6

Topic: C.08. Ischemia

Title: Novel high-density quantitative μECoG recordings to record spreading depolarizations after permanent cerebral ischemia in awake freely moving rats

Authors: K. PALOPOLI-TROJANI[1], M. TRUMPIS[1], J. VIVENTI[2], D. A. TURNER[3], *U. HOFFMANN[4]
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Abstract: BACKGROUND: The dynamic concept of the penumbra and the impact of cortical spreading depolarizations (CSDs) on ischemic cerebral stroke evolution are mainly based on short-term neurophysiological and functional imaging studies in anesthetized animals subjected to focal ischemia. The transfer of this concept to awake, freely moving animals is challenging, and therefore, has been limited due to technical considerations. To resolve these challenges, we demonstrate the simultaneous recording of both: ongoing spontaneous cortical activity and ultra-slow signals, such as CSDs, using novel high density microelectrocorticographic (μECoG) technology to create a real-time functional map of stroke boundaries. **METHODS:** μECoG

arrays. Passive, high-density µECoG arrays featuring very thin wires (25 µm) to allow high-density interconnections. Individual contacts 200 µm in diameter, provide a low-impedance interface and the 61 electrodes are arranged in an 8x8grid with 400-µm spacing. The total recorded area is ~3.5 mm x 3.5 mm. Data acquisition. We developed a high-density data acquisition system for highly miniaturized multiplexed neural signal acquisition. It is critically important to this project that this data acquisition system has DC-coupled amplifiers that allow us to record ultra-slow signals from the brain, particularly cortical spreading depressions (CSDs). Using this system, we can simultaneously record ultra-slow signals, including near DC and neural signals concurrently, in awake, freely moving animals. Implantation of µECoG array and induction of focal cerebral ischemia: a craniotomy was made over the right hemisphere, the electrode array was epidurally placed over the parietal-temporal cortex and encapsulated in cement. After three days recovery, rats were subjected to permanent middle cerebral artery occlusion; µECoG array was hooked up to the recording system via a tethered ultra-flexible µHDMI cable in the home cage of the animal and recordings were started. **RESULTS:** We demonstrate the detection of cortical spreading depolarizations (CSDs, slow DC field potential shifts) using the 61 channel µECoG array after induction of ischemic stroke in awake, freely moving rats continuously for up to seven days. The high density recordings reveal the evolving features of ongoing cortical activity after the initial ischemia, demonstrating the dynamic nature of stroke boundaries. **CONCLUSION:** In these novel experiments, we use high density µECoG continuous monitoring in non-anesthetized rats after focal ischemia revealing the dynamic nature of stroke boundaries as well as the role of CSD occurrences in secondary stroke expansion.

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Poster

475. Ischemia III

Location: SDCC Halls B-H

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Program #/Poster #: 475.16/U7

Topic: C.08. Ischemia

Support: VRP P1201708

Title: Glial engagement at the hematoma after intracerebral hemorrhage in the mouse

Authors: *K. GIORDANO[1,2], C. R. DENMAN[1,3,2], R. K. ROWE[1,2,4], J. LIFSHITZ[1,2,4], M. AKHTER[1,2,5]
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Abstract: Intracerebral hemorrhage (ICH) has the highest rate of mortality and one of the highest rates of morbidity among all stroke subtypes with as few as 20% of survivors regaining complete independence by 6 months post-injury. As a component of the ICH pathophysiology, the inflammatory response includes immune cell migration and glial activation. Brain microglia are dynamic sentries of the extracellular environment and activate morphologically and thereby functionally in response to stresses, such as injury. Microglia activation involves retraction and thickening of processes while producing immunoactive cytokines. Full activation manifests with an amoeboid morphology, whereas rod microglia are an alternative morphology. We hypothesized that in response to experimental ICH, microglia are activated and migrate to the injury site as evidenced by a change in morphology and cell number over time. CX3Cr1-eGFP mice were subjected to collagenase or saline intracerebral injection (0.5U in 1 µl over 4 min) through the cortex into the striatum (-0.10mm posterior, +2.0mm lateral, -2.5mm ventral from Bregma). At 7 days post-injury, microglia morphology and number in the cortex and striatum were analyzed by skeleton analysis to assess microglial process length, process endpoints, and cell counts. In ipsilateral ICH striatum, microglia had decreased process length and process endpoints compared to the contralateral hemisphere and saline controls, consistent with microglial activation. The perihematomal striatum and ipsilateral cortex of the needle track contained more microglia per field-of-view compared to the contralateral hemisphere and saline controls. Rod microglia were present in both the perihematomal striatum and ipsilateral cortex of ICH animals only. Thus, a key inflammatory response following ICH is microglia deramification (shorter and fewer processes/cell), indicating injury-induced activation localized to the injury site. More cells suggest either a proliferation or migration of microglia towards the injury site, likely through chemotaxis. Further, this is the first study to show the activated rod microglia morphology in ICH. Translationally, it is critical to investigate the time course of microglia activation in response to ICH in order to target anti-inflammatory treatments for ICH.
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Poster

475. Ischemia III

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Program #/Poster #: 475.17/U8

Topic: C.08. Ischemia

Title: Timing matters: The impact of hypothermia on human neural stem cell action *in vitro* supports the need to find optimal timing for combined cell-based therapy with hypothermia for perinatal hypoxic ischemic injury

Authors: *J. LAW[1,2], C. D. PERNIA[2], W. D. NILES, II[2], E. Y. SNYDER[2]
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Abstract: Purpose: As many as 8 of every 1000 live births experiences a lack of oxygen to the brain near the time of delivery, an injury called perinatal hypoxic ischemic injury (HII). If left untreated, up to 65% of these babies may have lifelong neurologic sequelae including cerebral palsy, epilepsy, learning disabilities, and autistic behaviors. Although hypothermia (HT) is standard-of-care (SOC) in treating HII, it is only marginally effective in moderate cases and ineffective in severe HII. We and others have reported the efficacy and safety of transplanted human neural stem cells (hNSCs) for salvaging injured brain parenchyma (aka the penumbra) leading to improved histologic and behavioral outcomes in rodent models of HII. None of these reports, however, evaluated hNSC action under SOC HT conditions. It remains uncertain whether HT antagonizes or complements hNSC function.
Methods: hNSCs were studied in vitro under normothermic (NT) (37°C) and SOC HT (33.5°C) conditions and evaluated on days 0, 1, 2, 3, and 6. Change in hNSC colony size over time was measured as a marker of colony growth, and migration was assessed using scratch assays. Total protein production was evaluated by BCA protein assay. For western analysis, antibodies to β3-tubulin (an immature neuronal marker) and proliferative cell nuclear antigen (PCNA - a marker of cell proliferation) were used.
Results: HT decreased the rates of hNSC proliferation and migration ($p=0.0006$ and $p<0.0001$, respectively) over time compared to NT. The doubling time for NT hNSCs was 5.2 days compared to 21.1 days for HT hNSCs. HT hNSCs exhibited significant differences in protein abundance over time by BCA analysis ($p=0.0004$) relative to NT hNSCs. Western blot analysis demonstrated no difference in β3-tubulin presence in NT vs. HT cells, however there was a strong trend toward a decrease in markers of cell division in HT compared to NT hNSCs ($p=0.06$). Most of these changes were not apparent until after three days of HT.
Conclusion: HT significantly altered hNSC proliferation, migration, and protein production in vitro. However, given that SOC HT is instituted for only three days following HII and most changes in HT hNSCs were not apparent until after three days of exposure, combining these two neuroprotective therapies seems feasible. Alternatively, optimal timing for the introduction of cell-based therapy may be after HT is completed. Coordinating therapies, whether concurrently or in sequence, to improve outcomes must be tested in animal models of HII. Furthermore, our results raise the question of whether endogenous hNSCs, required for repair and regeneration of the neonatal brain after HII, are also affected by HT.

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Poster

475. Ischemia III

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Program #/Poster #: 475.18/U9

Topic: C.08. Ischemia

Support: DFG Grant FOR1738

Title: Recent advances in hemorrhage-induced vasospasm: *In vivo* vasoactivity of heme degradation products (HDPs) on mouse cerebral vasculature using two-photon microscopy and MR perfusion imaging

Authors: A. JOERK[1], K.-H. HERRMANN[2], D. FREITAG[3], M. RITTER[5], N. LANGGUTH[1], A. SCHAEFGEN[1], R. A. SEIDEL[5,4], M. KRAEMER[2], G. POHNERT[5], M. WESTERHAUSEN[5], J. WALTER[3], R. KALFF[3], J. REICHENBACH[2], *O. W. WITTE[6], K. HOLTHOFF[1]
[1]Dept. of Neurol., [2]Dept. of Radiology, Med. Physics Group, [3]Dept. of Neurosurg., [4]Dept. of Anaesthesiology and Intensive Care Med., Univ. Hosp. Jena, Jena, Germany; [5]Inst. of Inorganic and Analytical Chem., Jena, Germany; [6]Hans Berger Dept. of Neurol., Friedrich Schiller Univ. Jena, Jena, Germany

Abstract: BACKGROUND: Delayed ischemic neurological deficit (DIND) caused by symptomatic cerebral vasospasm is supposed to be the most common determinant of unfavorable prognosis in patients suffer from subarachnoid hemorrhage (SAH). Actually, the guideline-based recommendations of vasospasm treatment fail to improve the clinical outcome. We hypothesize that heme degradation products (HDPs), originating from the intracranial hematoma surrounding the ruptured aneurysm, are involved in vasospasm pathogenesis by inhibiting BK_{Ca} potassium channels in vascular smooth muscle cells. HDPs, comprising propentdyopents (PDPs) and bilirubin oxidation products (BOXes), are present in the cerebrospinal fluid of SAH patients and induced an acute vasoconstrictive effect on arterioles in acute mouse brain slices.
METHODS: After subarachnoid HDP application in adult wildtype and BK channel deficient mice, we analyzed acute changes in blood flow velocity and diameter of pial and intracortical arterioles *in vivo* using two-photon laser scanning microscopy. To study the long-term effect of HDPs on cerebral perfusion, SAH was experimentally induced in mice by injection autologous blood or HDP isomers into the cisterna magna, followed by temporally high-resolution echo-planar MR imaging at 9.4T.
RESULTS: Consistent with our investigations on acute brain slices, subarachnoidally administered PDP and BOX isomers caused a sustainable diameter decrease of pial arterioles *in vivo*. Both, vasoconstriction and BFV reduction depend on BK_{Ca} channel activity, because it was absent in Slo1 knockout mice. These data were complemented by MR perfusion imaging where intrathecally injected blood and PDPs induced long-term cerebral perfusion deficits in living mice.
CONCLUSION: In addition to the acute vasoactivity, our data demonstrate a long-term effect of HDPs on cerebral perfusion which correlates with the onset of delayed vasospasm in SAB patients. These findings may promote novel strategies for vasospasm treatment.

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Poster

475. Ischemia III

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Program #/Poster #: 475.19/U10

Topic: C.08. Ischemia

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Turkish Neurological Society

Title: Evaluation of persistent microcirculatory dysfunction in salvageable ischemic penumbra due to dynamic stalls in capillary red blood cell flow

Authors: *E. ERDENER[1], J. TANG[1], K. KILIÇ[1], D. POSTNOV[1], S. KURA[1], S. SAKADZIC[2], D. A. BOAS[1]
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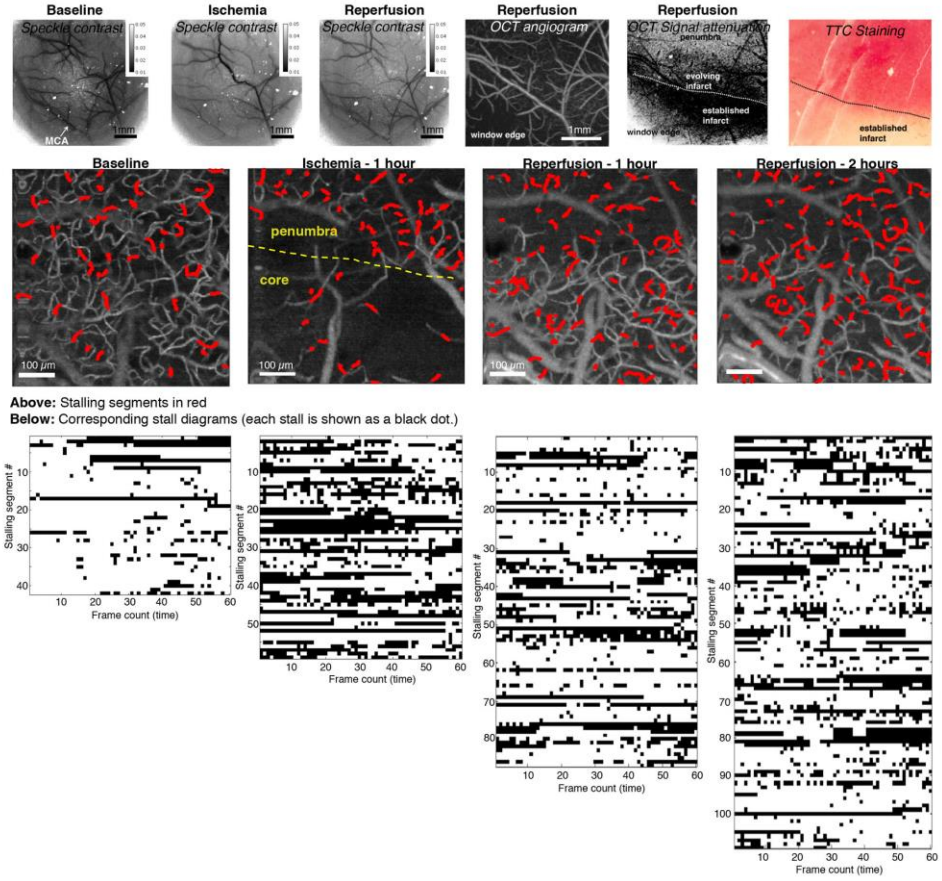
Abstract: Objective: We previously identified temporary flow interruptions in individual capillaries under physiological conditions using optical coherence tomography-angiography (OCTA). These stalls can potentially influence capillary transit time and oxygen extraction in pathological tissue . In this study, we characterized the frequency and duration of stalls in ischemic penumbra in a mouse model of distal middle cerebral artery (dMCA) stroke. **Methods:** C57BL/6 mice (n=10, male, ~3-month-old) were anesthetized with isoflurane. A craniotomy over dMCA, and a parietal closed cranial window were prepared. dMCA was occluded by compression with a blunted micropipette and was recanalized after 1 hour. Cerebral blood flow (CBF) was continuously monitored via laser speckle contrast imaging to confirm ischemia and reperfusion. OCTA time-series, and phase-resolved Doppler OCT data were collected at baseline, by 1 hour of ischemia, 1 hour and 2 hours after reperfusion. **Results:** Ischemic core was identified as the area that totally lacked capillary flow and also had decreased OCT signal penetration because of cellular swelling. In the surrounding ischemic penumbra, there was decreased CBF, decreased capillary density but relatively preserved signal penetration. CBF dropped to 13±4% and 47±6% of baseline in core and penumbra, respectively. In ischemic penumbra, fraction of stalled capillaries raised from 4±1% to 21±4% by 1 hour of ischemia. For 2 hours after recanalization stall fraction remained high (19±5% and 16±4%, respectively). Cumulative stall duration was 19±3% of observation time at baseline, increasing to 32±3% during ischemia and persisted at 35±3% and 29±2% after recanalization. No significant change in CBF or stall parameters was observed in sham group (n=4). **Conclusion:** Temporary stalls in capillary flow dramatically increases in the salvageable penumbra and remains high despite

recanalization. Measures to increase cellular passage through capillaries to improve microcirculation may have potential for decreasing stalls and preserving ischemic tissue at-risk.



Disclosures: E. Erdener: None. **J. Tang:** None. **K. Kiliç:** None. **D. Postnov:** None. **S. Kura:** None. **S. Sakadzic:** None. **D.A. Boas:** None.

Poster

475. Ischemia III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.20/U11

Topic: C.08. Ischemia

Support: NIH Grant NS069375
NIH Grant NS097945

Title: Chemogenetic modulation of noradrenergic tone in the pathogenesis of ischemic stroke

Authors: D. BRIGGS, K. RAVINA, S. KISLAL, R. LAM, C. XU, *M. SHAMLOO
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Abstract: The noradrenergic (NA) system is directly implicated in processes that govern cognitive function and neuroinflammation. Adrenergic receptors on microglia regulate neuroinflammation and the engagement of protective mechanisms critical to neuronal function and survival. Evidence suggests that degeneration of the locus coeruleus (LC), the primary source of noradrenaline in the brain, may reduce NA tone in the aging brain and increase the risk of stroke and neurological impairments. The aim of this study was to investigate the role of LC NA tone in the development of neuronal injury, neuroinflammation, and behavioral impairments following stroke. Using targeted designer receptors exclusively activated by designer drugs (DREADD) chemogenetic technology, we examined the functional consequences of inhibiting NA neuronal firing rates and experimentally reducing NA tone in the LC in a mouse model of stroke. Wild-type mice expressing Cre recombinase from the tyrosine hydroxylase or dopamine β-hydroxylase locus received bilateral injections of either control or inhibitory (Gi)-mCherry virus into the LC. Two weeks later, one cohort of mice received intraperitoneal injections of the DREADD agonist clozapine-N-oxide (CNO; 5 mg/kg) 15 min prior to and 2 h following 30 min of transient middle cerebral artery occlusion (tMCAo). Mice were sacrificed 6 h following occlusion onset. A second group of mice received CNO (2 mg/kg) via subcutaneous osmotic pumps implanted 24 h prior to or following 45 min tMCAo. Sensorimotor function was evaluated using the Beam-walk test and Neuroscore up to 15 days following stroke. Upon completion of behavioral testing mice were sacrificed and their brains assessed for neuroinflammatory markers and levels of inflammatory cytokines using qRT-PCR and immunohistochemistry. Down-regulating NA tone prior to stroke impaired sensorimotor function and enhanced neuroinflammation whereas down-regulating NA tone after stroke improved sensorimotor function and reduced neuroinflammation. Furthermore, treatment with xamoterol, a highly-selective β-adrenoreceptor 1 (ADRB1) agonist, improved functional recovery, reduced infarct volume, and mitigated neuroinflammation in rats following tMCAo. Collectively, these data suggest selective ADRB1 activation may confer neuroprotection against late-stage secondary injury and that NA tone plays a key role in the pathophysiology of ischemic stroke and the mechanisms that govern functional recovery.

Disclosures: D. Briggs: None. **K. Ravina:** None. **S. Kislal:** None. **R. Lam:** None. **C. Xu:** None. **M. Shamloo:** None.

Poster

475. Ischemia III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.21/U12

Topic: C.08. Ischemia

Support: NINDS Grant K08105914-01

Title: The effects of intraventricular hemorrhage injection in rats on spatial memory and dentate neurogenesis

Authors: T. BINYAMIN, K. KAMAL, A. IZADI, K. ONDEK, R. BERMAN, F. SHARP, *G. G. GURKOFF, B. WALDAU
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Abstract: Intraventricular hemorrhage from hypertension or aneurysm rupture can cause a range of neurological deficits and death. Cognitive deficits may prevent the return to work after recovery in over half of these patients, and impairments in memory can be seen over 10 years after initial insult. The etiology of the persistent memory impairment has not been characterized well on a cellular level. We created a rat intraventricular hemorrhage model to shed light on the cellular mechanism of memory decline after intraventricular hemorrhage. Rapid infusion of 200 microliters of blood or artificial CSF (aCSF) into the lateral ventricle in rats showed a significant increase in size of the lateral ventricles after one week compared to animals, which received no injection ($p<0.05$). Therefore, rapid ventricular volume expansion alone caused prolonged hydrocephalus. Next we examined four groups of animals after intraventricular hemorrhage in the Morris water maze: Group 1 received an intraventricular injection of 200 microliters of autologous blood over two minutes, Group 2 received an intraventricular injection of 200 microliters of aCSF over two minutes, Group 3 received an intraventricular injection of five microliters of thrombin over 15 minutes, and Group 4 received an intraventricular injection of five microliters of aCSF over 15 minutes. After one week of recovery, all groups received an intraperitoneal injection of 5-bromo-2'-deoxyuridine (BrdU) twice daily for 5 days. The animals subsequently underwent Morris water maze testing four weeks after injury. The intraventricular hemorrhage group (Group 1) performed with higher latencies than its control (Group 4), but a rapid 200 microliter aCSF (Group 2) injection as well as small volume thrombin injection (Group 3) also increased latencies compared to Group 4. BrdU analysis of the subgranular zone of the dentate gyrus showed decreased dentate neurogenesis after intraventricular hemorrhage compared to control. We conclude that intraventricular hemorrhage may decrease dentate neurogenesis, and decreased dentate neurogenesis may lead to a worse performance in the Morris water maze.

Disclosures: T. Binyamin: None. **K. Kamal:** None. **A. Izadi:** None. **K. Ondek:** None. **R. Berman:** None. **F. Sharp:** None. **G.G. Gurkoff:** None. **B. Waldau:** None.

Poster

475. Ischemia III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.22/V1

Topic: C.08. Ischemia

Support: SEP-CONACYT GRANT: 256503

Title: Neuroprotective effect of N,N'-dialkylated analogues of dapsone in a focal ischemia/perfusion model in Wistar rats

Authors: D. ZAMORA-MONDRAGON[1], *L. A. TRISTAN-LOPEZ[2], A. ORTIZ-PLATA[3], M. MENDEZ-ARMENTA[3], A. DIAZ-RUIZ[4], S. MEZA-TOLEDO[5], C. RÍOS[4]
[1]Ingeniería Bioquímica, Inst. Tecnológico de Milpa Alta, Mexico City, Mexico; [3]Lab. de Patología Exptl., [4]Dept. de Neuroquímica, [2]Inst. Nacional de Neurología y Neurocirugía, Mexico City, Mexico; [5]Lab. de Quimioterapia Exptl., Escuela Nacional de Ciencias Biológicas del Inst. Politécnico Nacional, Mexico City, Mexico

Abstract: Dapsone (DDS) is a drug used as a first line option therapy against leprosy and several dermatologic diseases. Since some N,N'-dialkylated analogues of DDS have shown remarkable properties as antiepileptic and anti-excitotoxic molecules in addition of a better toxic profile producing significant lower levels of metabolic methemoglobinemia, we have synthesized a homologous series including: N,N'-dimethyldapsone (Me-DDS), N,N'-diethyldapsone (Et-DDS), N,N'-dipropyldapsone (Pr-DDS) and N,N'-dibutyl dapsone (Bu-DDS) and evaluated their neuroprotective effect in a focal ischemia/reperfusion model in rats.
Wistar male rats (270-300gr; n=4-6) were administered with either DDS or any of the four N,N'-dialkylated analogues (i.p. 0.05 and 0.1 mmol/Kg), using a control group injected only with dimethylsulfoxide as vehicle (440 µL/Kg). Each treatment was injected 30 minutes after occlusion of middle cerebral artery and reperfusion was established 120 minutes before. Rats were evaluated for neurological and behavioral outcomes every 24 hour until sacrifice at 96 hours with Capdeville and Thiyagarajan scales. Sacrificed rats were perfused and fixed with a 4% paraformaldehyde solution, brains were dissected-out, embedded in parafin, cut for corpora striata and hippocampi observation and finally hematoxylin and eosine stained to measure infarction area using J image software.
When comparing striatal infarction areas from animals receiving the 0.05 mmol/Kg dose to those observed in control group, we found significant reduction for DDS, Me-DDS, Et-DDS and Pr-DDS groups (29-40%). Animals receiving 0.1 mmol/Kg of DDS, Me-DDS, Et-DDS and Bu-DDS also reduced striatal damage between 12-32%. Hippocampal infarction areas comparison between control group and rats receiving 0.05 mmol/Kg dose of DDS and Bu-DDS showed significant protection (25 and 33% respectively). Group administered with 0.1 mmol/ Kg of Me-DDS also showed a 42% reduction in damaged area (Mann-Whitney test;$p<0.05$). Likewise, neurological and behavioral outcomes assessed by the Capdeville and the Thiyagarajan scales showed significant protection against deficit for most of the groups treated with DDS and the N,N'-dialkylated molecules when compared to scores observed in control groups (repeated measures ANOVA, $p<0.05$).

Disclosures: D. Zamora-mondragon: None. **L.A. Tristan-lopez:** None. **A. Ortiz-plata:** None. **M. Mendez-armenta:** None. **A. Diaz-ruiz:** None. **S. Meza-toledo:** None. **C. Ríos:** None.

Poster

475. Ischemia III

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.23/V2

Topic: C.08. Ischemia

Support: NIH grant NS060703
NIH grant NS067525
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NIH grant DK38226
NIH grant HL034300

Title: The contribution of TRPV1 channels to 20-HETE-aggravated ischemic neuronal injury

Authors: *Z. YANG[1], J. R. FALCK[3], R. C. KOEHLER[2]
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[3]Biochem., Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: 20-Hydroxyeicosatetraenoic acid (20-HETE), a cytochrome P450 (CYP) 4A/4F-derived metabolite of arachidonic acid, contributes to ischemic brain injury in adults and the newborns. Our previous work has indicated that 20-HETE can aggravate injury directly within neurons. However, little is known about mediators of 20-HETE neurotoxicity after ischemia. Transient receptor potential cation channel subfamily V member 1 (TRPV1), the nonselective cation channels with massive Ca^{2+} permeability, are widely distributed in the brain and interact with 20-HETE in neural and non-neural tissues. Therefore, we hypothesize that TRPV1 plays a role in 20-HETE's toxicity in primary cortical neurons after oxygen-glucose deprivation (OGD) and in neonatal mouse brains after hypoxia-ischemia (H-I). Double-immunofluorescent staining indicated that TRPV1 and CYP4A signals were colocalized in neurons. Fluo-4 NW calcium assay results revealed that the 20-HETE mimetic agonist 20-5,14-HEDGE significantly increased early neuronal Ca2+ signals, which were attenuated by the TRPV1 antagonist capsazepine. Furthermore, genetic or pharmacologic TRPV1 inhibition attenuated 20-5,14-HEDGE-induced toxicity in cultured neurons. TRPV1 genetic inhibition and CNS-penetrable TRPV1 antagonist A784168 also protected neurons after OGD, and 20-HETE synthesis inhibitor HET0016 did not produce additional effects. Moreover, A784168 and HET0016 individually attenuated brain injury in mixed-sex groups of neonatal mice at 1 d after H-I, but the drug combination did not provide additional protection. TRPV1 genetic inhibition also protected neonatal brains at 1 d after H-I, but further analysis indicated that the protective effects were observed only in male TRPV1 knockout mice. PKC-or Src-dependent phosphorylation directly potentiates NMDA receptor-mediated neurotoxicity. H-I induced PKC-dependent phosphorylation at NMDA NR1 Ser896, phospho-Src at Tyr416 (indicative of Src activation),

and Src-dependent phosphorylation at NR2B Tyr1472 in brain tissues at 3 h of recovery. HET0016 and A784168 each attenuated H-I-induced phosphorylation of these sites. HET0016 and A784168 in combination, however, did not provide additive effects. Moreover, we did not find significant changes in total NR1, NR2B, or Src after H-I or/and HET0016 and A784168 treatment. Therefore, we conclude that TRPV1 channels are involved in 20-HETE's neurotoxicity after ischemia.

Disclosures: Z. Yang: None. **J.R. Falck:** None. **R.C. Koehler:** None.

Poster

475. Ischemia III

Location: SDCC Halls B-H

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Program #/Poster #: 475.24/V3

Topic: C.08. Ischemia

Support: NIH 5T32HL007224

Title: Role of TRPV4 and PLA2g6 in post-stroke hydrocephalus

Authors: *J. W. SHIM[1], F. NIPA[2]
[1]Med., Boston Univ., Boston, MA; [2]Boston Univ. Sch. of Med., Boston, MA

Abstract: Aim: Permeability and intracranial compliance are known to contribute to barrier dysfunction and pressure-volume regulation within the brain but how either or interaction of both are involved in pathogenic mechanisms of hydrocephalus remains elusive. The objective of this study was to better understand the role of permeability and vascular stiffness, a critical determinant of intracranial compliance in post-stroke hydrocephalus through transient receptor potential cation channel subfamily V member 4 (TRPV4) and phospholipase A2 group6 (PLA2g6). **Methods**: Wistar polycystic kidney (wpk) rats with hydrocephalus were used to characterize the localization of TRPV4 in choroid plexus, ependyma and cerebral cortex. Aortic stiffness was assessed in vivo using ultrasound and compared to age-, diet-, and gender-matched mice with constitutive deletion of PLA2g6. Gene expression analysis was conducted on aortic medial RNA and validated by elastic fiber staining. Elastin gene expression was quantified in the thoracic aorta of male mice with young and old age and of young mice fed with high fat high sucrose (HFHS) diet. Cell-specific effect on elastin gene expression and arterial stiffness was further tested in a mouse model with smooth muscle cell (SMC)-specific impairment of PLA2g6. **Results**: TRPV4 was elevated in choroid plexus and ependyma of wpk rats with rapidly developing severe hydrocephalus. We found reactive astrocytosis and neural identity of TRPV4+ cells in an early postnatal brain of the wpk rats. Strikingly, when double-stained with doublecortin (DCX) in a midbrain region in which dorsal hippocampus lies (bregma -3.4 mm), more than 50 % of TRPV4+ cell and its extension were co-labeled with DCX+ cells in the

coronal section adjacent to the ventricular surface. In vascular stiffness study, mice experiments revealed that aging and HFHS-diet induced arterial stiffening in wild type (WT) animals but not in PLA2g6 knockout mice. The SMC-specific knockout of PLA2g6 recapitulates the protective effect in that PLA2g6 impairment in SMC alone was sufficient to prevent the development of diet-induced arterial stiffening in young mice. **Conclusion**: These results suggest that targeting TRPV4 should be regionally specified for cerebral epithelia but not neural cells in the cortex while vascular cell-specific impairment of PLA2g6 may provide a protective effect against loss of vascular compliance in the brain. Molecular targets promoting cerebral epithelia-specific inhibition of TRPV4 and vascular SMC-specific PLA2g6 may provide novel therapeutic approaches for the treatment of post-stroke hydrocephalus.

Disclosures: J.W. Shim: None. **F. Nipa:** None.

Poster

475. Ischemia III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.25/V4

Topic: C.08. Ischemia

Title: Azithromycin has an innovative neuro-protective role in a neonatal mouse model of periventricular leukomalacia (PVL)

Authors: *N. ZAGHLOUL[1], K. R. AYASOLLA[2], M. N. AHMED[3]
[1]Pediatrics, Cohen's Children Med. Ctr., Manhasset, NY; [3]Pediatrics, [2]Feinstein Inst. for Med. Res., Manhasset, NY

Abstract.Abstract1:

Background: PVL is the most common cause of cerebral palsy in premature infants. Microglia is the main inflammatory cell involved in the pathogenesis of PVL. In this study, we propose that azithromycin administration ameliorates the inflammatory process leading to decreased brain injury induced by Hypoxia-ischemia (HI).

Objective: To examine the neuroprotective function of azithromycin as a new therapeutic approach in neonate mouse model of PVL.

Design/Methods: PVL neonate mouse model was established by temporary bilateral carotid ligation at P5, followed by hypoxia exposure 8% for 20 min. Three neonate groups were studied. N=30 pups /group. RA control, (HI) + saline injection and (HI) + azithromycin injection. 2 doses of Azithromycin were injected IP at a dose of 20mg/kg at P5 (2 hours after HI insult) and at P6. At defined time points following HI, brain inflammatory cytokines, immunostaining (neurons: NeuN; astrocytes:GFAP; for Microglia: Iba1,CD68,arginase 1; oligodendrocyte: CNPase; apoptosis:caspase 3) and western blots for phosphor stress kinases (

pAKT, pp38, pSAPK, pERK, pCREB and pP65) were performed. Oxiselect ROS assay was performed. MicroRNA profile panel was studied using a custom designed microarray plate.

Results: Azithromycin treated pups showed minimal paresis and co-ordination deficits as compared to saline treated HI group, which had severe insult. Histopathology showed ventriculomegally, neuronal necrosis and apoptosis in saline treated HI group which was ameliorated in azithromycin treated HI group. There was a significant decrease in IL 12p70, IL6, KC GRO in the azithromycin treated HI vs. saline treated HI. Quantitative immunostaining showed significantly less injury in HI azithromycin treated (more NeuN, olig 2, CNPase and less expression of GFAP, caspase 3) associated with a shift towards an M2 microglial phenotype (increased arginase 1 and decreased in CD68), vs. the saline treated group. There was a significant decrease in pAKT, pP38, pSAPK, pERK, pCREB and pP65 in the HI azithromycin treated vs. saline treated pup brains. There was a significant decrease in brain intracellular ROS levels in the HI azithromycin treated vs. saline treated pups. MicroRNA, analysis showed a unique and innovative role of azithromycin in attenuating specific microRNA expression among HI treated group. (Table 1)

Conclusion(s): Azithromycin offers significant protection in PVL. It shifts microglia towards an M2 phenotype. It decreases the inflammatory milieu by decreasing pro-inflammatory cytokines, NF-KB activity and intracellular ROS levels. Azithromycin has an innovative role by ameliorating specific microRNA expression which was previously were linked to brain hypoxia and neuro-inflammation and demylenation.

Table 1: MicroRNA pattern in HI and HI+ Azithromycin grups in comparison to RA group.

miR	Fold Increase in HI group	Fold Increase in HI+Azithro group	miR	Fold Decrease in HI group	Fold Decrease in HI + Azithro group
miR-1a-2-5p	6.7	3.1	miR-1061-3p	-8.4	-3.9
miR-344i	5	2.4	miR-224-4p	-10.3	-2.3
miR-7046-3p	6.5	0	miR-432	-11	-2.6
miR-7050-3p	6.4	3.8	miR-466i	-11.4	-5.4
miR-7228-5p	5.6	0	miR-509	-9.1	-2.3
miR-7090-3p	6	3.8	miR-546	-9.2	-3
			miR-669i	-9.4	-2.6
			miR-6926-5p	-13.3	-2.5

Disclosures: N. Zaghloul: None. **K.R. Ayasolla:** None. **M.N. Ahmed:** None.

Poster

475. Ischemia III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.26/V5

Topic: C.08. Ischemia

Support: Medical Research Council

Title: Investigating the expression of neuroserpin and its role in neonatal hypoxic-ischaemic encephalopathy

Authors: *J. FISCHER, A. HOERDER-SUABEDISSEN, K. PARLEY, Z. MOLNÁR
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Abstract: Background: Perinatal hypoxic ischaemia is one of the most prevalent causes of neonatal morbidity and mortality worldwide. Hypothermia is currently the only available treatment option with limited clinical efficacy. Neuroserpin, an inhibitor of tissue plasminogen activator, has been shown to result in a reduction in brain damage and overall functional improvements in models of adult cerebral infarction (Millar et al. 2017, Front Cell Neurosci. 11: 78). It has therefore been hypothesised that it may also reduce damage caused by perinatal hypoxic ischaemia. Previous work in the lab using a rat model of unilateral mild and moderate hypoxic injury (Okusa et al. 2014, Ann Clin Transl Neurol, 1: 679-691) suggested an increase in neuroserpin expression on the affected side prompting further research in the mouse model.
Methods: Our study had two goals. (1) We determined the expression pattern of neuroserpin in the developing human fetal brain using late first as well as second trimester brain sections to track its expression. A particular focus was placed on the expression within the subplate. (2) We studied a neuroserpin knock-out mouse to shed light on potential neuroprotective properties that this protein may possess (Madani et al. 2003, Mol Cell Neurosci, 23, 473-494). A modified Rice-Vannucci model was employed which involves unilateral carotid artery ligation with subsequent hypoxia to induce hypoxic ischaemic encephalopathy in one brain hemisphere of P8 mice. This model attempts to replicate perinatal hypoxic injury in humans. Mice were sacrificed at P10 and brains were extracted and cut into 1.0-1.5mm sections. Sections were stained with Triphenyltetrazolium chloride to determine the area of ischaemic damage. Sections of wild-type mice were then resectioned after fixation to carry out immunohistochemistry to determine neuroserpin expression on the affected and unaffected side. GFAP and IBA have been used as further markers of damage.
Results: (1) Neuroserpin was shown to be widely expressed throughout the cortex of the developing human fetal brain. The highest levels of expression are found in the subplate in the second trimester. (2) Our experiments in the neuroserpin KO mouse show that neuroserpin has no statistically significant effect on ischaemic damage following hypoxic-ischaemic injury in the

knockout versus the wild-type mice (7.53 mm^2 vs. 6.18 mm^2 respectively, p=0.35, n=25). An effect size of 21% was non-significant in part due to high variability that is common in the outcomes of the Rice-Vannucci model.

Disclosures: J. Fischer: None. **A. Hoerder-Suabedissen:** None. **K. Parley:** None. **Z. Molnár:** None.

Poster

475. Ischemia III

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Program #/Poster #: 475.27/V6

Topic: C.08. Ischemia

Support: DGAPA/UNAM IN207018
DGAPA/UNAM IN201817
DGAPA/UNAM AI200717
CONACYT (285004)
Pilgrim´s Pride

Title: Effect of GH and IGF-1 treatments after hypoxic-ischemic injury in chicken cerebellar cell cultures

Authors: M. BALTAZAR[1], J. AVILA-MENDOZA[2,4], C. MARTÍNEZ-MORENO[1], M. CARRANZA[2], C. ARAMBURO[2], *M. LUNA[3]
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Abstract: Perinatal hypoxic-ischemic (HI) brain damage is a major cause of mortality and long-term neurological impairment in children. The rapid growth of the cerebellum in the last half of fetal development makes it more vulnerable to a HI injury. Several studies have shown that growth hormone (GH) and insulin-like growth factor-1 (IGF-1) are upregulated in different brain areas after damage by hypoxia. Moreover, there is increasing evidence suggesting that GH and IGF-1 treatments are able to induce neuroprotection and neural-regeneration in the CNS. In this study, we evaluated the effects of GH and IGF-1 treatment on cell survival after an acute HI injury in primary cell cultures of embryonic chicken cerebellum. In addition, we evaluated the cerebellar expression of GH and IGF-1 mRNA in normal and hypoxia-low glucose (HLG) conditions. To induce neural damage in primary embryonic cerebellar cultures, cells were maintained in hypoxic conditions (0.5-5% O2), and incubated in low glucose media (1 g/L) for 12 h, and subjected to a 24 h of reoxygenation. Cell cultures were treated with 1 nM recombinant chicken GH (rcGH) and/or 40 nM recombinant human IGF-1 (hIGF-1) to examine their neuroprotective effects. We observed that incubation of cells in HLG caused a significant

decrease in cell viability (51.6 ± 2.9 %) as well as a pronounced increase in apoptosis (122.0 ± 4.5 %,) and necrosis (538.6 ± 92.1 %), while treatment with GH increased cell viability (76.1 ± 4.1 %), and decreased apoptosis (105.0 ± 3.9 %) or necrosis (73.8 ± 11.1 %), On the other hand, IGF-1 treatment only increased cell viability (70.1 ± 4.2 %) without affecting apoptosis (105.0 ± 3.9 %) and necrosis (73.8 ± 11.1 %). After incubation in HLG conditions, cerebellar cell cultures significantly increased GH and IGF-1 mRNA expression were increased by (~3 fold). GH gene silencing with small interfering RNA (siRNA) decreased both, GH mRNA expression (1.6-fold) and IGF-1 (0.5-fold) mRNA expression in the HLG group, suggesting that GH regulates IGF-1 expression under HLG conditions. Our results strongly suggest that both, local and exogenous GH act as a neuroprotective factor and they regulate IGF-1 expression under HLG conditions. We thank Gerardo Curtois, Nydia Hernández, Dra. Olivia Vázquez Martínez, for technical assistance.

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Poster

475. Ischemia III

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.28/V7

Topic: C.08. Ischemia

Support: NIH GRANT RO1NS084057

Title: Correlation between the serum levels of 24S-hydroxycholesterol and hypoxic-ischemic brain injury in neonatal mice

Authors: *F. LU[1], J. ZHU[2], F. CHEHAB[2], D. M. FERRIERO[3], X. JIANG[3]
[1]Univ. of California, San Francisco, San Francisco, CA; [2]Lab. Med., UCSF, San Francisco, CA; [3]Pediatrics, Univ. of California San Francisco, San Francisco, CA

Abstract: Background/Objective: Maintenance of cholesterol homeostasis is crucial for brain development due to its importance in membrane integrity, myelination, synaptogenesis and neurotransmission. Brain cholesterol relies on de novo synthesis and is cleared primarily by conversion to 24S-hydroxycholesterol (24S-HC) with brain-specific cholesterol 24-hydroxylase (CYP46A1). This study was undertaken to investigate the impact of hypoxia-ischemia (HI) on cholesterol turnover in the neonatal mouse brain. **Methods:** Postnatal day 9 C57BL/6 pups were subjected to HI using the Vannucci model. CYP46A1 expression was assessed by western blotting and its cellular localization was determined by immunofluorescence staining. The amount of brain cholesterol, the levels of 24S-HC in the cortex and in the serum was measured by ELISA. **Results:** There was a transient loss of brain cholesterol at 6hr after HI. CYP46A1

was significantly upregulated at 6hr and 24hr following HI with a concomitant increase of 24S-HC in the ipsilateral cortex and in the serum. The serum levels of 24S-HC correlated with those in the brain, as well as with necrotic and apoptotic cell death evaluated by the expression of spectrin breakdown products and cleaved-caspase 3 at 6hr and 24hr after HI. **Conclusions:** Enhanced cholesterol turnover by activation of CYP46A1 represents disrupted brain cholesterol homeostasis early after neonatal HI. 24S-HC might be a novel blood biomarker for severity of neonatal hypoxic-ischemic brain injury with potential clinical application.

Disclosures: F. Lu: None. **J. Zhu:** None. **F. Chehab:** None. **D.M. Ferriero:** None. **X. Jiang:** None.

Poster

475. Ischemia III

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 475.29/V8

Topic: C.08. Ischemia

Support: NCTR Protocol C13096

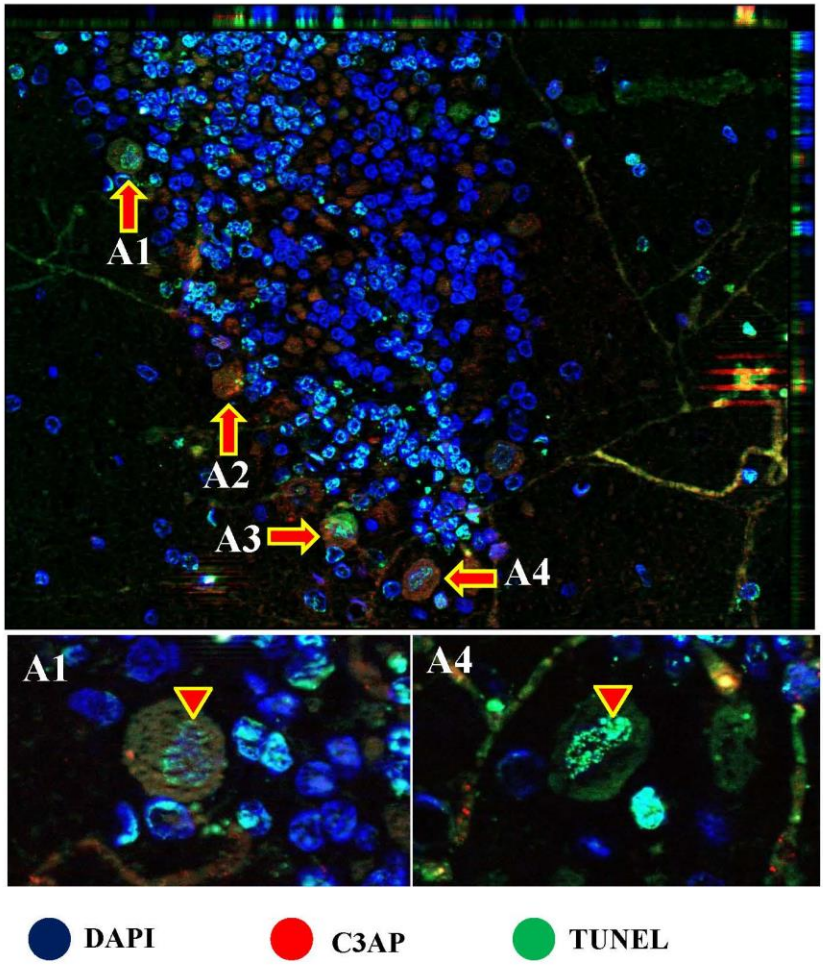
Title: Conventional histological assessment of ischemic damage and defining cerebellar apoptotic Purkinje cell death in rats

Authors: *Z. HE[1], L. CUI[2], T. A. PATTERSON[3], S. A. FERGUSON[4]
[1]Div. of Neurotoxicology, Natl. Ctr. For Toxicology Res., Jefferson, AR; [2]Neurotoxicology, NCTR, Jefferson, AR; [3]Office of the Director, Natl. Ctr. for Toxicological Res., Jefferson, AR; [4]Neurotoxicology, Natl. Ctr. Toxicological Res., Jefferson, AR

Abstract: Assessment of acute ischemic damage to define cerebellar Purkinje cell death is elusive. This study examined Purkinje cell death following transient global ischemia in rats. In sham-operated rats, Purkinje cells display various forms including “dark neurons”, making it difficult to distinguish normal from damaged Purkinje cells. In ischemic groups, as verified by significant hippocampal CA1 neuronal loss, dead cerebellar Purkinje cells were defined with the following morphological criteria (2 or more required): 1) reduced numbers of Purkinje cells/increase in the interval distance between two adjacent Purkinje cells; 2) significantly increased peripheral cellular empty/stainless space; 3) perinuclear or whole-cellular eosinophilia; and 4) significantly condensed granular nucleic aggregation and/or interstitial eosinophilia. Quantitative Purkinje cell loss indicated a significant difference between ischemic groups and sham controls. Triple fluorescent labeling including TUNEL- and caspase 3 active peptide (C3AP)-immunoreactivity and DAPI labeling defined cerebellar Purkinje cell death. In young adult female rats subjected to 20 minutes of ischemia and surviving for 4 days, single or collected Purkinje cells displayed TUNEL-positive immunoreactivity with or without cytosolic

C3AP immunoreactivity. A subset of Purkinje cells simultaneously displayed three biomarkers termed “apoptotic trilogy” (Fig. 1A1), by which occurrence of apoptosis was both immunohistochemically and morphologically defined: nucleic TUNEL immunoreactivity and blebbing and cytosolic C3AP immunoreactivity. Apoptotic bodies limited to the cytosolic compartment were found in a subset of the Purkinje cells. In conclusion, histological methods, while requiring a higher morphological standard, remain indispensable in defining cerebellar Purkinje cell death. A subset of cerebellar Purkinje cells does experience caspase-dependent apoptosis following ischemia.

Fig. 1. Immunofluorescent labeling ischemic damage (4 days survival)



Disclosures: Z. He: None. **L. Cui:** None. **T.A. Patterson:** None. **S.A. Ferguson:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.01/V9

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DOD SCI 150225

Title: Characterization of the spinal ejaculation generator in male mice

Authors: *S. GAIKWAD[1], M. D. STAUDT[2], L. M. COOLEN[3]
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Abstract: Spinal Cord Injury (SCI) is a debilitating life changing event. Surveys among SCI men place recovery of sexual function as a high priority issue, but research on effects of SCI on sexual function is hindered by limited understanding of spinal control of sexual reflexes. A spinal ejaculation generator (SEG) has been delineated in male rats and has been shown to be anatomically and neurochemically identical in humans. The SEG consists of a population of lumbar spinothalamic cells (LSt) that control ejaculation via axonal projections to sacral nucleus of bulbocavernosus and autonomic centers. LSt cells control ejaculation via release of the neuropeptides galanin, cholecystokinin (CCK), gastrin releasing peptide (GRP), and enkephalin. Thus far, the SEG has been delineated in male rats, revealing important information. However, understanding of ejaculatory function will be improved with use of transgenic mouse models and molecular tools. Hence, the goal of this study was to investigate the neuroanatomy, neurochemistry, and functionality of the SEG in male mice. Adult male C57Bl/6 adult mice were perfused and spinal cord sections were immunoprocessed for galanin, a marker for LSt cells. LSt cells were found to be distributed at L3 and L4 spinal levels in grey matter surrounding the central canal, a pattern similar to that observed in rat and human SEG. Moreover, LSt cells co-localized galanin, CCK, and GRP, and neurokinin-1 and androgen receptors. As in rats, LSt cells made axonal connections with choline acetyltransferase-positive autonomic and motor neurons. Using unilateral hemisection at the lumbar level, it was demonstrated that LSt cells also project to the thalamic parvocellular subparafascicular nucleus. To establish the functional involvement of the mouse SEG, male mice were perfused after different elements of mating behavior for visualization of LSt cell neural activation. Ejaculation, but not mounts or intromissions, induced cFos activation of LSt cells. Finally, a commonly used paradigm to study ejaculatory reflexes was investigated: the dorsal nerve of penis (DPN) was stimulated in anesthetized and spinalized male mice and penile striated muscle EMG was recorded. DPN stimulation yielded bursting of the bulbocavernosus muscle. However, the stimulation parameters required and the characteristics of the bursting patterns slightly differed from those used and observed in male rats. Together, these findings show that the morphological and physiological characteristics of

mice SEG are similar to those found in rats and humans and thus allow for the use of mouse models to study the SEG.

Disclosures: S. Gaikwad: None. **M.D. Staudt:** None. **L.M. Coolen:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.02/V10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DOD SCI 150225

Title: Contusion spinal cord injury decreases glutamatergic axon inputs to spinal ejaculation generator in male rats

Authors: *K. K. SONI[1], J. E. SLEDD[2], J. W. WIGGINS[3], L. M. COOLEN[4]
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Abstract: Spinal cord injury (SCI) is a devastating trauma leading to widespread disruption of motor, sensory, and physiological functions, including an-ejaculation in >85% of SCI patients. Regaining sexual function is of high priority to SCI patients. Ejaculation is a reflex controlled by a spinal ejaculation generator (SEG), consisting of a population of lumbar spinothalamic cells (LSt cells) in lumbar 3-4. LSt cells convert sensory inputs during sexual activity into coordinated autonomic and motor output required for ejaculation. We recently demonstrated that sensory stimulation was unable to trigger ejaculatory reflexes in male rats with contusion injury, suggesting a similar severe ejaculatory dysfunction as in human patients. Sensory inputs critical for ejaculatory function originate from the dorsal penile nerve and trigger ejaculation via activation of glutamatergic receptors expressed in LSt cells. Therefore, we hypothesize that SCI causes a disruption of glutamatergic inputs to the spinal ejaculation generator, thereby disrupting the relay and processing of sensory signals required to trigger ejaculation. Male Sprague Dawley rats received a contusion injury at spinal levels T6-7 or a sham surgery. Locomotor activity was recorded weekly and confirmed a moderate deficit in locomotor activity in SCI animals. Six weeks following contusion or sham injury, animals were perfused and spinal cords were immunohistoprocessed for galanin (LSt cell marker), synaptophysin (axon terminal marker), and either vesicular glutamate transporter 1 (Vglut1) or 2 (Vglut2). Confocal analysis was conducted to quantify the putative synaptic inputs to LSt cells. Results showed that SCI did not alter the numbers of galanin-positive cells, hence did not ablate LSt cells. However, SCI significantly reduced both VGlut1- and VGlut2-inputs to LSt cells. In contract, SCI did not affect galanin-inputs on LSt cells, suggesting that LSt cell connections to other LSt cells remained intact.

Finally, SCI did not affect the numbers of synaptophysin-only inputs to LSt cells. The latter finding is somewhat surprising as it suggests that SCI did not impact supraspinal inputs onto LSt cells. However, at this time, the supraspinal inputs to LSt cells are unidentified and thus remain an area of active investigation. Together, these data suggest that SCI impairs excitatory glutamatergic inputs to LSt cells, which in turn contribute to the loss of sensory processing and ejaculatory dysfunction. Future studies will confirm if Vglut2 along with Vglut1 is expressed in dorsal penile nerve afferents.

Disclosures: K.K. Soni: None. **J.E. Sledd:** None. **J.W. Wiggins:** None. **L.M. Coolen:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.03/V11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DOD SCI 150225 to LMC

Title: Effects of contusion spinal cord injury on neuropeptide expression in the spinal ejaculation generator in rats

Authors: *J. W. WIGGINS[1], J. E. SLEDD[2], L. M. COOLEN[3]
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Abstract: Spinal cord injury (SCI) causes sexual dysfunction including anejaculation in men. Ejaculation is a spinal reflex controlled by a spinal ejaculation generator (SEG) located in the lumbosacral spinal cord. The SEG is comprised of a population of lumbar spinothalamic (LST) neurons located in the L3 - L4 spinal cord, lateral to the central canal in lamina X and VII. LST neurons express the neuropeptides gastrin releasing peptide (GRP), galanin, enkephalin and cholecystokinin. These neurons control ejaculation via intraspinal connections to autonomic and motor nuclei, where all four neuropeptides are released from LST axonal projections to trigger ejaculation. We have previously shown that chronic contusion injury impairs ejaculation in male rats 4-6 weeks after injury. Here, we tested the hypothesis that contusion injury causes a disruption of the neuropeptides that are expressed in LSt cell bodies and their axonal projections to autonomic and motor nuclei. Male Sprague Dawley rats received either a contusion or sham surgery at spinal levels T6-7. Six weeks later, animals were perfused, and spinal cords were immunoprocessed for galanin and GRP for cell counts, and for galanin, choline acetyl-transferase (ChAT) and synaptophysin for axon projection analysis. Results show that numbers of cells immunoreactive for galanin are not altered by SCI, suggesting that LSt cells are not ablated by SCI. In addition, preliminary analysis of numbers of galanin on ChAT positive cell

soma in the sacral parasympathetic nucleus showed no reduction in LSt projections to this nucleus after SCI. In contrast, GRP immunoreactivity was decreased in LSt cells following SCI, evident by fewer GRP and galanin/GRP dual labeled cells. To further investigate this specific loss of GRP expression in LSt cells, an in-situ hybridization analysis was conducted. Male rats received SCI or sham surgery and were perfused 8 weeks later. Lumbar spinal cord tissue was sectioned and galanin and GRP mRNA visualized using dual fluorescent RNAscope. Immunofluorescent signal for galanin and GRP mRNA was imaged by confocal microscopy and optical density analysis was performed in ImageJ. Preliminary results showed that SCI caused reduction in both GRP and galanin mRNA in SCI animals compared to controls. In conclusion, chronic contusion injury decreased neuropeptide expression for galanin and GRP in the SEG, with a marked reduction in GRP peptide localization. Since both peptides have facilitative roles for ejaculation, such loss may contribute to ejaculatory dysfunction following SCI.

Disclosures: J.W. Wiggins: None. **J.E. Sledd:** None. **L.M. Coolen:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.04/V12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Grant from the Deutsche Forschungsgemeinschaft (SFB 1158)

Title: Correlation or causation - nociceptive fiber sprouting and spinal cord injury induced neuropathic pain?

Authors: *C. SLIWINSKI, M. MOTSCH, N. WEIDNER, R. PUTTAGUNTA
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Abstract: A large proportion of patients suffering from spinal cord injury (SCI) develop neuropathic pain (NP). Despite its frequently severe and disabling nature NP remains a largely unexamined consequence of SCI lacking effective treatment options.
Previously, we have shown that aberrant structural plasticity in primary nociceptive afferents is associated with the development of below-level NP after a moderate (50 kDyn) T11 spinal cord contusion injury in female C57BL/6 mice. In particular, peptidergic calcitonin gene related peptide expressing ($CGRP^+$) fibers showed a higher labeling-density in deeper laminae of the lumbar (L4-L6) dorsal horn. Initiation of sensorimotor activity either 7 days post-injury (dpi) or following the establishment of sensory alterations at 42 dpi, ameliorated mechanical allodynia and normalized CGRP-labeling density towards pre-injury levels (35 and 74 dpi).
To further understand if SCI-induced aberrant structural rearrangements arise prior to and may

be responsible for the development of NP, we took advantage of sensory neuron specific ($Na_v1.8$) SNS^{Cre}::$R26^{LSL\text{-}tdTomato}$ (SNS-tdTomato) mice to label all nociceptive fiber projections into the dorsal horn.
Using the same contusion model in female SNS-tdTomato mice, correlates of NP including mechanical allodynia and thermal hyperalgesia were analyzed in the hindpaws using behavioral pain measurements at varying timepoints post injury. Animals were compared at 7 and 21 dpi for nociceptive fiber density at the first time point when mechanical allodynia is reliably detectable and when it is fully established.
Similar to previous wildtype animals, SNS-tdTomato mice showed the SCI-induced aberrant mechanical and thermal sensation. Injured mice developed mechanical hypersensitivity to small-diameter von Frey filaments (0.16g) at 7 dpi, which was stable until the end of the experiment (ANOVA $p<0.001$, PLSD $p<0.0001$ at 21 dpi). Furthermore, SCI animals showed a significant decrease in the response latency to heat stimuli compared to sham mice (ANOVA $p<0.0001$; PLSD $p<0.0001$).
Analysis of $CGRP^+$ and $tdTomato^+$ fibers in deeper laminae (III-IV) of the dorsal horn indicated a higher labeling-density in SCI compared to sham mice both at 7 and 21 dpi (t-test, $p=0.0081$ for CGRP and $p=0.045$ for tdTomato at 7 dpi), suggesting that structural rearrangements in nociceptive fibers parallel the development of mechanical allodynia. To further specify the initiation point of these structural changes, SNS-tdTomato animals will be analyzed at 1, 3 and 5 dpi. Additionally the
ablation of these fibers will allow for the examination of their contribution to the development of NP following SCI.

Disclosures: C. Sliwinski: None. **M. Motsch:** None. **N. Weidner:** None. **R. Puttagunta:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

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Program #/Poster #: 476.05/V13

Topic: C.11. Spinal Cord Injury and Plasticity

Support: TWU Department of Biology
The Southeast Missouri State University Department of Physics and Engineering Physics
Quality Enhancement Program Grant TWU

Title: Neurite outgrowth on inhibitory substrate by delivering Y-27632 using polymeric nanocarriers

Authors: *S. SEBASTIAN[1], R. AMMASSAM VEETTIL[1], S. GHOSH[2], D. HYNDS[1]
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Abstract: The molecular mechanisms directing neurite outgrowth and regeneration involve both stimulatory and inhibitory influences. Chondroitin sulfate proteoglycan (CSPG) is an inhibitory molecule upregulated following spinal cord injury (SCI) and may contribute to unsuccessful axon regeneration. Previous studies have shown that CSPGs activate Rho GTPase and that inhibition of Rho kinase (ROCK) activity with Y-27632 reverses or reduces CSPG inhibition. We demonstrated that 50 to 400µM concentration of Y-27632 treatment resulted in increased neurite outgrowth in B35 cells. However, targeting therapeutics specifically to corticospinal motor neurons (CSMNs) that are damaged during SCI is challenging. To address these concerns, we have developed a bio-compatible polymer encapsulated magnetic nanocarrier system (PE-MNC) with a proven uptake preference by CSMNs compared to glial cells in rat mixed cortical culture. These thermo-responsive PE-MNCs have a diameter of 230nm at room temperature and 180nm at physiological temperature. In the present study, we are loading PE-MNCs with optimum concentration of Y-27632 and determining the release kinetics of Y-27632 at physiological temperature. Moreover, we are determining the neurite outgrowth of B35 cells and P0 rat CSMNs plated on patterned substrata of CSPG stripes by delivering Y-27632 using PE-MNCs. Following treatment, neurite outgrowth of B35 cells and CSMNs on inhibitory substrate is quantified and compared with that of cells treated with Y-27632 alone. Drug release kinetics from PE-MNCs are quantified using HPLC and neurite outgrowth is quantified using Nikon A1 confocal system. Together, these results will lead to the development of a potential nanocarrier system that can be used for targeted drug delivery to damaged CSMNs during SCI treatment.

Disclosures: S. Sebastian: None. **R. Ammassam Veettil:** None. **S. Ghosh:** None. **D. Hynds:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

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Topic: C.11. Spinal Cord Injury and Plasticity

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R56NS096028
Paralyzed Veterans of America Research Foundation - Grant #3054
5R01DA022727-11
1R01NS106906-01
5 R01 MH100093-05

Title: Modulating the EphB2-NMDA receptor interaction in superficial dorsal horn attenuates neuropathic pain following cervical spinal cord injury

Authors: *N. M. HEINSINGER, W. ZHOU, J. L. WATSON, A. FALNIKAR, E. V. BROWN, B. A. CHARSAR, M. B. DALVA, A. C. LEPORE
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Abstract: In a rodent model of cervical spinal cord injury (SCI), we examined the contribution of altered EphB2 receptor-NMDA receptor (NMDAR) interaction to both excitatory synaptic neurotransmission in the superficial dorsal horn (DH) and persistent neuropathic pain (NP). The development of NP occurs in a significant portion of individuals affected by SCI, resulting in debilitating and often chronic physical and psychological burdens. Importantly, this pathological pain is particularly refractory to treatment, urgently calling for the identification of mechanistic targets that both robustly regulate pathological pain and avoid the devastating effects of opioid based interventions. Hyperexcitability of DH circuitry ("central sensitization") is a major substrate for NP after SCI. Studies have shown that NP is linked to EphB/ephrinB signaling through potentiation of NMDAR function, suggesting that the EphB-NMDAR interaction may be an important target for control of SCI-induced NP. In particular, we previously reported that EphB2 activation stimulates a direct interaction between EphB2 and the NMDAR via a single extracellular amino acid of EphB2 (Y504), thus promoting NMDAR synaptic localization and excitatory synapse function. Using a rodent model of unilateral cervical contusion SCI, we observe a persistent at-level NP phenotype in the form of forepaw thermal hyperalgesia and mechanical allodynia. We find that EphB2 expression is upregulated in superficial lamina of the ipsilateral DH after cervical contusion in intact cervical regions caudal to the lesion (i.e. at the location of primary afferent input from the plantar surface of the forepaw). Confocal imaging reveals significantly increased co-localization of EphB2 and the GluN1 NMDAR subunit at vGlut1-positive synaptic sites in superficial DH neurons after cervical contusion, indicating an enhanced interaction between EphB2 and the NMDAR at putative excitatory glutamatergic synapses. Lastly, lentiviral shRNA knockdown of EphB2 via anatomically-targeted intraspinal DH injections performed at 7 days post-cervical contusion reversed already-established thermal hyperalgesia. Collectively, these findings suggest that enhanced EphB2 expression and EphB2-NMDAR interaction underlies alterations in excitatory synaptic transmission in the DH and consequently persistent NP following SCI.

Disclosures: N.M. Heinsinger: None. **W. Zhou:** None. **J.L. Watson:** None. **A. Falnikar:** None. **E.V. Brown:** None. **B.A. Charsar:** None. **M.B. Dalva:** None. **A.C. Lepore:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

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Program #/Poster #: 476.07/V15

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H Neilsen Foundation
Discovery Theme Initiative - The Ohio State University

Title: Promoting structural and functional reorganization of neuronal circuits after spinal cord injury

Authors: *A. TEDESCHI, M. LARSON, A. ANNETT, W. A. STALKER, W. SUN
Neurosci., The Ohio State Univ., Columbus, OH

Abstract: Spinal cord injury (SCI) causes devastating neurological deficits and long-term disability due to axon regeneration failure. We recently discovered that administration of a potent gabapentinoid commonly used to treat various neurological disorders, promotes robust regeneration of ascending sensory axons in adult mice by blocking Alpha2delta2, a neuronal receptor and intrinsic molecular brake of axon growth and regeneration. Here, we explored the possibility that the same treatment strategy may prove similarly effective in promoting structural plasticity and regeneration of descending motor pathways after a cervical SCI. We also provided evidence that enhanced assembly and function of motor connectivity promotes recovery of forelimb function after SCI. Our findings provide novel insight into structural and functional reorganization of neuronal circuits after SCI, facilitating the design of translational research aimed at regaining neurological functions after injury to the spinal cord.

Disclosures: A. Tedeschi: None. **M. Larson:** None. **A. Annett:** None. **W.A. Stalker:** None. **W. Sun:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

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Program #/Poster #: 476.08/V16

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS RO1NS091582-01A1
NINDS T32 NS077889

Title: Myelin modulates macrophage inflammatory responses after spinal cord injury

Authors: *T. J. KOPPER[1], B. ZHANG[2], J. C. GENSEL[3]
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Abstract: Spinal cord injury (SCI) produces a chronic inflammatory state primarily mediated by resident microglia and infiltrating monocytes (here, collectively referred to as macrophages). These chronically activated SCI macrophages adopt a pro-inflammatory, pathological state that

continues to cause additional damage after the initial injury and inhibits recovery. While the pathological outcomes of this activation state after SCI are well documented, the mechanisms that drive this continued response are poorly understood. Previously we demonstrated that myelin debris directly stimulates M1 macrophages in-vitro (LPS and INF-gamma treated bone marrow derived macrophages) to potentiate their M1 responses as measured by IL10/IL12 cytokine profiles, reactive oxygen species production (ROS). After injury, macrophages clear and accumulate myelin debris long after injury, therefore we hypothesize that this is a key mechanism driving chronic pro-inflammatory macrophage activation after SCI. Here, we propose that the effects of myelin on M1 macrophages may be mediated though the activation of the enzyme cytosolic phospholipase A2 ($cPLA_2$). $cPLA_2$ releases arachidonic acid from cellular membranes. Free, active arachidonic acid invokes direct pro-inflammatory functions or, through synthesis pathways, forms various eicosanoids with pro-inflammatory properties. This is the basis for our central hypothesis that increased $cPLA_2$ activity in myelin laden SCI macrophages releases arachidonic acid thereby driving chronic SCI inflammation and tissue damage. Indeed, we have since identified $cPLA_2$ activity in myelin-laden macrophages in-vivo at 7 and 28 days after SCI. Further we have found that that chemical inhibition of this enzyme In-vitro reduces myelin's neurotoxic effects on macrophages, and reduces ROS production. Ongoing studies aim to definitively link this continued $cPLA_2$ activity to potentiated pro-inflammatory activation in myelin-loaded macrophages, and explore potential therapeutics to block these pathways after SCI.

Disclosures: T.J. Kopper: None. **B. Zhang:** None. **J.C. Gensel:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

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Program #/Poster #: 476.09/W1

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation
NIH NS104422
NIH NS091723

Title: Moderate pain input, given within days of a contusion injury, can expand the area of hemorrhage and undermine behavioral recovery

Authors: *M. M. STRAIN[1,2], T. JOHNSTON[1], Y. J. HUANG[1], J. A. REYNOLDS[1], R. E. BAINE[1], J. A. DAVIS[1], M. K. HENWOOD[1], G. N. K. FAUSS[1], J. W. GRAU[1]
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Abstract: Spinal cord injuries are often accompanied by injuries to other parts of the body (polytrauma). The impact of pain input on tissue loss and recovery can be modeled by applying a noxious stimulus (peripheral electrical stimulation at an intensity that engages pain fibers) or the application of the TRPV1 agonist capsaicin. In rats, electrical stimulation or capsaicin treatment a day after a contusion injury increases tissue loss (secondary injury) and impairs long-term recovery. Recent evidence suggests that pain input enhances tissue loss due to a breakdown of the blood-spinal cord barrier and an expansion of hemorrhage. Currently, little is known regarding the circumstances under which this effect emerges. The present study explored this issue by assessing how the effect of stimulation varies as a function of intensity, duration, and time since injury. Male Sprague Dawley rats received a moderate contusion injury at T12 using the MASCIS device. In Experiment 1, noxious stimulation (6 min of intermittent shock at an intensity of 1.5 mA) was applied 1, 4, or 14 days after injury and tissue was collected 3 hrs later. We found that stimulation 1-4 days after injury increased the infiltration of hemoglobin into the injury site. Stimulation 2 weeks after injury had no effect. Next, we assessed the minimum duration of stimulation that induces hemorrhage. A day after injury, contused rats received 14.4, 72, or 360 s of intermittent shock and tissue was collected 3 hr later. Only 72-360 s of shock induced hemorrhage. These shock conditions also produced an acute disruption in locomotor performance. Finally, we compared the effect of stimulation given at 0.17, 0.5, or 1.5 mA applied for 6 min a day after injury. Shocks at an intensity of 0.5 or 1.5 mA produced an acute disruption in locomotor performance and hemorrhage. The results suggest that even moderate pain input can affect the development of secondary injury.

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Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.10/W2

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Campus Alberta Neuroscience pilot project

Title: Acute CXCR4 blockage impairs spinal cord injury recovery

Authors: *A. TORRES ESPÍN[1], I. FRANCOS-QUIJORNA[2], J. AMO-APARICIO[2], A. SÁNCHEZ FERNÁNDEZ[2], R. LÓPEZ-VALES[2], K. FOUAD[1]
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Abstract: Hematopoietic stem cell (HSC) recruitment from the blood into damaged tissue is a key component of physiological repair, contributing to the correct development of the wound healing process. Therefore, the pharmacological mobilization of HSC from the bone marrow to the blood has been proposed and studied as a treatment for several pathologies, including neurological disorders. The most successful approach in several published studies consists of blocking the chemokine receptor 4 (CXCR4), an essential regulator of the HSC residence in the bone marrow, to promote recovery. We were asking whether a similar recovery could be achieved in a rat model of spinal cord injury (SCI), and the answer seems to be NO. In fact, we found the opposite effect. Immediately after a thoracic contusion SCI in rats, the selective CXCR4 antagonist AMD3100 (or vehicle) was administered and the locomotion of the animals was studied for 4 weeks using the BBB rating score and kinematics. Here we show that indeed, immediate blocking of CXCR4 after SCI increases the mobilization of CXCR4+ cells into the blood analyzed by flow cytometry, but instead of improving motor recovery, it prevents it. Consequently, we conducted experiments to understand this phenomenon. For example, blocking CXCR4 might distort the cell mobilization and injury infiltration dynamics after SCI, affecting the process of scarring and damage control at the lesion site. CXCR4 is also involved in the niche and injury homing of several cell types beyond HSCs, including granulocytes, monocytes, lymphocytes, mesenchymal stem cells, pericytes and neural stem cells. Therefore, disturbing the physiological process that 'fights' against tissue degeneration after SCI by blocking CXCR4 can enlarge the damage, ultimately reducing functional recovery.

Disclosures: A. Torres Espín: None. **I. Francos-Quijorna:** None. **J. Amo-Aparicio:** None. **A. Sánchez Fernández:** None. **R. López-Vales:** None. **K. Fouad:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

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Topic: C.11. Spinal Cord Injury and Plasticity

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NIH Grant 1NSO82446
University of Missouri Spinal Cord Injury/Disease Research Program (SCIDRP) Grant

Title: Gene expression changes in ascending dorsal column sensory neurons after spinal cord injury

Authors: *E. E. EWAN, M. MAHAR, D. CARLIN, V. CAVALLI
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Abstract: Spinal cord injury (SCI) damages long projecting axons leading to loss of sensory and motor function. In contrast, injury to the peripheral branch of dorsal root ganglion (DRG) sensory neurons leads to axon regeneration and functional recovery, mostly through the activation of a pro-regenerative program. Many studies indicate that SCI fails to activate a pro-regenerative program in DRG neurons, which consequently do not regenerate their centrally projecting axons after injury. Our understanding of the extent to which, if any, DRG sensory neurons produce a pro-regenerative response following SCI is limited by the fact that previous studies have analyzed whole lumbar DRG responses to SCI. Since most lumbar DRG neurons synapse locally upon entering the spinal cord, a very small percentage of DRG neurons ascend the spinal cord dorsal column and are injured after thoracic SCI. Furthermore, neurons account for 10% of all cells within the DRG. To address this problem, we analyzed the transcriptional response of proprioceptive and low threshold mechanoreceptive (LTMR) L4 DRG neurons after thoracic SCI or sciatic nerve crush injury (SNC). We used FACS sorting of YFP positive L4 DRG neurons from the YFP16 mouse line, in which YFP is expressed in proprioceptive and LTMR sensory neurons, followed by RNAseq analysis. We found that more genes were upregulated after SNC than SCI; yet several unique gene clusters were differentially expressed after SCI compared to PNS injury. Gene ontology analysis of these gene clusters specific to SCI revealed upregulation of transcription factor activity and DNA binding, as well as downregulation of some genes associated with actin binding. As expected, we found that many known regeneration-associated genes had increased upregulation after PNS injury (e.g., ATF3, Jun, Sox11 and SCG10) than after SCI. These results indicate that DRG neurons can respond to an injury to their central axon, albeit to a different extent than after PNS injury. Future studies will assess whether these differentially expressed genes contribute to the lack of a pro-regenerative response after SCI, and whether they can be manipulated to promote axon regeneration.

Disclosures: E.E. Ewan: None. **M. Mahar:** None. **D. Carlin:** None. **V. Cavalli:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.12/W4

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01 NS091582

Title: The role of arginase in macrophage-mediated repair in spinal cord injury

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Abstract: CNS macrophages activated by spinal cord injuries (SCI) have both reparative and pathological properties. Pro-inflammatory (also called M1) macrophages predominate and typically cause neurotoxicity. Anti-inflammatory macrophages (also called M2) are transient and promote axon growth and remyelination. Driving macrophage activation towards anti-inflammatory phenotypes enhances SCI recovery, but the underlying basis of the improvement is not yet fully comprehended. Discerning the mechanism of this macrophage-mediated repair is vital since macrophages express great plasticity and adapt their phenotype in response to microenvironmental cues. Arginase-1 (Arg1) is a hallmark of anti-inflammatory macrophage activation. Arg1 diverts arginine from iNOS to reduce the toxic potential of nitric oxide, a harmful free radical. In addition, byproducts of arginase-mediated arginine breakdown increase axon growth and cellular repair. We hypothesize that the reparative effects of anti-inflammatory macrophages are dependent on the production of Arg1. To test our hypothesis, we generated macrophage-specific arginase knockout animals. Further, azithromycin (AZM) is a macrolide antibiotic with anti-inflammatory characteristics that directly alters macrophage activation. SCI mice treated with AZM have improved functional recovery concomitant with increased anti-inflammatory macrophage activation. Therefore, we used AZM, in combination with our KO animals, to determine the role of arginase in immunomodulatory therapies for SCI. We observed that the efficacy of AZM treatment for reducing pro-inflammatory macrophage-mediated neurotoxicity is dependent upon arginase expression. Ongoing studies are evaluating the long-term (28dpi) effects of knocking out macrophage arginase in SCI recovery and AZM treatment in vivo. Understanding the anti-inflammatory mechanism of macrophage activation will offer novel therapeutic strategies for treating SCI.

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Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.13/W5

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Wings for Life Individual Grant
NS09881
EB014986
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

Title: Enhancing corticospinal regeneration after spinal cord injury

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Abstract: The corticospinal tract (CST) is the most important voluntary motor projection in humans and is particularly refractory to regeneration after spinal cord injury (SCI). Recently we reported that CST axons regenerate into neural progenitor cell (NPC) grafts of spinal cord identity placed into sites of SCI. Here we aim to identify transcriptional mechanisms associated with active CST growth and regeneration after SCI. We have successfully isolated the translational profile of growing CST neurons by polyribosome purification from the Glt25d2-BAC-TRAP mouse line. mRNAs actively bound to the ribosome were immunoprecipitated and purified from the motor cortex 10 days, 14 days, and 21 days after injury with or without an NPC graft, constructing a CST transcriptome library to reveal early master regulators responsible for regeneration, followed by effector molecules involved in axon attachment and growth. The CST regenerating transcriptome was compared to the non-regenerating transcriptome where a distinct regeneration profile was identified. We next aim to test the hypothesis that drug-based amplification of the transcriptional growth state will significantly enhance CST growth and regeneration *in vitro* and *in vivo*. To address this we developed a medium-throughput *in vitro* screening system of postnatal day 12 cortical neurons isolated from the UchL1-GFP mouse line in which CST neurons are GFP positive within the motor cortex. We have successfully established a methodology to culture CST neurons *in vitro* where *in silico* signatures of CST regeneration will help identify perturbagens that promote growth.

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Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.14/W6

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H Neilsen Foundation

Title: Effects of Ketogenic diet in mitochondrial function after Spinal Cord Injury

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Abstract: Spinal Cord Injury (SCI) pathophysiology can be attributed to either primary physical injury or the delayed, secondary injury cascades which begins after the initial injury and can persist for several months. A better understanding of the secondary injury mechanisms is essential in developing potential therapies to prevent damage, increase neuroprotection, restore metabolic deficits and finally promote functional recovery following SCI. Indeed, previous studies have shown that a dysregulated metabolism and energetic deficits linked to mitochondrial bioenergetics deficiencies are severely affected after SCI. Thus, neuroprotection and reduced oxidative stress are associated with improved cellular bioenergetics. In this regard, cerebral metabolism of ketones after traumatic brain injury (TBI) it's been previously shown to improve secondary neuropathology by decreasing oxidative stress, increasing antioxidants, and reducing inflammation. Previous work in our lab has shown the neuroprotective and improved behavioral effects of KD after SCI in rats. We hypothesized that ketogenic diet (KD) a high fat, low carbohydrate diet that is been already validated as non-pharmacological treatment for some forms of drug-resistant epilepsy will improve mitochondrial function after SCI. Using a C5 hemi-contusion model in adult male rats we examined the states of mitochondrial respiration and assessed the different components of the electron transport system (ETS). Starting 4 hours following C5 hemi-contusion injury, animals were fed either a standard control diet (SD) or KD. As expected, mitochondrial function was reduced after SCI. However, administration of KD increased mitochondrial biogenesis and partially rescued function of Complexes I, II, and III at 7 days after SCI. KD also triggered changes in the activity and total expression levels in kinases and transcription factors (i.e. mtFAM, ERK1/2, NRF2) involved in signaling pathways previously associated with the activation of the nuclear and mitochondrial transcription machinery. Consequently, these changes might induce an increase in the synthesis of ETS components and antioxidants which could explain the partial bioenergetics recovery observed in our SCI model. Moreover, we observed an increase in the neuronal marker NeuN in the animals treated with KD, suggesting that a neuroprotective effect could also be contributing the bioenergetics rescue. In summary, KD improves the post-SCI metabolism by rescuing mitochondrial bioenergetics dysfunction and might be a beneficial treatment for acute SCI.

Disclosures: O. Seira: None. **K.L. Kolehmainen:** None. **J. Liu:** None. **R. Boushel:** None. **W. Tetzlaff:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.15/W7

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DOD Award: W81XWH-17-1-0629

Title: Opioid-immune interactions after SCI

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Abstract: Opioids are among the most effective and commonly prescribed analgesics for the treatment of acute pain after spinal cord injury (SCI). We have shown, however, that morphine administration in the early phase of SCI undermines locomotor recovery in a rodent contusion model. We found that the adverse effects of morphine appear to be mediated by activation of Kappa Opioid Receptors (KORs). In addition, inhibiting glial activation with minocycline blocks the morphine-induced attenuation of locomotor function. We hypothesize that morphine acts on classic opioid receptors on immune cells to produce excitotoxicity. To test this, we used flow cytometry to determine whether morphine increases the innate immune response after SCI. First, subjects were given a moderate spinal contusion injury. On the day following surgery, half of the subjects were treated with morphine (i.v.) for 1, 3, or 7 days. The remaining subjects served as controls, receiving an equivalent volume of 0.9% saline. Subjects were euthanized on days 2, 4, or 8 (24 hrs after the final dose of morphine). A 1.5 cm section of injured spinal cord was collected and the tissue was enzymatically and mechanically dissociated. Cells were incubated with antibodies to identify macrophage and microglia populations. Additional antibodies were included to differentiate between M1 (pro-inflammatory) and M2 (anti-inflammatory) microglia and macrophages, as well as antibodies for the KOR. Our results indicate that higher numbers of macrophages and microglia can be detected as early as 3 days after morphine administration, relative to saline-treated controls. In addition, morphine increases the expression of KORs on the immune cells. Given the clinical utility of opioid analgesics, it is imperative that we fully understand the effects of morphine in mediating the immune response after SCI. We must develop safe and effective therapeutic strategies for the use of opioids in pain management after SCI.

Disclosures: M.N. Terminel: None. **K. Brakel:** None. **M. Hook:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.16/W8

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Davidson Research Initiative

Title: *In vivo* validation using CRISPR/Cas9 of a putative downstream effector of notch expressed in neurons

Authors: *A. LEONARD, R. EL BEJJANI
Davidson Col., Davidson, NC

Abstract: The highly conserved Notch signaling pathway is required for neuronal differentiation, and it inhibits axon regeneration. The mechanism of function of Notch in some of these neuronal processes is has not been elucidatednow well understood. Using CRISPR/Cas9, we sought to replace the promoter of a putative downstream effector of Notchlin-10/X11, a putative downstream effector of Notch, in order to determine if Notch plays a role in its expressiondescribe the putative regulation by Notch. Our gene of interest, *lin-10*, was chosen due to its significant number of LAG-1 binding sites, coupled with data suggesting that *lin-10* inhibits regeneration. Our goal is to generate two new strains. First, weWe will first, want to delete the *lin-10* promoter using CRISPR/Cas9 genome editing. Second, weWe will then want to replace the promoter with a promoter containing scrambled LAG-1 binding sites. This would allow us to test for a potential connection between Notch and *lin-10* expression *in vivo*. Our initial attempts at deleting the promoter failed. Using a dual-guide RNA approach, we consistently made only one double stranded cut resulting in Indels at the *lin-10* locus but no large deletions. This was confirmed by PCR in 40 strains of injected worms. We have since moved on to new strategies that we hope will produce large deletions. We are using a dual-guide RNA system with the addition of a repair oligo that spans the cut sites, but screening for successful deletions with this strategy has been labor intensive. For this reason, we are also designingmaking use of as a self-excising cassette that, if inserted, should facilitate the process of screening for deletions. We would like to obtain two separate mutants, however, If these strategies to delete and then replace the *lin-10* promoter do not work, we may will resort to trying to replace the promoter all in one step using a SEC described by *Dickinson et al 2015*. This is a last resort for us because we believe a two-step process that gives us both a large deletion and a scrambled promoter strain will be valuable for assessing the interaction between Notch, *lin-10*, and axon regeneration. This work will be important for furthering the understanding of the Notch signaling pathway's effect on axon regenerationmay identify LIN-10/X11 as a novel downstream effector of Notch signaling in neurons.

Disclosures: A. Leonard: None. **R. El Bejjani:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

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Program #/Poster #: 476.17/W9

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Swiss National Science Foundation
advanced ERC grant (Nogorise) to MES
ETH ‘Eat to learn to move’ network
Spinal Cord Consortium of the Christopher and Dana Reeve Foundation

Title: The spinal transcriptome after cortical stroke — In search of target-derived molecular factors regulating spontaneous compensatory axon growth in the spinal cord

Authors: *J. KAISER, M. A. MAIBACH, I. SALPETER, M. E. SCHWAB
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Abstract: Functional improvements, if they occur, are mostly seen within the first few weeks to months after the stroke in human stroke survivors, highlighting a period of heightened plasticity early after injury. Reorganization of the motor circuitry has been causally linked to the improved outcome in stroke patients, primates as well as rodents. After a large insult to the motor areas of one hemisphere in adult mice, the contralesional corticospinal tract (CST) re-innervates the stroke-denervated hemicord by growing new collaterals across the midline, e.g. on cervical levels of the spinal cord. The underlying molecular mechanisms of growth induction, midline crossing and target innervation of these adult, fully differentiated and functionally integrated CST fibers are yet unclear. In adult mice, following a large insult to the motor cortex, CST sprouting on cervical levels C5-C6 revealed the primary target area of the re-innervating CST fibers as the intermediate pre-motor laminae (Lam5-7). This area was analyzed for gene expression changes after stroke at time points corresponding to key events of post-stroke structural plasticity: initiation of sprouting (4+7dpi), growth phase (14dpi), maximal sprout density (28d) and pruning phase (42dpi). RNA-Seq (Illumina Hi-Seq) reads were mapped to the mouse genome and quantified for differential expression analysis. Genes were ranked by their fold change to controls, and differentially regulated genes for each time point were identified. This unbiased approach allows for evaluation of the spinal transcriptome in response to de- and re-innervation. The differentially regulated transcriptomes were further analyzed using network enrichment analysis, revealing two phases within the spinal target area of re-innervating CST fibers: (1) an early inflammatory phase (4-7dpi), during which activation of microglia in the pre-motor spinal layers can be observed; and (2) a highly dynamically regulated late phase during which molecules involved in tissue repair processes dominate (28-42dpi). Here, differentially up-regulated genes include molecules that are able to rescue neurite outgrowth under inhibitory conditions. These results show that the stroke-denervated spinal grey matter, in particular its intermediate, premotor laminae, express growth factors and represent a growth-promoting environment for sprouting CST fibers originating from the contralesional motor cortex.

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Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.18/W10

Topic: C.11. Spinal Cord Injury and Plasticity

Title: TGF-ß1 as a modulator of structural plasticity after large motor cortex stroke

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Abstract: Functional recovery of skilled forelimb movements after a large insult to the primary motor and premotor cortex involves activation of the contralateral hemisphere with the contralesional corticospinal tract growing new collaterals across the midline into the denervated hemicord on cervical levels of the spinal cord. The underlying molecular mechanisms of growth induction, midline crossing and target innervation ofthese adult, fully differentiatedand functionally connectedcorticospinal tract (CST) fibres are yet unclear. In the current study, we observed an upregulation of gene expression of transforming growth factor ß1 (TGF-ß1) within the stroke-denervated spinal cord at early time points after stroke. In vitro analysis revealed that TGF-ß1 robustly rescues neurite outgrowth in a growth inhibitory environment and signals via the canonical ALK5/SMAD3 axis. Furthermore, we show crosstalk between TGF-ß1 elicited signaling and the inhibitory neurite outgrowth modulator RhoA. These results suggest a regulatory role for TGF-ß1 in the context of post-stroke structural plasticity. Viral overexpression within the spinal cord grey matter allows for assessment of the effect of TGF-ß1 on re-innervation of the stroke-denervated spinal hemicord by contralesional CST fibres and causally linked functional recovery. Additionally, a corticospinal tract specific ablation of TGF-ß1 signalling by knock-down of TGFß-RII will allow to assess the effect of TGF-ß1 on structural CST plasticity directly.

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Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.19/W11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NS094527
NR013601

Title: The voltage-gated proton channel Hv1 impairs recovery after mouse spinal cord injury through NOX2/ROS signaling

Authors: M. MURUGAN[1], J. ZHENG[2], Y. LI[3], J. HE[5], B. SABIRZHANOV[6], L.-J. WU[7], *J. WU[4]
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Abstract: The voltage-gated proton channel Hv1 is a recently cloned ion channel that rapidly removes protons from depolarized cytoplasm and is highly expressed in the immune system. Hv1 is required for high-level NADPH (NOX)-dependent ROS (reactive oxygen species) production during the phagocyte respiratory burst. Excessive NOX2/ROS production is known to be critical in the pathophysiology of spinal cord injury (SCI) as it non-selectively damages neurons and glia. We previously reported that in the CNS, Hv1 is expressed by microglia but not neurons or astrocytes in the mouse brain. Microglial Hv1 regulates intracellular pH and aids in NOX2-dependent generation of ROS. Thus, Hv1 is a unique target for controlling multiple NOX activities and ROS production. In mouse models of brain ischemia, our studies point to an acute neuroprotection phenotype in Hv1 knockout (KO) mice. However, neither the precise cellular mechanisms underlying this finding nor critical role of Hv1 in the pathophysiology of SCI are fully understood. In the present study we report a rapid and persistent up-regulation (40 folds) of Hv1 mRNA up to 28 days in the injured spinal cord after a moderate contusion. This was confirmed in CD11b-selective microglia/macrophages isolated from adult spinal cord tissue at 3 days post-injury. Western blot (WB) and immunohistochemistry (IHC) showed that SCI elevates Hv1 protein expression predominantly in microglia/macrophages. Hv1 KO mice exhibited significantly attenuated NOX2/ROS production, IL-1β signaling, and neuronal cell death at 3 and 7 days post-injury. Increased spare white matter in Hv1 KO mice is correlated with improved motor function. Furthermore, mice lacking Hv1 appeared reduced mechanical/thermal hyperesthesia after SCI. Taken together our data suggest an important role for Hv1 in regulating NOX2/ROS-mediated functional damage post-SCI. Thus, Hv1 represents a potential therapeutic target that may lead to novel clinical therapeutic strategies.
Key words: spinal cord injury, Hv1, NOX2, ROS, neuroinflammation.

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Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

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Program #/Poster #: 476.20/W12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NS094527
NR013601

Title: Activation of cPLA2 contributes to lysosomal defects leading to impairment of autophagy after spinal cord injury

Authors: *Y. LI[1], J. W. JONES[3], C. SARKAR[1], M. A. KANE[3], E. Y. KOH[2], M. M. LIPINSKI[1], J. WU[1]
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Abstract: The autophagy-lysosomal pathway plays an essential role in cellular homeostasis and a protective function against a variety of diseases. However, under certain circumstances pathologically increased autophagy can contribute to cell death. This may occur particularly when lysosomal function is impaired and autophagic degradation is not able to proceed to completion, leading to pathological accumulation of dysfunctional autophagosomes. We have previously shown that autophagy is inhibited and contributed to injury after contusion spinal cord injury (SCI). Here we examine mechanism of autophagy and lysosomal defects following SCI. Expression levels and processing of the lysosomal enzyme cathepsin D (CTSD) were decreased at 2h after SCI. Enzymatic activity of CTSD and another lysosomal enzyme, alkaline phosphatase, were decreased 24h post-injury, indicating lysosomal damage. Sub-cellular fractionation confirmed lysosomal membrane permeabilization (LMP) and leakage of lysosomal content into the cytosol. cPLA2 is an enzyme that cleaves fatty acyl linkage in the phospholipids of cellular membranes and increased activity of cPLA2 may be involved in membrane damage. cPLA2 was activated in the lysosomal fraction, accompanied by increased accumulation of the autophagosomal marker LC3-II and its substrate p62. To directly assess the extent and mechanism of damage to lysosomal membranes, mass spectrometry (MS)-based lipidomics was applied to compare the lipid composition of lysosomal membranes purified from sham or injured spinal cord at 2h post-injury. Our data demonstrate increases in several classes of lysosophospholipids- the products of phospholipases (PLAs), as well as accumulation of PLA activator, ceramide. Inhibition of cPLA2 decreased lysosomal damage, restored autophagic flux, and reduced neuronal cell damage. Taken together our data implicate lysosomal defects in the pathophysiology of SCI and further indicate that cPLA2 activation leads to lysosomal damage

that causes neuronal autophagosome accumulation associated with neuronal cell death.
Key words: spinal cord injury, autophagy, lysosomal damage, cPLA2

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Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.21/W13

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Characterization of the transcription factor network underlying regeneration reveals novel intrinsic inhibitors

Authors: *Y. CHENG[1], A. ZHANG[2], K. GAO[2], A. BERNSTEIN[2], V. CHANDRAN[1], C. J. WOOLF[3], M. V. SOFRONIEW[4], D. H. GESCHWIND[2]
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Abstract: Central nervous system (CNS) neurons display highly restricted regenerative capacity compared to their peripheral nervous system (PNS) counterparts and insufficient cell intrinsic growth program contributes to this. We have comprehensively analyzed large scale transcriptomic data from regenerating PNS neurons to identify a transcriptional program associated with regeneration, linking multiple known pathways via a set of core transcription factors (TF). To further characterize the regulatory hierarchy, we used a mutual information based network analysis to compare multiple PNS and CNS injury data sets to identify a core set of five TFs (Jun, STAT3, SOX11, SMAD1, and ATF3) that was preserved across all PNS datasets, but not in the CNS datasets. We observed that two TFs, REST and CTCF, interacted with top-tier TFs in the CNS, but not the PNS, which bio-informatics predicted would disrupt the core regenerative network, thus limiting intrinsic regenerative capacity. We first tested this hypothesis *in vitro* via REST overexpression or deletion experiments in dorsal root ganglia (DRG) neurons. Indeed, REST over-expression inhibited neurite outgrowth, while REST deletion enhanced neurite extension of DRG neurons cultured on CSPG, a growth-inhibitory molecule increased in CNS injured tissue. To further investigate the role of REST in CNS regeneration in vivo, we induced a conditional deletion of REST in mouse cortex, followed by complete spinal cord lesion and anterograde labeling of corticospinal tract (CST) axons. Conditional deletion of REST led to significantly more CST axons proximal to the lesion site that also express more growth associated proteins, including GAP43, indicating that REST deletion promotes axon growth after injury. Lastly, we sorted and profiled the injured CST neurons with or without REST deletion to determine whether regeneration related pathways were

upregulated in regenerating axons. In conclusion, using integrative functional genomics approaches, we identified a hierarchical TF regulatory network underlying regeneration, and potential putative regulators, including REST, which was predicted to inhibit the pro-regenerative components of the network. These data provide a proof of principle and formal experimental testing of network predictions, showing how gene networks can be used to discover effective drugs for neural repair.

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Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.22/W14

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Heterogeneous secondary injury response following traumatic injury at different levels of the spine

Authors: *J. HONG[1], M. CHAMANKHAH[2], A. CHANG[2], A. BADNER[2], M. ZAVVARIAN[2], C. AHUJA[2], M. FEHLINGS[2]
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Abstract: Purpose: Cervical spinal cord injury (cSCI) accounts for the majority of SCI cases, frequently resulting in tetraplegia and poor outcomes. To date, the majority of pre-clinical research into SCI has utilized animal models harboring injuries in the thoracic spinal cord (tSCI). However, anatomical differences in the vascularization and susceptibility to blood-spinal cord-barrier (BSCB) disruption exist between cSCI and tSCI. This, in conjunction with clinical observations of spinal cord level-specific heterogeneity in response to surgical and pharmacological intervention, warrants a rigorous delineation of the differential vertebral level-specific molecular pathology of SCI.
Method: Female Wistar rats were subjected to moderate-severe clip-compression SCI to the C6-7 and T6-7 spinal cord with level and time-matched laminectomized shams serving as controls. The rats were then sacrificed at 3, 7, 14, and 56 days post-surgery. Ultrasound and Power Doppler imaging was used to assess the gross pathology of the injured cord. RNA sequencing was used to evaluate the genome-wide changes over time. Protein analyses were performed using Western blotting and ELISA, while tissue level work was done using immunohistochemistry.
Results: We have observed striking variability in the formation of the cystic cavity and hemorrhage after cSCI and tSCI as early as 3-days post-SCI. Moreover, RNA-sequencing at this time-point identified over 1500 genes differentially expressed (DEGs) between cSCI and tSCI.

By cross-referencing recently published single-cell RNA-sequencing databases, we mapped these DEGs and found the majority to be associated with structural and functional components of astrocytes and pericytes—both key regulators of the BSCB. We then surveyed each component of the neurovascular unit and found baseline reductions in pericyte coverage within the cervical cord along with rapid contractile pericyte differentiation exclusively in cSCI—a hallmark of BSCB disruption. Moreover, there was a striking loss of ZO1, occludin and claudin-5, all key tight junction (TJ) proteins of the BSCB in cSCI, but not tSCI.
Conclusions: Collectively, these findings provide strong evidence that acute tissue loss in cSCI compared to tSCI may be a result of an increased anatomical susceptibility to BSCB disruption, and that the mitigation of acute BSCB disruption may be—hierarchically—a better upstream therapeutic target than the current immune and neuroprotective strategies in trial.

Disclosures: J. Hong: None. **M. Chamankhah:** None. **A. Chang:** None. **A. Badner:** None. **M. Zavvarian:** None. **C. Ahuja:** None. **M. Fehlings:** None.

Poster

476. Spinal Cord Injury and Plasticity: Cellular and Molecular Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 476.23/W15

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Minnesota State Office for Higher Education Spinal Cord Injury and Traumatic Brain Injury Research Grant Program (FP00093993)

Title: A comprehensive combinatorial approach: Neuromodulation of the injured spinal cord using epidural stimulation and rapamycin loaded scaffold seeded with genetically modified Schwann cells

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Abstract: Spinal cord injury (SCI) results in cell death, demyelination, and axonal loss. The spinal cord has a limited ability to regenerate and current therapies for SCI are not efficacious. Encouraging results using epidural electrical stimulation (EES) to elicit volitional control of motor function in humans with SCI has been largely attributed to the presence of functionally silent fibers and to the combination of EES with locomotor training. Currently there is limited knowledge on the mechanisms underlying EES efficacy. This limitation is partially due to a lack of a SCI animal model that represents humans clinically diagnosed with complete spinal cord

injury, who possess functionally silent connections. Another area of investigation has been the use of biodegradable scaffolds to fill areas of lost tissue. Our lab has developed a novel hydrogel scaffold composed of oligo(poly(ethylene glycol) fumarate) (OPF) in a multichannel design. The transplantation of these scaffolds seeded by glial cell derived neurotrophic factor (GDNF) secreting Schwann cells or containing rapamycin microspheres and Schwann cells aid recovery after injury in rats. These studies demonstrate that a combinatorial approach to therapy is likely to have the most beneficial effect given the heterogenic nature of SCI pathophysiology. In this study we combined EES with scaffolds incorporated with rapamycin and GDNF secreting Schwann cells implanted in rats with complete thoracic (T9) spinal cord transection. We hypothesized that electrical field applied within the region of regeneration (T8 and T10) and at the locomotor circuitry (S1 spinal segment) below the injury would increase neural tissue reconnection through the scaffold and improve motor function in rats following injury. Our results show consistent motor evoked responses in hind limb muscles when stimulating rostral to the injury level by 2 weeks post-implantation. These observations of regeneration across the scaffold were further confirmed when the spinal cord was transected a second time 6 weeks post initial SCI, which resulted in complete loss of EES-evoked activity across the scaffold implantation site. Open field evaluation of hind limb motor functions showed that combination of OPF scaffold and EES can facilitate functional recovery already at 1-2 weeks after transection. After re-transection at 4 weeks, rats hind limb motor function declined to levels that were not different from controls. These results suggest EES with hydrogel scaffolds containing GDNF expressing Schwann cells and rapamycin-releasing microspheres promotes functional reconnection across the spinal cord injury.

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Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

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Program #/Poster #: 477.01/W16

Topic: C.11. Spinal Cord Injury and Plasticity

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ALARME Foundation
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Roland and Fabien Loos PhD Fellowship
Craig H. Neilsen Foundation 381357
Dr. Miriam and Sheldon G. Adelson Medical Foundation
Wings for Life

Title: Identifying factors that stimulate or improve propriospinal axon regrowth after severe spinal cord injury

Authors: *M. A. ANDERSON[1], T. M. O'SHEA[2], J. E. BURDA[2], Y. AO[3], S. BARLATEY[1], A. M. BERNSTEIN[2], J. H. KIM[2], N. D. JAMES[1], A. ROGERS[2], B. KATO[2], A. WOLLENBERG[4], R. KAWAGUCHI[5], G. COPPOLA[5], C. WANG[6], T. J. DEMING[4], Z. HE[6], G. COURTINE[7], M. V. SOFRONIEW[8]
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Abstract: Propriospinal neurons can relay functional information past incomplete spinal cord injuries (SCI) and are good candidates to target for restoring neural connectivity across anatomically complete SCI. Propriospinal neurons do not regrow spontaneously across complete SCI lesions and the molecular requirements to stimulate or improve such regrowth are not characterized. In this study we are examining, individually and in combination, various mechanisms with the potential to stimulate or improve propriospinal axon regrowth in both mice and rats, including (i) biomaterial depots that locally deliver axon-specific chemoattraction in the form of glial cell-derived growth factor (GDNF) that has previously been reported to stimulate propriospinal axon growth after SCI; (ii) inducing growth supportive extracellular matrix by increasing the local expression of laminin; and (iii) activating propriospinal neuron intrinsic growth programs by using adeno-associated viral vectors (AAV) to deliver manipulations previously reported to activate intrinsic growth programs of other central nervous system neurons. Supported by NIH-NINDS NS084030 and F32NS096858, the ALARME Foundation, the International Foundation for Research in Paraplegia, the Roland and Fabièn Loos PhD fellowship award, the Craig H. Neilsen Foundation #381357, the Dr. Miriam and Sheldon G. Adelson Medical Foundation, and Wings for Life.

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Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

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Program #/Poster #: 477.02/W17

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01 NS1069080 (VJT and JRB)

NIH R01 NS085426 (VJT)
Craig H. Neilsen Foundation #382566 (VJT)
Drexel University Dean's Fellowship for Excellence in Collaborative or Themed Research (EM)

Title: Delaying pharmacological inhibition of spinal soluble tumor necrosis factor alpha (sTNFa) signaling diminishes the development of autonomic dysreflexia after complete high thoracic spinal cord injury

Authors: *E. MIRONETS[1], P. OSEI-OWUSU[2], V. BRACCHI-RICARD[4], R. FISCHER[4], T. M. SALTOS[3], E. COLLYER[3], J. R. BETHEA[4], V. J. TOM[3]
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Abstract: Cardiovascular disease and peripheral immune dysfunction are two major causes of mortality and morbidity in people with spinal cord injuries (SCI). These consequences are attributed to the development of autonomic dysreflexia (AD), a life-threatening syndrome characterized by intense episodes of hypertension in response to sensory stimuli caudal to the injury. Over time, AD intensifies partly due to excitability driven by aberrant plasticity of circuits that participate in the spinal sympathetic reflex. Since sTNFa signaling has been correlated with neuronal hyperexcitability, we hypothesize sustained sTNFa signaling plays a crucial role in AD. We previously demonstrated that inhibition of sTNFa signaling via intrathecal administration of a sTNFa biologic (XPro1595) below a complete T3 transection (T3Tx) immediately post-SCI mitigates AD and attenuates consequent immunosuppression and vascular dysfunction. Here, we explored if delaying intrathecal XPro1595 administration for a more clinically-relevant timeframe of 3 days post-SCI also effectively diminishes AD and ensuing immune and vascular dysfunction. We found that XPro1595 rats had less severe colorectal distension-induced AD than saline animals for the duration of the experiment (up to 8 weeks post-T3Tx). To determine if this attenuated AD is associated with improved peripheral immune function, we extracted spleens for flow cytometric analysis of leukocytes 8 weeks post-SCI. We found that T3Tx-saline animals had splenic atrophy, suggestive of diminished immunity. T3Tx-XPro1595 had spleen weights that were undistinguishable from uninjured animals. These data suggest that spinal sTNFa signaling plays a critical role in AD development and ensuing peripheral consequences. In ongoing experiments, we are assessing whether mesenteric arteries from XPro1595-treated animals have more normal responses to vasopressors than saline-treated ones and how inhibiting sTNFa affects injury-induced plasticity of the spinal sympathetic reflex circuit (i.e. nociceptive primary afferents; sympathetically-associated interneurons) histologically. We will also assess the immune profile of rats with chronic SCI in response to a viral influenza. This will allow us to better understand how SCI rodents respond to an immune challenge. Furthermore, we will assess whether intrathecal XPro1595 treatment can improve the immune response to influenza. Collectively, our data provide further demonstration that the neuroimmune response plays a crucial role in the development of AD.

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Poster

477. Spinal Cord Injury III

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 477.03/W18

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Canada Graduate Scholarship: Masters Award
Ontario Graduate Scholarship: Doctoral
Institute of Medical Science Open Fellowship

Title: Drug repurposing: High dose human intravenous immunoglobulin g for treatment of traumatic cervical spinal cord injury

Authors: *J. CHIO[1,2], J. WANG[1], A. BADNER[1,2], J. HONG[1,2], M. CHAMANKHAH[1], M. FEHLINGS[1,3]
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Abstract: After spinal cord injury (**SCI**), neuroinflammation exacerbates damage from initial trauma. Severity of neuroinflamation depends on integrity of the blood-spinal cord-barrier (**BSCB**), which consists of astrocytes, pericytes and endothelial cells. After SCI, a compromised BSCB enhances neuroinflammation by facilitating immune cell migration. Through targeting neuroinflammation, immunosuppressants are used to treat SCI patients. However, as selective components of neuroinflammation are beneficial after SCI, immunomodulation is more effective than general immunosuppression. Human intravenous Immunoglobulin G (**hIgG**) is a clinically-approved immunomodulatory therapy for neuroinflammation. Although we have shown that administration of hIgG (0.4g/kg) at 15 minutes post-SCI is beneficial for functional recovery and tissue preservation, the optimal dose and mechanism of hIgG are unknown.
We use a clinically-relevant rat model of C7/T1 SCI, where female Adult Wistar rats received a 35 g clip compression-contusion injury. At 15 minutes post-SCI, a single bolus hIgG (0.02, 0.2, 0.4, 1, 2g/kg), methylprednisolone (0.03 g/kg, immunosuppressant) or vehicle was administered intravenously. Tissue was collected at 24 hours and six weeks post-SCI to evaluate hIgG's acute and chronic effects. Weekly functional assessments were performed to study functional recovery. At 24 hours post-SCI, hIgG co-localized with rat pericytes, astrocytes and endothelial cells in the spinal cord. Relative to hIgG (0.4g/kg), hIgG (2g/kg) achieved superior protective effects on spinal cord vasculature and reduced spinal cord inflammation. Intriguingly, despite the anti-inflammatory effects on spinal cord, hIgG (2g/kg) increased serum levels of inflammatory cytokines. The reduction of inflammation may be mediated by interfering will immune cell infiltration, as hIgG co-localized (without decreasing protein expression) of vascular cell adhesion molecule-1; an adhesion molecule used by immune cells to extravasate into inflamed

tissue. Furthermore, relative to hIgG (0.4g/kg), the early effects mediated by hIgG (2g/kg) translated into significantly better long-term benefits. These were indicated by enhanced tissue preservation, blood flow and functional recovery at six weeks post-SCI.
Together, this work supports the underlying rationale of immunomodulatory therapy in attenuating the effects of the acute inflammatory response after SCI. hIgG (2g/kg) is an exciting therapeutic approach, where administration of a clinically-relevant biomolecule with a minimally invasive technique mitigates SCI pathology through antagonizing immune cell infiltration.

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Poster

477. Spinal Cord Injury III

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Program #/Poster #: 477.04/X1

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant F31NS100303
CHN Grant 340884
NIH Grant R01NS083942

Title: Bad to the bone: Spinal cord injury disrupts hematopoietic and immune cell function in the bone marrow niche

Authors: *R. S. CARPENTER, J. M. MARBOURG, A. M. DORRANCE, P. G. POPOVICH
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Abstract: Systemic immune system dysfunction is a major consequence of spinal cord injury (SCI). The injury disrupts spinal circuitry that is essential for maintaining homeostatic control between the brain and peripheral immune tissues. The result is that SCI individuals have suppressed systemic immunity and are more susceptible to infection than are abled-bodied individuals. Post-SCI immune suppression is due in part to the death or dysfunction of mature immune cells in the spleen. Because spinal autonomic circuitry also innervates bone marrow, a primary generative lymphoid organ, SCI may adversely affect the formation of new white blood cells from hematopoietic stem and progenitor cells (HSPCs) in bone marrow. Here, we used a mouse model to determine how SCI affects the activity of HSPCs in bone marrow, blood and spleen. *In vivo* imaging and flow cytometry reveal a rapid increase in HSPC proliferation in bone marrow niches during the first 7 days after SCI, peaking at 3 days post-injury (dpi). SCI bone marrow (3 dpi) plated in an *ex vivo* MethoCult culture assay generated fewer mature immune cells than sham-injured bone marrow indicating that SCI impairs HSPC differentiation.

However, these same cells have superior engraftment potential when injected into transplant recipient mice when compared with bone marrow grafts derived from naïve or sham-injured mice. Phenotypic and molecular analysis of SCI bone marrow revealed that SCI increases CXCL12 and CXCR4 expression. Since CXCL12-CXCR4 signaling is critical for HSPC retention in bone marrow, an increase in this ligand-receptor pair after SCI could impair HSPC mobilization. New data show that after SCI HSPCs and mature leukocytes become trapped in bone marrow and that this sequestration is due in part to increased CXCL12-CXCR4 signaling. Importantly, we can boost HSPC mobilization after SCI by injecting mice with Plerixafor (AMD3100), an FDA-approved CXCL12-CXCR4 antagonist. Daily injections of AMD3100 for 3 days post-SCI increased HSPC mobilization into blood, improved HSPC trafficking to the spleen, and reversed SCI-induced leukopenia in blood (vs. vehicle controls). Future experiments will determine if dysregulated CNS communication to bone marrow after SCI impairs HSPC function and mobilization, and whether targeting CNS-bone marrow and CXCL12-CXCR4 signaling can boost innate and adaptive immune function. These data indicate that the bone marrow niche is a novel target for improving immune system function and preventing immune-related morbidity and mortality after SCI.

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Poster

477. Spinal Cord Injury III

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Program #/Poster #: 477.05/X2

Topic: C.11. Spinal Cord Injury and Plasticity

Support: CIHR grant MOP119281

Title: Microbiome transplant attenuates anxiety/depression-like behavior in a rat model of spinal cord injury

Authors: *E. K. SCHMIDT, P. J. F. RAPOSO, K. K. FENRICH, K. FOUAD
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Abstract: Microbiome transplant attenuates anxiety/depression-like behaviour in a rat model of spinal cord injury
Secondary consequences of spinal cord injury (SCI) beyond paralysis can negatively affect a person’s quality of life. For example, SCI is frequently associated with increased incidences of depression and anxiety; however, beyond a possible contribution of post injury- inflammation, the mechanisms of this relationship are currently not well understood. Human and animal studies suggest that depression and anxiety are associated with changes in the composition of the

intestinal microbiome population (dysbiosis). Recent research in mice has found that SCI increases intestinal permeability and induces dysbiosis. We propose that SCI-induced dysbiosis may provide a link to the increased rate of mental health disorders following SCI. The objective of the current study is to establish a model of depression and anxiety following SCI in female rats and to determine whether the microbiome plays a role in the observed behavioural changes. To test this, rats underwent a battery of tests to assess baseline levels of depression- and anxiety-like behaviour. Microbiome composition was analyzed using CHROMagar orientation plates and 16s rRNA analysis. Rats then received a mild cervical contusion or sham operation. Following injury, SCI rats displayed increased symptoms of anxiety and depression compared to sham controls as measured using the elevated plus maze. Rats with a SCI also displayed an altered microbiome composition compared to sham animals. To determine if there is a link between SCI-induced dysbiosis and behavioural changes we administered a microbiome transplant immediately after injury to restore/maintain a healthy microbiome composition. Not only did this treatment decrease SCI-induced dysbiosis, the microbiome transplant also increased exploratory behaviour in the elevated plus maze. These results indicate that a mild SCI can induce behavioural changes and intestinal dysbiosis, and that treating dysbiosis can prevent the development of depression- and anxiety-like symptoms following SCI.

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Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

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Program #/Poster #: 477.06/X3

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DOD W81XWH-16-1-0349
NIH HL51971
GM104357 (ARC)

Title: Acute but sustained treatment with cannabinoid receptor-2 agonist preserves hind limb bone density in mice after SCI

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Abstract: Spinal cord injured individuals exhibit a greater risk of developing osteoporosis compared to uninjured individuals with the prevalence of osteoporosis in SCI patients ranging as high as 75%. The development of age-dependent osteoporosis represents a significant health risk

in the general population, but such risk carries a far greater burden for those living with SCI. Bone fractures in patients with SCI often occur in areas devoid of normal sensory function. As a result, these individuals may be unaware that a fracture has occurred, leading to potentially fatal consequences. Current therapies for SCI-induced osteoporosis are focused mainly on bisphosphonates, most commonly used to treat osteoporosis in the ageing population. Unfortunately, bisphosphonates are only mildly effective in treating SCI-induced osteoporosis and can, paradoxically, exacerbate bone loss in SCI patients when used for long-term, chronic treatment. Cannabinoids, particularly agonists of the cannabinoid receptor-2 (CB2) class, have shown promise as therapeutic agents in experimental models of age-dependent osteoporosis by modulating the ratio of osteoblast-to-osteoclast activity. However, it is unknown whether CB2 agonists would improve osteoporosis in SCI. We therefore hypothesized that a selective CB2 agonist, HU-308, would attenuate onset of osteoporosis in a mouse model of SCI. Methods: Adult, male, C57BL6 mice received a full spinal transection lesion at T9. Treatment with either vehicle or CB2 agonist HU-308 (10 mg/kg) was initiated at 3 hours post-SCI and continued once daily for 40 days by IP injection. Non-injured mice served as age-matched controls. Mice were euthanized at 40 days with hind limb femurs and tibiae collected, processed and scanned using 3D micro-CT. Bone density measurements were made in tibiae (rostral and proximal) and femur (rostral and proximal). Results: HU-308 preserves bone density in the distal tibia compared to vehicle-treatment ($p>0.001$) with drug-treated bone showing nearly age-matched, control levels. Drug-treated proximal tibiae were significantly preserved compared to vehicle-treated ($p>0.05$). HU-308 efficacy was not observed in proximal or distal femur. Conclusions: HU-308 shows promise as a novel treatment to attenuate onset of osteoporosis following spinal cord injury. We are currently exploring whether a delay in CB2 agonist treatment can elicit a reversal of hind limb osteoporosis in chronically-injured mice.

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Poster

477. Spinal Cord Injury III

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH grant NS094527
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Title: Sexual difference on neuroinflammation and functional recovery after SCI

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Abstract: Spinal cord injury (SCI) causes not only sensorimotor deficits, neuropathic pain, and autonomic dysfunction but also varying degrees of neuropsychological abnormalities including cognitive impairment and depression, with no effective treatment. Biological sex differences in the epidemiology of SCI have been reported that males have a higher likelihood of getting a SCI than females. Sexual disparities in response to SCI in human and rodent have been previously reported, however, little is known about the effect of biological sex on remote brain dysfunction as well as injury mechanisms. In the present study, young adult male and female C57BL/6 mice subjected to moderate/severe thoracic contusion injury were evaluated for their functional outcomes using a battery of behavioral tests including motor function, cognition, and depression. In assessment of motor function, female mice were generally more active, as evidenced by greater distance traveled in the open field and higher numbers of total arm entries in the Y-maze. After SCI, female mice had better Basso Mouse Scale than that in male animals beginning 4 weeks post-injury. CatWalk analysis showed similar motor coordination in two sex groups. SCI in male mice caused poor performance in the novel object recognition and Y-maze tests indicating impairment of cognition, however, injured female mice showed less deficits in these tasks. To assess depressive-like behavior, tail suspension, forced swim, and novelty-suppressed feeding were employed. Male mice after SCI were more likely to develop depression, but not female animals. In contrast, both sexes had similar response to mechanical and thermal stimulation at the hind-paws. To explore the effects of sex on SCI-mediated neuroinflammation, about 800 genes selected from Neuroinflammation panel were analyze in injured spinal cord tissues and cerebral cortex by NanoString technology. The data showed robust differential changes between sexes not only in injured site but also in the remote cerebral cortex. Collectively, these findings indicate that SCI leads to a more aggressive neuroinflammatory profile in male compared with female mice. Different functional recovery after SCI suggests that biological sex should be considered when designing new therapeutic agents.

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Poster

477. Spinal Cord Injury III

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Topic: C.11. Spinal Cord Injury and Plasticity

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Title: Immediate elimination of the axon-glial complex achieves successful axon regeneration in cordotomized adult rats

Authors: *T. NISHIO[1], H. FUJIWARA[2], I. KANNO[3]
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Abstract: After a transection of the spinal cord in mature mammals, severed axonal ends show a rapid retraction within 0.5-1 hour of axotomy and then attempt regeneration in 6 hours. It is known that the initial growth response by axons is robust, but regenerative axons hardly grow across the lesion site. Regarding the cause of this limited regeneration, the presence of several types of axon-growth inhibitors has been shown in mature mammalian central nervous system (CNS), such as myelin-associated inhibitors or glial scar-related extracellular matrix molecules. However, the actual cause remains elusive.
We focused on the early axonal responses to transection of the spinal cord in adult rats. Local axonal tracing and quantitative analysis revealed that axonal regrowth had already started within 4 hours of cordotomy, and we called axons that would start regenerating within hours of corodotomy as “regenerative pioneering axons”. Notably, the regenerative pioneering axons reached the lesion site in 4 hours of cordotomy showing a characteristic snaking morphology. At the lesion site, we found abnormal axon fragments, which frequently formed an aggregate. Electron microscopy further revealed that the aggregate was composed of unmyelinated axons and astroglial processes, which made a direct contact with axons. Thus, we named the aggregate as “axon-glial complex”, AGC. Considering a possible role of the AGC as physicochemical barriers for regenerative pioneering axons, we examined the effects of prompt elimination of the barriers on axonal growth beyond the lesion site. To be more specific, we surgically eliminated the AGC by making additional cord section near the primary section and removing the injured white matter tissue from the lesion site (surgical debridement). Under the treatment, the regenerative pioneering axons successfully traversed the lesion site through an AGC-eliminated area within 4 hours of cordotomy. To exclude axonal sparing, we made an epoxy-based sheet with pores (pore size was 125 micrometer in diameter) using SU-8 photoresist and inserted it into the AGC-eliminated lesion site. The pioneering axons successfully extended beyond the sheet and formed fascicles 24 hours post-surgery.
We further tested a chemical elimination of the AGC with a protease. We injected a Bromelain solution near the lesion site one hour after a cordotomy and found a successful regeneration. These results suggest that the AGC at the lesion site would be a novel cause of failed regeneration and that regenerative pioneering axons have a powerful growth engine even in mature CNS.

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Poster

477. Spinal Cord Injury III

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Program #/Poster #: 477.09/X6

Topic: C.11. Spinal Cord Injury and Plasticity

Support: International Spinal Research Trust TRI004_01
United Kingdom Medical Research Council G1002055

Title: Immune-evasive gene switch allows regulated delivery of chondroitinase and long term delivery restores reaching and grasping function after cervical spinal cord injury

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Abstract: Chondroitinase ABC is a promising preclinical therapy that promotes functional neuroplasticity after CNS injury by degrading extracellular matrix inhibitors. Efficient delivery of chondroitinase ABC to the injured mammalian spinal cord can be achieved by viral vector transgene delivery. This approach dramatically modulates injury pathology and restores sensorimotor functions. The ability to exert control over chondroitinase gene expression would further optimise this system and enable the therapeutic time window to be explored. Prior experimental gene regulation platforms are likely to be incompatible with the non-resolving adaptive immune response known to occur following spinal cord injury. Therefore, here we apply a novel immune-evasive dual vector system, in which the chondroitinase gene is under a doxycycline inducible regulatory switch, utilizing a chimeric transactivator designed to evade T cell recognition. Using this novel vector system, we demonstrate tight temporal control of chondroitinase ABC gene expression, effectively removing treatment upon removal of doxycycline. This enables a comparison of short and long term gene therapy paradigms in the treatment of clinically-relevant cervical level contusion injuries in adult rats. We reveal that transient treatment (2.5 weeks) is sufficient to promote improvement in sensory axon conduction and ladder walking performance. However, in tasks requiring skilled reaching and grasping, only long term treatment (8 weeks) leads to significantly improved function, with rats able to accurately grasp and retrieve sugar pellets. The late emergence of skilled hand function indicates enhanced neuroplasticity and connectivity and correlates with increased density of vGlut1+ innervation in spinal cord grey matter, particularly in lamina III-IV above and below the injury. Thus, our novel gene therapy system provides an experimental tool to study temporal effects of extracellular matrix digestion as well as an encouraging step towards generating a safer chondroitinase gene therapy strategy, longer term administration of which increases

neuroplasticity and recovery of descending motor control. We are currently utilising this system to compare acute and delayed administration of chondroitinase in order to assess its potential in the treatment of chronic spinal cord injury.

Disclosures: E.R. Burnside: None. **F. de Winter:** None. **N.I. Roopnarine:** None. **A. Didangelos:** None. **N.D. James:** None. **J. Verhaagen:** None. **E.M. Muir:** None. **E.J. Bradbury:** None.

Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 477.10/X7

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Bryon Riesch Paralysis Foundation 133-PRJ84LQ
Donation from the Fraternal Order of Eagles

Title: Local sustained interleukin-10 delivery reduces inflammation and improves motor function after spinal cord injury

Authors: *D. J. HELLENBRAND, A. G. GABLEMAN, E. DAI, J. B. SPORLEDER, S. HENRY, S. D. ORTMANN, J. C. GOTCHY, A. S. HANNA
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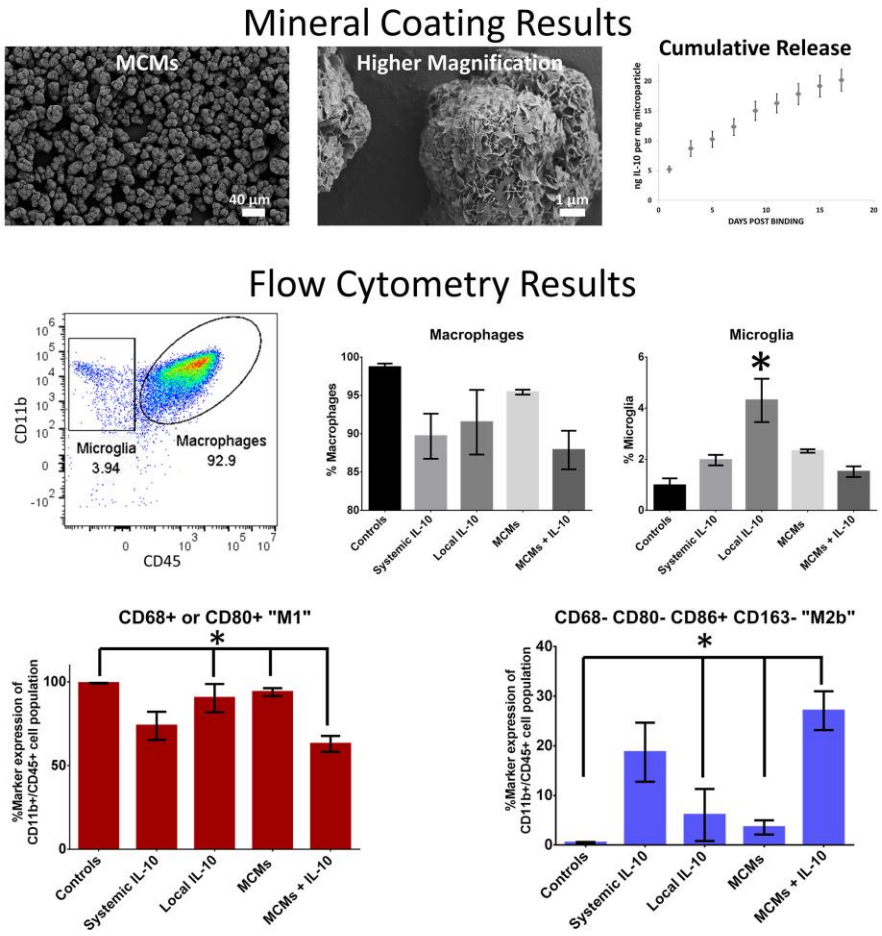
Abstract: The anti-inflammatory cytokine interleukin-10 (IL-10) has been explored previously as a treatment method for spinal cord injury (SCI) due to its ability to attenuate pro-inflammatory cytokines and reduce apoptosis. Primary limitations when using IL-10 are that it is rapidly cleared from the injury site and that it does not cross the blood spinal cord barrier. Here, mineral-coated microparticles (MCMs) were used to obtain a local sustained delivery of IL-10 directly into the injury site. Female Sprague-Dawley rats were contused at T10 and treated with either an intraperitoneal injection of IL-10, an intramedullary injection of IL-10 or MCMs bound with IL-10 (MCMs+IL-10). After treatment, cytokine levels were measured in the spinal cord, functional testing and electrophysiology were performed, axon tracers were injected into the brainstem and motor cortex, macrophage levels were counted, and lesion size was measured. When treated with MCMs+IL-10, IL-10 was significantly elevated in the injury site, inflammatory cytokines were significantly suppressed, prompting a larger ratio of M2 to M1 antigen expressing macrophages. Significantly more axons were preserved within the rubrospinal and reticulospinal tracts through the injury site when treated with MCMs+IL-10; however, there was no significant difference in corticospinal tract axons preserved, regardless of treatment group. The rats treated with MCMs+IL-10 were the only group with a significantly higher functional score compared to

injured controls 28 days post-contusion. These data demonstrate that MCMs can effectively deliver IL-10 for an extended period of time, aiding in functional recovery after SCI.



Mineral coated microparticles deliver a sustained release of interleukin-10 . Flow cytometry, performed 7 days after spinal cord injury in rats, reveals a shift in CD45+ CD11b+ macrophages to an early stage M2 phenotype.
*P<0.05 (Tukey's Test); error bars represent ± SEM

Disclosures: D.J. Hellenbrand: None. **A.G. Gableman:** None. **E. Dai:** None. **J.B. Sporleder:** None. **S. Henry:** None. **S.D. Ortmann:** None. **J.C. Gotchy:** None. **A.S. Hanna:** None.

Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 477.11/X8

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Inhibition of IL-17A promotes tissue repair by ependymal cells after spinal cord injury

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Abstract: Spinal cord injury (SCI) results in the loss of neurons and axonal connections, leads to impairment of neurotransmission in central nervous system. In mammals, although the spontaneous tissue recovery is observed after SCI, it is not sufficient to restore the neural functions. Thus, it is required to reveal the molecular mechanism of spontaneous tissue repair after SCI to develop the effective treatment. In this study, we focused on ependymal cells (ECs), lining the central canal, which act as neural stem cells after SCI. Recent studies revealed that ECs are involved in tissue repair by differentiation into astrocytes and oligodendrocytes. On the other hand, peripheral immune cells infiltrate into the injured spinal cord, and induce the inflammation by secreting various pro-inflammatory cytokines. However, it remains unclear whether inflammatory signals are associated with ECs functions. Here, we examined the role of inflammatory signals for the ECs activity after SCI.
To clarify whether ECs express the receptor for pro-inflammatory cytokines after SCI, we isolated the ECs from the injured spinal cord, and found that ECs express the receptor for interleukin (IL)-17A, which is a pro-inflammatory cytokine. IL-17A was significantly increased after 7 days of SCI, and γδT cells were the main source of IL-17A. Neurosphere assay showed IL-17A inhibits the proliferation of ECs in vitro. In addition, we investigated whether IL-17A inhibition promotes the motor recovery and tissue repair by treatment with anti-IL-17A neutralizing antibody, or lentivirus injection, encoding flox-flanked dominant negative form of IL-17A receptor, into FoxJ1-CreERT2 mice (ECs specific Cre mouse line). As a result, inhibition of IL-17A signaling improved the motor function and promoted the ECs proliferation. These results suggest that IL-17A signaling disturbs tissue repair by inhibiting the proliferation of ECs after SCI. Thus, we propose that inhibition of IL-17A can be an effective treatment for repairing the tissue.

Disclosures: H. Miyajima: None. **S. Tanabe:** None. **M. Fujitani:** None. **T. Yamashita:** None.

Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 477.12/X9

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NRF-2016M3A9E8941668

Title: Ursodeoxycholic acid inhibits inflammatory responses and promotes functional recovery after spinal cord injury in rats

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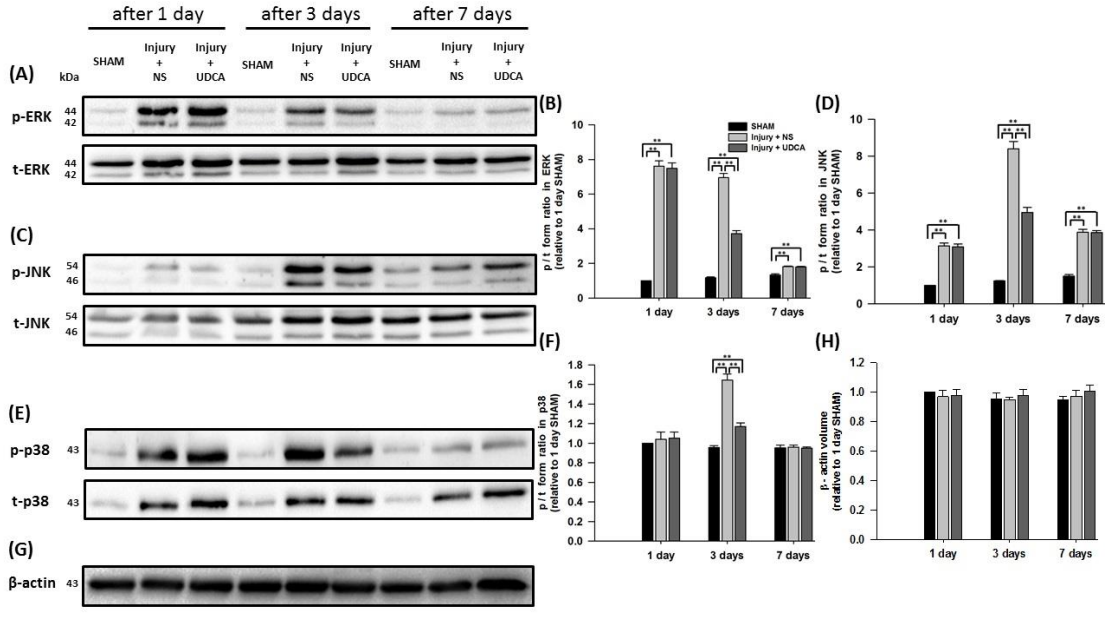
[2]CHA Univ., Gyeonggi-do, Korea, Republic of

Abstract: Purpose: The aim of this study was to investigate the anti-inflammatory effects by ursodeoxycholic acid (UDCA) in rats with a spinal cord injury (SCI).**Methods:** A moderate mechanical compression injury was imposed on adult Sprague-Dawley (SD) rats. The post-injury locomotor functions were assessed using the Basso, Beattie and Bresnahan (BBB) locomotor scale and the tissue volume of the injured region was analyzed using hematoxylin and eosin staining. The pro-inflammatory factors were evaluated by immunofluorescence (IF) staining, a quantitative real-time polymerase chain reaction (qRT-PCR) and enzyme-linked immunosorbent assay (ELISA). The phosphorylation of the extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 in mitogen-activated protein kinase (MAPK) signaling pathways related to inflammatory responses were measured by western blot assays.**Results:** UDCA improved the BBB scores and promoted the recovery of the spinal cord lesions. UDCA inhibited the expression of glial fibrillary acidic protein (GFAP), tumor necrosis factor-α (TNF-α), ionized calcium-binding adapter molecule 1 (iba1), and inducible nitric oxide synthase (iNOS). UDCA decreased the pro-inflammatory cytokines of TNF-α, interleukin 1-β (IL-1β), and interleukin 6 (IL-6) in mRNA and protein levels. UDCA increased the anti-inflammatory cytokine interleukin 10 (IL-10) in the mRNA and protein levels. UDCA suppressed the phosphorylation of ERK, JNK and the p38 signals. **Conclusion:** UDCA reduces pro-inflammatory responses and promotes functional recovery in SCI rats. These results suggest that UDCA is a potential therapeutic drug for SCI.



Disclosures: S. Sohn: None. **W. Ko:** None.

Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 477.13/X10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: MRC G1002055
MRC/ERA-NET-NEURON M4/ROO5532/1

Title: Molecular and cellular responses of immune cells following therapeutic targeting of the extracellular matrix after spinal cord injury

Authors: *I. FRANCOS-QUIJORNA[1], E. R. BURNSIDE[1], J. VERHAAGEN[2], E. J. BRADBURY[1]
[1]Inst. of Psychiatry, Psychology & Neurosci., King's Col. London, London, United Kingdom; [2]Neth Inst. Neurosc, Amsterdam, Netherlands

Abstract: Spinal cord injury (SCI) causes irreversible axonal damage and neuronal death, resulting in permanent disability for which there are no effective treatment. In addition to the initial mechanical injury, a wide range of secondary cellular and molecular events occurs after SCI, constituting the secondary injury, which lead to further tissue damage and consequently functional impairments. One major contributor to this pathological cascade is the inflammatory response which is aggressive and unresolved. The factors that impede the clearance of immune cells after the injury have not been fully characterized and several lines of evidence imply a role for chondroitin sulphate proteoglycans (CSPGs) in SCI inflammation. Recent work has shown that modifying CSPGs in the extracellular matrix (ECM) with the enzyme chondroitinase-ABC (ChABC) can reduce secondary injury pathology. However, the mechanisms that underlie immunomodulatory effects of ChABC after SCI are not yet understood.
To evaluate whether ECM alteration modulates the inflammatory response after SCI we performed a large-scale digestion of inhibitory scar matrix with ChABC delivered via lentiviral vector (LV-ChABC) after thoracic SCI in adult female rats. By flow cytometry, we then assessed the number of microglial cells, macrophages and neutrophils within the injury epicentre. Our results show that ECM digestion by LV-ChABC promotes inflammatory resolution after SCI revealed by accelerated clearance of neutrophils (Ri: 48.9 vs 37.1hr) and reduced accumulation of macrophages (1803 ± 405 vs 790 ± 120 cells) and microglial cells (5540 ± 834 vs 3181 ± 636 cells) 7 days after the injury compared with control animals (LV-GFP). We next evaluated which immune cell populations are modulated by LV-ChABC. Following assessment of the expression of CSPG receptors in each immune cell type, we analysed the mRNA expression of different phenotypic markers within the FACS sorted immune cell populations and found that microglial cells from LV-ChABC treated animals had significantly higher expression of anti-inflammatory

markers (Arginase I and CD206) 7 days post- injury. We are currently assessing changes in cytokine and chemokine expression and potential signalling pathways involved in ECM-immune interactions. These data suggest that ECM alteration after SCI impedes the inflammatory resolution which contributes to tissue damage and functional impairments. Understanding the cellular and molecular mechanisms underlying ECM-mediated modulation of the inflammatory response may lead to more effective therapies to treat SCI.

Disclosures: I. Francos-Quijorna: None. **E.R. Burnside:** None. **J. Verhaagen:** None. **E.J. Bradbury:** None.

Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 477.14/X11

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Vitamin D improves the wellness of myelin sheath after experimental spinal cord injuries in normal and induced vitamin D-deficient rats

Authors: N. LI, Y. MIN, *G. K. LEUNG
The Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Background: Demyelination occurs immediately after traumatic spinal cord injury (TSCI) and lasts for months. Spontaneous remyelination is reported incomplete that may result in limited neurological recovery. Several lines of evidence showed that vitamin D (VD) is a promising molecule in improving functional recovery after spinal cord trauma, and it was often linked its anti-inflammatory effects. A recent study demonstrated that VD promoted oligodendrocyte maturation in vitro, shedding light on another potential mechanism of its therapeutic benefit after TSCI. Thus, our study aims to examine its effects on myelin wellness in animal TSCI models. Methods: Two cohorts of rats were used: 1) Sprague-Dawley rats fed with normal diet; and 2) induced VD-deficient SD rats raised with non-VD diet. Two TSCI models were conducted to each cohort: i) moderate injury using vessel clip contusion (10g x 5 min); ii) severe transection injury with a blade cut. Animals were either treated with coconut oil vehicle or VD (500IU/kg/day) for two months. Hindlimb motor function was evaluated every week after injury. Myelin sheath was examined by transmission electron microscopy (TEM) and western blotting. Rat oligodendrocytes and dorsal root ganglions were co-cultured to investigate the impact of VD on myelin formation *in vitro.* Results: VD-treated rats displayed a better functional recovery in both models, but this therapeutic effect was attenuated by pre-deficiency. TEM scanning showed that: 1) myelin damage was more severe in the transection model than the contusion model, and demyelination was obvious not only in the epicenter but also in the 0.5 cm rostral area; 2) VD treatment increased the thickness of myelin when compared with vehicle

control. 4) myelin was thinner in deficient animals than that in normal ones. These results were further confirmed in the proteomic tests. In vitro administration of 1,25(OH)D3 favored the maturation of oligodendrocyte, and promoted the myelin formation with DRG axons in co-culture system, suggesting that VD-enhanced oligo maturation might partially contributed to the in vivo myelin protection. Conclusions: Our study provides mechanistic evidence that VD favors neurological recovery by increasing the myelin wellness after TSCI. We also value the importance of maintaining VD sufficiency in TSCI as deficient animals respond worse to VD treatment.

Disclosures: N. Li: None. **Y. Min:** None. **G.K. Leung:** None.

Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 477.15/X12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: American Association of Anatomists
Ontario Institute for Regeneration Medicine
Krembil Foundation

Title: Using metformin to activate endogenous neural precursor cells in the spinal cord

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Univ. of Toronto, Toronto, ON, Canada

Abstract: Spinal cord injuries (SCI) result in devastating functional deficits with minimal treatment options. Endogenous neural precursor cells (NPCs) exist within the spinal cord and are located in the periventricular region lining the central canal. While normally relatively quiescent and non-neurogenic, these NPCs are activated in response to injury. Enhancing and harnessing the potential of resident NPCs may improve structural and functional outcomes following SCI. The FDA-approved drug metformin (MET) has demonstrated efficacy in promoting neural repair in the injured brain where it expands the size of the NPC pool and promotes both oligogenesis and neurogenesis from NPCs. Here, we seek to determine whether it has a similar effect on NPCs within the spinal cord. Using the in vitro colony forming assay (neurosphere assay) we examined the size of the neural stem cell pool in the spinal cord following 7 days of *in vivo* MET treatment. Females demonstrated a three-fold increase neural stem cells, while males did not show any expansion in response to MET treatment. Interestingly, the sex dependent expansion of the neural stem cell pool was not coincident with the effects of MET on the differentiation profile the neural stem cell progeny. Neurospheres were plated in the presence of differentiation media, and then stained for markers of mature neural cell phenotypes. We found neurons (β-III-

tubulin), oligodendrocytes (O4) and astrocytes (GFAP) within the spheres, and determined that in both sexes, MET increases oligogenesis compared to vehicle-treated controls. Our data reveal that MET has differential effects on spinal cord NPCs of males and females. By expanding the NSPC pool in females, and augmenting oligogenesis in both sexes, MET treatment represents a viable therapeutic strategy for enhancing neural repair post spinal cord injury.

Disclosures: E.A. Gilbert: None. **W. Xu:** None. **C.M. Morshead:** None.

Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 477.16/X13

Topic: C.11. Spinal Cord Injury and Plasticity

Support: FAPESP 2013/16134-6
FAPESP 2014/06892-3
CNPq

Title: Mesenchymal stem cell treatment reduces astrogliosis and microglial reaction and improves motoneuron survival after spinal ventral root crush in mice

Authors: *L. P. CARTAROZZI[1], M. PEREZ[1], F. KIRCHHOFF[3], Â. C. M. LUZO[2], A. L. OLIVEIRA[1]
[2]Med. Fac., [1]Univ. of Campinas, Campinas, Brazil; [3]Univ. of Saarland, Homburg, Germany

Abstract: Rupture and stretching of spinal roots are common incidents that take place in high energy accidents. The proximal axotomy of motoneurons by crushing of ventral roots is directly related to the degeneration of half of the lesioned population within the first two weeks. Moreover, only a small percentage of surviving motoneurons can successfully achieve regeneration after such a proximal lesion, and new treatments are necessary to improve this scenario. In this sense, mesenchymal stem cells (MSC) are of great interest once they secrete a broad spectrum of bioactive molecules that are immunomodulatory and can act in the restoration of the environment after lesion. The present work aimed at studying the effects of human mesenchymal stem cells (hMSC) therapy after ventral root crush (VRC) in mice. We evaluated motoneuron survival, glial reaction, and synapse preservation at the ventral horn. For this purpose, C57BL/6J were submitted to the crush of L4 to L6 ventral roots, and treatment with a single intravenous injection of adipose-derived hMSC. Evaluation of the results was carried out 7, 14 and 28 days after injury. Analysis of motoneuron survival and astrogliosis showed that hMSC treatment resulted in higher motoneuron preservation (motoneuron survival ipsi/contrataleral ratio: VRC group = 0.53, VRC + hMSC group = 0.66; $p<0.01$), combined with reduction of astrogliosis (ipsi/contralateral GFAP immunolabeling: VRC group = 4.7, VRC +

hMSC group = 2.5; p<0.001). Microglial reaction was more intense in non-treated animals, becoming reduced in about 20% after hMSC injection (ipsi/contralateral Iba-1 immunolabeling: VRC group = 3.7, VRC + hMSC group =2.5; p<0.05). The glial reactivity modulation directly influenced synaptic inputs in apposition to axotomized motoneurons. Thus, in the hMSC-treated group, synaptic maintenance was increased (ipsi/contralateral synaptophysin immunolabeling: VRC group = 0.53, VRC + hMSC group = 0.64; p<0.05). Overall, the present data show that systemic injection of hMSC has neuroprotective and anti-inflammatory effects, decreasing reactive astrogliosis and microglial reaction. Also, such cell therapy results in motoneuron preservation, combined with significant maintenance of spinal cord circuits, in particular, those related to the ventral horn.

Disclosures: L.P. Cartarozzi: None. **M. Perez:** None. **F. Kirchhoff:** None. **Â.C.M. Luzo:** None. **A.L. Oliveira:** None.

Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 477.17/X14

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Mesenchymal stromal cell-derived extracellular vesicles alleviate major pathological hallmarks of spinal cord injury

Authors: *P. ROMANELLI[1,2,3], L. BIELER[1,2,3], C. SCHARLER[1,4,3], K. PACHLER[1,5,3], C. KREUTZER[1,2,3], P. ZAUNMAIR[1,2,3], L. AIGNER[1,6,3], F. RIVERA[1,3,7], E. ROHDE[1,5,3,8], B. BRUNO[1,2,3], K. SCHALLMOSER[3,8], M. GIMONA[1,5,3], D. STRUNK[1,4,3], S. COUILLARD-DESPRES[1,2,3]
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Abstract: Traumatic spinal cord injury (tSCI) is an unforeseen catastrophic event that profoundly change the life of affected individuals. The phase of secondary damages induced after lesion is characterized by strong inflammatory processes leading to further neuronal and functional losses. In this study, we assessed the impact of systemic application of purified extracellular vesicles (EVs) secreted from human umbilical cord mesenchymal stromal cells (hUC-MSCs), on the functional and structural outcomes following tSCI in a rat model. SCI was obtained in female Fisher 344 rats of 10 weeks of age by applying a 200 kdyn contusion lesion at thoracic level 8 resulting in a moderate to severe incomplete SCI. The rats were randomly

divided in treatment groups receiving acutely an intravenous application of either vehicle, $1x10^6$ hUC-MSCs, or purified EVs secreted by the corresponding amount of cells, and again 24 hours after contusion. Sham rats underwent the same surgical procedure but did not receive a contusion. Histological analyses were performed 14 days after contusion. Treatment with EVs or hUC-MSCs significantly reduced the local inflammation, compared to vehicle-treated rats, as revealed by the lower density of microglia/macrophages residing in the peri-lesion area. Similarly, a significant reduction of astrogliosis, according to the GFAP expression level, and scarring, based on collagen accumulation within the lesion and peri-lesion areas, were observed in the spinal cords of hUC-MSCs and EVs-treated groups, in comparison to the vehicle-treated group. In conclusion, our study demonstrated that treatments with hUC-MSCs and EVs efficiently decreased the inflammatory response and scarring associated with the phase of secondary damages during the 2 weeks following tSCI.

Disclosures: P. Romanelli: None. **L. Bieler:** None. **C. Scharler:** None. **K. Pachler:** None. **C. Kreutzer:** None. **P. Zaunmair:** None. **L. Aigner:** None. **F. Rivera:** None. **E. Rohde:** None. **B. Bruno:** None. **K. Schallmoser:** None. **M. Gimona:** None. **D. Strunk:** None. **S. Couillard-Despres:** None.

Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 477.18/Y1

Topic: C.11. Spinal Cord Injury and Plasticity

Support: KAKENHI 17K10943
KAKENHI 16H05443
KAKENHI 26462769

Title: Effect of human mesenchymal stromal cells (hMSCs) on CCL5 expression and macrophage polarization after spinal cord injury

Authors: *H. OHTAKI[1], K. YAGURA[1,3], T. TSUMURAYA[3], A. SATO[3], J. WATANABE[5], K. MIYAMOTO[4], Y. HIRAIZUMI[2], K. HONDA[1]
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Abstract: Spinal cord injury (SCI) is mainly caused by traffic and sports accidents, and is often subjected to permanent motor dysfunction. Mesenchymal stem/stromal cells (MSCs) have been attracted to be suppressed and/or resolved the SCI in animal and clinical experiments. Microglia/macrophages (MG/MΦ) mobilize to injury site and contribute to both deterioration

and resolution of the inflammation. We have reported that transplantation of human MSCs (hMSCs) suppressed neural injury along with an induction of alternative activating MG/MΦ (M2-type MG/MΦ) after brain ischemia and SCI. However, it remains unclear the mechanism of hMSCs with MG/MΦ. In the present study, we determined that a chemokine, CCL5 and M2-type MG/MΦ markers were increased after hMSCs transplantation. Then we determined cellular localization CCL5 and the receptors to estimate the role of CCL5 after the SCI. Male C57/BL6 mice were subjected to SCI between TH9 and 10 intervertebral with thin razor. The hMSCs (5 $x10^5$ cells) injected one caudal vertebral at day 1. The mice were monitored locomotor activity with Basso mouse scale, and evaluated the injury size at 14 days. Moreoevr, the spinal cord (TH7 to 12) was collected and carried out quantitative PCR and immunohistochemistry for CCL5, the receptors, and MG/MΦ markers. The expression *ccl5* drastically increased 14 days after SCI. Although all receptors increased at day1, and *ccr1* and *ccr3* were returned to basal level by day 7, *ccr5* kept higher level for 2 weeks. The CCL5 and CCR5 localized in neurons and microglia. hMSCs injection further increased *ccl5* expression but not CCR5, and increased significantly M2-type MG/MΦ marker, *arg1*, *chil3* and *il4* gene expressions at day 14. The mice injected hMSCs improved locomotor activity and suppressed injury area. Injection of mouse recombinant CCL5 also increased the expression of *chil3*. These results suggest that CCL5 which increased the expression by hMSCs might be migrated macrophages into injury region and polarized to M2-type MG/MΦ activation communicating with hMSCs.

Disclosures: H. Ohtaki: None. **K. Yagura:** None. **T. Tsumuraya:** None. **A. Sato:** None. **J. Watanabe:** None. **K. Miyamoto:** None. **Y. Hiraizumi:** None. **K. Honda:** None.

Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 477.19/Y2

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NYSCIRB

Title: Spinal cord injury site modulation platform with nanotechnology and stem cells

Authors: *J. L. PALUH[1], Z. T. OLMSTED[1], A. SCIMEMI[2], Y. XIE[1]
[1]Nanobioscience, SUNY Polytechnic Inst., Albany, NY; [2]SUNY Albany, Albany, NY

Abstract: Extensive efforts to accelerate treatments in spinal cord injuries (SCI) are challenged in part by a need for comparative uniformity and reproducibility. The overarching goal of our research is to test a generalizable strategy for cell delivery and modulation of both therapeutic cells and the injury site to optimize integration and repair. A uniform platform would more coherently bring together the most exciting research strategies in the SCI field being evaluated

by many laboratories to create synergistic rapid advances. Towards this goal we are applying biocompatible hydrogel ribbon platforms with human iPSC-derived neural stem cell technologies and nanoparticle delivered enzymes in a dual spinal treatment enhancing platform (2STEP). This platform will be tested for re-establishment of neural connectivity and behavior in a rat hemicontusion model of SCI. Nanoparticle delivered modulators include chondroitinase enzymes to block inhibitory extracellular matrix signals as well as modulators of neural stem cell differentiation when multipotent cells are used and regulators of spinal motor neuron maturation as well as optimizing ratios of oligodendrocyte co-delivery. The current work focuses on the hydrogel ribbon-cell + modulator studies to validate release times and electrophysiological potential of cells in ribbons. Scientific rigor is being ensured by appropriate controls, replicate sizes and quantitative assays to complement any qualitative analyses and with validated reagents. These initial studies use published hiPSC lines developed and comprehensively characterized in the Paluh laboratory that are from population diverse sources that include self-defined African American and Hispanic Latino original tissue sources. The current exploratory research brings together expertise in population diverse analysis of pluripotent and neural human stem cell biology, neuronal microtubule cytoskeleton and electrophysiology, nanotechnology and materials engineering. This work is supported by a grant from the New York State Department of Health Spinal Cord Injury Review Board (NYSCIRB).

Disclosures: J.L. Paluh: None. **Z.T. Olmsted:** None. **A. Scimemi:** None. **Y. Xie:** None.

Poster

477. Spinal Cord Injury III

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 477.20/Y3

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS Grant R01NS076976
NIH Grant P40 0D010996

Title: Olfactory ensheathing cell transplantation combined with epidural stimulation and climb training enhances axonal connectivity across a severe spinal cord injury

Authors: *K. L. INGRAHAM, M. A. THORNTON, M. D. MEHTA, T. MORAD, P. AKKARA, A. TIERNO, A. YEUNG, E. A. DALE, H. ZHONG, V. R. EDGERTON, P. E. PHELPS
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Abstract: The transplantation of olfactory ensheathing cells (OECs) is a promising treatment for spinal cord injury (SCI) in part because of their beneficial effects on axonal outgrowth. This study asks if combining OEC transplantation with long-term epidural stimulation and climb

training, another effective treatment for SCI, would improve axonal outgrowth and connectivity with hindlimb motor circuits. Two weeks after a severe SCI at T8-T9, the injury sites of young adult female Fischer-344 rats (n=9) were transplanted with either OECs, or media within a fibrin matrix. Spinal rats received epidural stimulation while performing a climbing task 3 times/week for 5 months. A trans-synaptic retrograde tracer, Psuedorabies Virus (PRV), was injected into two hindlimb muscles before perfusion. Compared to media controls, we found that OEC-treated rats had more 5-HT-positive axons and a greater density of neurofilament (NF)-positive axons in the injury site and that many of these axons were associated with OECs. We also detected several PRV-labeled cells rostral to the injury site that often suggest some reconnectivity with hindlimb locomotor circuits. Axon myelination and the presence of myelinating cells within the injury site were also analyzed. Together, these findings show that long-term treatment with OECs, epidural stimulation, and climb training can improve axonal connectivity in a severe SCI model.

Disclosures: K.L. Ingraham: None. **M.A. Thornton:** None. **M.D. Mehta:** None. **T. Morad:** None. **P. Akkara:** None. **A. Tierno:** None. **A. Yeung:** None. **E.A. Dale:** None. **H. Zhong:** None. **V.R. Edgerton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroRecovery Technologies. **P.E. Phelps:** None.

Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

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Topic: C.11. Spinal Cord Injury and Plasticity

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the California Institute for Regenerative Medicine
the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation
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Title: Migration and differentiation of astroglia after transplantation of human neural stem cells into site of spinal cord injury

Authors: B. LIEN[1], M. TUSZYNSKI[2,3], *P. P. LU[2,4]
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Abstract: Neural stem cells (NSCs) can differentiate into both neurons and glia after transplantation into site of spinal cord injury (SCI). The neuronal component of stem cell grafts has the potential to form functional relays across sites of SCI. The glial component, on the other hand, may re-form a blood-brain barrier (BBB), support neuronal function and potentially contribute to remyelination. We performed a long-term, 18-month study focused on astrocyte maturation, migration and safety following implantation of human NSCs into a site of right-sided C5 hemisection in immunodeficient rats. 23 rats were enrolled in the study; 18 were grafted. Animals were sacrificed either 1 mo (N=3), 3 mo (N=3), 6 mo (N=5), 12 mo (N=3) or 18 mo (N=4) after grafting and were compared to lesion controls (N=5). Notably, NSCs that adopted a neuronal fate did not migrate from the lesion site (Lu et al, J Clin Invest 2017; 127:3287-3299). In contrast, grafted cells that adopted astrocyte fates exhibited long-distance migration from the implantation site, through host white matter, both rostral and caudal to the lesion. Cells migrated from the lesion slowly, at a mean rate of 2-3 mm per month. By 18 months, astrocytes migrated 9 spinal cord segments, caudally to the mid thoracic level, and rostrally into the brainstem. Human cells divided continuously as they migrated. The migrating human astrocytes joined the endogenous population of astrocytes in the host spinal cord and formed gliovascular units with human astrocytic processes interacting with host endothelial cells. No adverse consequences of this extended glial migration were detected.

Disclosures: B. Lien: None. **M. Tuszynski:** None. **P.P. Lu:** None.

Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 477.22/Y5

Topic: C.11. Spinal Cord Injury and Plasticity

Support: The Craig H. Neilsen Foundation # 476719

Title: Pioglitazone maintains mitochondrial respiration following spinal cord injury via interaction with mitoNEET

Authors: *S. P. PATEL[1], D. H. COX[2], W. M. BAILEY[2], H. C. WILLIAMS[2], J. C. GENSEL[3], P. G. SULLIVAN[4], A. G. RABCHEVSKY[3]
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Abstract: mitoNEET is a homodimer protein present within the outer membrane of mitochondria comprising a redox active [2fe-2S] cluster that has an essential role in regulating energy metabolism, iron homeostasis, and production of reactive oxygen species in mitochondria. mitoNEET is also a primary target of type II diabetes drug, pioglitazone (Pio), which we have recently shown to be neuroprotective after contusion spinal cord injury (SCI) and traumatic brain injury in mice. Accordingly, the current study was designed to test the novel hypothesis that Pio maintains mitochondrial respiration following SCI via its specific interaction with mitoNEET protein. Adult male C57BL/6 (n=80) or mitoNEET knockout (n=32) mice received either T9 laminectomy (sham; n=16) or contusion SCI (75 kdyn, IH Impactor; n=96), and 3 hr later they were treated i.p. with either Vehicle (1:1 DMSO + polyethylene glycol 400), Pio (1, 10, 20 or 40 mg/kg) or NL1, a specific mitoNEET ligand (10, 20 or 40 mg/kg), followed by boluses at 24 and 48 hr post-injury. At 49 hr post-injury, mitochondria were isolated from 5 mm of spinal cord centered on injury site and assessed for their respiration in terms of oxygen consumption rate (OCR) using Seahorse XF$^{(e)}$ 24 Extracellular Flux Analyzer. The OCR for naïve mitoNEET KO mice mitochondria was found to be ~25% lower than for naïve WT mitochondria, and SCI significantly reduced OCR in both WT and mitoNEET KO mice; the latter ~25% lower than WT. However, while treatments with Pio or NL1 in WT injured mice significantly maintained mitochondrial OCR to near normal levels in a dose-dependent manner, neither Pio nor NL1 were effective in preserving OCR in mitoNEET KO mice. These results indicate that the protection afforded by Pio is related to its interactions with the mitochondrial protein, mitoNEET, and not entirely dependent upon activation of Peroxisome Proliferator Activated Receptor (PPAR) as customarily reported. Ongoing experiments are extending the effective therapeutic time windows after SCI for both Pio and NL1 before assessing their long-term effects on functional neuroprotection.

Disclosures: S.P. Patel: None. **D.H. Cox:** None. **W.M. Bailey:** None. **H.C. Williams:** None. **J.C. Gensel:** None. **P.G. Sullivan:** None. **A.G. Rabchevsky:** None.

Poster

477. Spinal Cord Injury III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 477.23/Y6

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH R01 NS069765
U2FP
HKSCIF

Title: An innovative chondroitin sulfate proteoglycan reduction peptide (CRP) to repair chronic spinal cord injury

Authors: *C.-Y. LIN[1], K. LI[1], J. SILVER[2], A. SPARKS[1], Y.-S. LEE[1]
[1]Neurosci, Cleveland Clin., Cleveland, OH; [2]Dept Neurosci, Case Western Reserve Univ., Cleveland, OH

Abstract: No effective therapeutic strategy has been developed to treat chronic spinal cord injury (SCI), which is the major condition among most patients with SCI. Chondroitin sulfate proteoglycans (CSPGs) are the major inhibitory extracellular matrix components of the glial scar and perineuronal net (PNN) and they are significantly upregulated after SCI. Here we describe the development of approaches to globally modulate CSPGs using a novel CSPG Reduction Peptide (CRP) that eliminates CSPGs through lysosomal degradation as a potential therapeutic strategy to treat chronic SCI. An initial *in vitro* study, using axon growth inhibitory Neu7 astrocytes, showed the efficacy of CRP to remove CSPGs through the lysosomal degradation mechanism. We further tested in vivo, the effects of CRP and its combination with the Intracellular Sigma Peptide (ISP) that targets the CSPG receptor in repairing a chronic T8 contusive SCI in the adult rat. There were five experimental groups including sham, SCI + scrambled peptides, SCI+CRP, SCI+ISP, and SCI+CRP+ISP. The contused animals received peptide treatments beginning at 2 months post injury. All peptides were delivered systemically through daily subcutaneous injections in the back above the injury site for 3 months. The BBB open field test and kinematic analyses on a treadmill showed locomotor improvements in both CRP and CRP+ISP cohorts but not in the ISP alone or scrambled peptide groups when results were compared between the baseline scores (2 months post injury) and those at the end of the observation period (5 months after SCI). Bladder functional improvements (observed using metabolic cages as well as urodynamic analyses) were only present in the CRP and CRP+ISP groups. The improved bladder activities were inhibited by a 5HT-1A receptor antagonist indicating a contribution of the serotonergic system to recovery. Our anatomical studies revealed that CRP and CRP+ISP promoted substantial axonal regeneration through and beyond the lesion and/or sprouting of serotonergic and tyrosine hydroxylase fibers far distal to the lesion site. Interestingly, NG2+ cells in the lesion epicenter appeared to provide a substrate upon which regenerating axons crossed through the scar. In addition, the CRP and CRP+ISP treatments clearly reduced scar as well as PNN CSPGs, increased intensity of serotonergic fiber immunoreactivity, and increased intensity of synaptic markers at lumbo-sacral levels. Our data suggest that CRP and the combination of CRP+ISP can reduce both scar and PNN associated CSPGs to enhance both regeneration and sprouting to promote the restoration of locomotor and bladder function after chronic T8 contusive SCI in adult rats.

Disclosures: C. Lin: None. **K. Li:** None. **J. Silver:** None. **A. Sparks:** None. **Y. Lee:** None.

Poster

477. Spinal Cord Injury III

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Program #/Poster #: 477.24/Y7

Topic: C.11. Spinal Cord Injury and Plasticity

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NIH NS047101

Title: Functional improvement by human neural progenitor cells following severe spinal cord injury (SCI) is supported by tissue-type plasminogen activator

Authors: Y. SHIGA[1], A. SHIGA[1], P. MESCI[2], H. KWON[1], C. BRFAULT[3], J. KIM[4], E. MANTUANO[3], S. OHTORI[5], A. MUOTRI[2], S. L. GONIAS[3], *W. M. CAMPANA[1]
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Abstract: Spinal cord injury (SCI) is associated with severe motor and sensory impairments. Chronic pain develops in 70% of SCI patients. Recently neural stem cells (NSCs) grafted into injured spinal cords show great promise by extending large numbers of axons that are associated with motor improvement, albeit after one year (Lu et al., 2017). Effects of NSCs on pain outcomes remain unknown. Study goals were: 1) to optimize grafting conditions to better facilitate motor recovery; and 2) to relieve neuropathic pain behaviors associated with SCI. We optimized grafting conditions by using human induced pluripotent stem cells (iPSCs) derived neural progenitor cells (*h*NPCs) expressing high levels of nestin (Chailangkam et al., 2016). *h*NPCs also express LDL-receptor-related protein-1 (LRP1), that we have shown promotes cell survival. *h*NPCs were grafted using an optimized fibrinogen/thrombin matrix, and growth factor cocktail. We also studied the effects of adding enzymatically-inactive tissue plasminogen activator (EI-tPA). This derivative of an FDA-approved drug demonstrates anti-inflammatory activity (Mantuano et al., 2017) and functions as a neurogenesis factor via NMDAR/LRP1 cell-signaling. In cultured *h*NPCs, EI-tPA increased nestin, sox2 and a pre-neuronal marker CD24 mRNA, by 2-3 fold in 48 hrs. Adult immunodeficient rats received severe T3 spinal cord compression (T3SCI) or sham surgeries. One week following SCI, *h*NPCs expressing GFP, were grafted into the lesion site. BBB and forelimb neuropathic pain behaviors scores were evaluated weekly for four months. Significant functional motor recovery occurred after 6 weeks and continued to improve over 4 months in *h*NPCs treated with EI-tPA (***$P<0.005$). Accordingly, tibialis anterior muscle weights were greater in EI-tPA groups (*$p<0.05$). *h*NPCs differentiated into mostly neurons and integrated into host tissues. Graft-derived βIII-tubulin positive axons

emerged from grafts within 8 weeks and extended through T8 after 4 months. Density of graft-derived axons was greater in EI-tPA treated groups. Markers of motor neuron maturity, ChAT and MNX1, appeared by 8 weeks. T3SCI lesions induced the development of forelimb spontaneous lifting and tactile allodynia, as we described (Lee-Kubli et al., 2016) but remained unchanged by any treatment group. Notably, graft-derived neurons expressed, Lbx1, a marker of sensory relay neurons, suggesting some development of sensory fates. Thus, grafted *h*NPCs treated with EI-tPA in the injured spinal cord facilitate functional motor recovery without exacerbating or mitigating pain, supporting the feasibility and safety of this approach for clinical translation.

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Poster

477. Spinal Cord Injury III

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Program #/Poster #: 477.25/Y8

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NINDS-NIH 1R01NS092875
New York State Spinal Cord Injury Research Program

Title: Paired brain and spinal cord stimulation augments muscle responses through convergence of the corticospinal tract and large diameter afferents on spinal interneurons

Authors: *H. PARK, A. PAL, J. B. CARMEL
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Abstract: We have developed a neuromodulation paradigm that pairs stimulation of motor cortex and dorsal spinal cord to strengthen spared neural circuits after neurological injuries that cause damage to the corticospinal tract (CST). Sub-threshold spinal cord stimulation strongly augmented cortical motor evoked potentials (MEPs) when they arrive synchronously in the spinal cord. However, the circuit-level mechanism of the augmentation has not been determined. We hypothesized that the CST and large diameter afferents converge onto premotor spinal interneurons during paired stimulation. To test our hypothesis, we selectively inactivated each of these tracts with a chemogenetic method (Designer Receptor Exclusively Activated by Designer Drug, DREADD) during paired stimulation. For CST inactivation, we injected an AAV into the forelimb area of a motor cortex and another into the cervical spinal cord; doubly infected corticospinal neurons express inhibitory DREADD (Fig. 1A). For inactivation of large diameter afferents, we injected AAV5 into cervical dorsal root ganglia (Fig. 1B); the tropism of this virus

is for large-diameter neurons. When the CST was inactivated with the designer drug, clozapine N-oxide (CNO), the number of paw adjustment in pasta manipulation test was decreased and the MEPs augmentation was abolished in the targeted forelimb. Inactivation of large diameter afferents also abolished the MEPs augmentation in the targeted forelimb. In both cases, paired stimulation effects returned when CNO washed out (Fig. 1C). In addition, interneurons were activated after repeated paired stimulation in the deep dorsal horn and medial intermediate zone where the CST axon and large diameter afferents overlap. Thus, we demonstrate that the CST and large diameter afferents are necessary for the effects of paired stimulation, and the site of their convergence is likely interneurons in deep dorsal horn and medial intermediate zone. Understanding the systems-level mechanisms of paired stimulation could help to improve its targeting and efficacy for restoring function after injury.

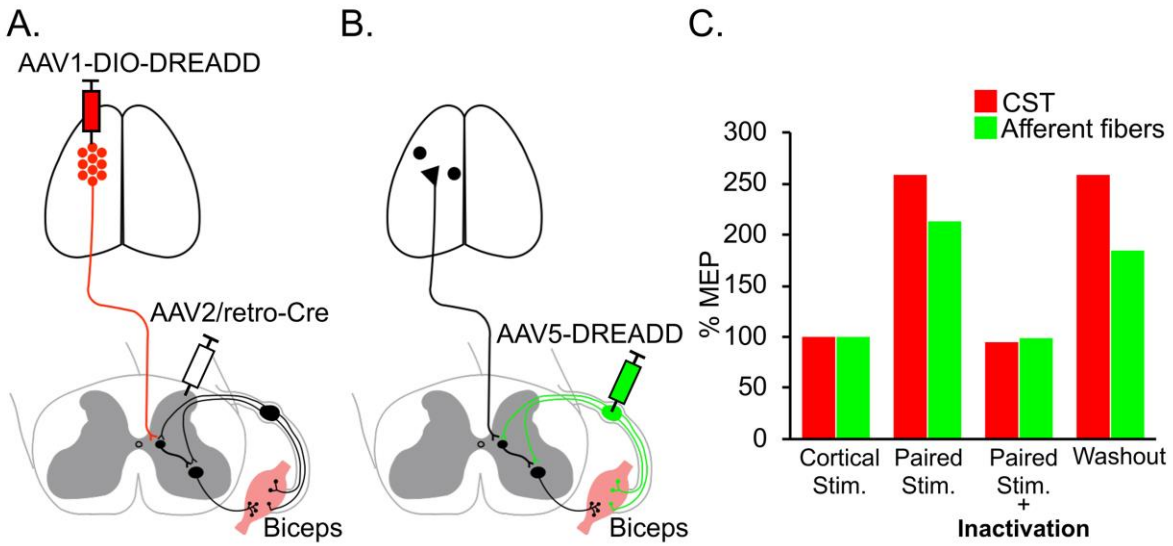

Figure 1. Selective inactivation of CST or large diameter afferents. A. Method for CST inactivation. AAV1-hSyn-DIO-hM4D(Gi)-mCherry was injected into the forelimb area of a motor cortex and AAV2/retro-hSyn-EBFP-Cre was injected into the cervical spinal cord at C5, C6 contralaterally. B. Method for large diameter afferent inactivation. AAV5-hSyn-hM4D(Gi)-mCherry was injected into C5, C6 and C7 dorsal root ganglia. C. % MEP augmentation before, during, and after inactivation.

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Poster

477. Spinal Cord Injury III

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH-NINDS NS084030

Craig H. Neilsen Foundation #381357
Dr. Miriam and Sheldon G. Adelson Medical Foundation
Wings for Life

Title: Injectable polypeptide hydrogels and Ribotag neural stem cells as tools to study cell grafting survival and differentiation outcomes in spinal cord injury

Authors: *T. M. O'SHEA[1], A. L. WOLLENBERG[2], J. H. KIM[1], Y. AO[1], A. CZECHANSKI[3], L. G. REINHOLDT[3], T. J. DEMING[2], M. V. SOFRONIEW[1]
[1]Neurobio., [2]Bioengineering, Chem. and Biochem., UCLA, Los Angeles, CA; [3]The Jackson Lab., Bar Harbor, ME

Abstract: Repopulating non-neural lesion cores of traumatic spinal cord injuries (SCI) with neural tissue via grafting of neural stem/progenitor cells (NSPC) can aid axon regeneration and reorganization of damaged neural circuits. However, NSPC graft necrosis, cell migration away from lesions as well as spontaneous and uncontrollable graft cell differentiation remain key challenges limiting the translational potential of NSPC transplantation. To address these challenges we developed two tools to facilitate rigorous cell and molecular biological evaluation of NSPC grafting in murine SCI studies. Firstly, an injectable polypeptide hydrogel based on non-ionic methionine-sulfoxide was synthesized to act as a cell carrier to protect transplanted cells during injection and initial exposure to the hostile SCI lesion microenvironment. The hydrogel was combined with a neural stem cell line that was derived via neural induction of mouse embryonic stem cells that contain a Ribotag allele to facilitate cell specific genetic evaluation of grafted cells from whole tissue *in vivo* as well as identification of NSPC and their progeny by immunohistochemistry. NSPC suspended in hydrogels showed cell viability comparable to standard culture conditions. Owing to its non-fouling sulfoxide functionality, the hydrogel showed superior preservation of NSPC stemness and multipotency in serum rich environments *in vitro* compared to various cell adhesive materials. NSPC in hydrogels injected into both uninjured forebrain and crush SCI showed enhanced survival compared to cells in media and remained local to the injection site or lesion compartment. Without the inclusion of specific molecular cues to drive differentiation, NSPC displayed an immature astroglial phenotype *in vivo*. In acute and chronic crush SCI, these immature astroglial cells integrated into preserved neural tissue immediately adjacent to the lesion compartment and acted as cellular substrates that supported regrowth of propriospinal axons. Inclusion of various differentiation directing small molecule morphogens into hydrogels altered the phenotypic distribution of grafted cells *in vitro* and *in vivo*. These findings suggest that the polypeptide hydrogel and Ribotag NSPC are powerful tools for the study of NSPC transplantation in CNS injury.

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Poster

477. Spinal Cord Injury III

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Program #/Poster #: 477.27/Y10

Topic: C.11. Spinal Cord Injury and Plasticity

Support: FAPESP 2015/26206-0
FAPESP 2014/06892-3
CNPq 300552/2013–9

Title: Restauration of sensory-motor integration after dorsal rhizotomy and repair with platelet-rich plasma (PRP) associated with transgenic human embryonic stem cells (hESC) overexpressing FGF-2

Authors: *M. V. DE CASTRO[1], S. KYRYLENKO[2], M. SANTANA[1], Â. LUZO[1], A. OLIVEIRA[1]
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Abstract: Motor coordination involves specific neural processes including sensory input, perceptual and cognitive processing. It is dependent on delicate sensory-motor integration, which is particularly evident in the spinal cord. In this sense, primary afferent inputs enter the spinal cord through dorsal roots, projecting directly or indirectly to the motoneurons present in the ventral horn. Dorsal roots can be affected by a wide range of lesions, leading to a significant loss of sensorial information, greatly affecting motor behavior. Due to the possibility of generating inflammation and neuropathic pain, surgical procedures do not prioritize the repair of the afferent component. In this context, new therapies need to be developed for dorsal root repair. A promising treatment is the use of platelet-rich plasma (PRP), an adhesive and inductive element for nerve regeneration. Therefore, the present study evaluated the motor and sensory improvement following dorsal root repair with PRP associated with modified human embryonic stem cells. Thus, female adult Lewis rats (LEW/HsdUnib; n=5 per group) were subjected to unilateral rhizotomy (RZ) of the L4-L6 dorsal roots and divided into the following groups: (1) Unlesioned/Control; (2) RZ without repair; (3) RZ followed by root repair with PRP (RZ+PRP); (4) RZ followed by root repair with PRP associated with modified human embryonic stem cells (RZ+PRP+hESC). PRP was obtained from human blood subjected to centrifugation steps. It was characterized regarding platelet concentration, integrity, and viability. For cell therapy, hESCs were bioengineered to overexpress a human fibroblast growth factor 2 (FGF-2). The reflex arc recovery was evaluated daily through the electronic von-Frey method, during eight weeks, while changes in the glial response (GFAP and Iba1) and excitatory synaptic circuits (VGLUT1) were evaluated by immunofluorescence, eight weeks after lesion. The results indicate that PRP is

efficient to repair dorsal rhizotomy, allowing the reentrance of VGLUT1 positive primary afferents within the spinal cord. PRP application did not exacerbate astroglial (GFAP) and microglial (Iba1) reactivity, restoring the reflex of paw withdrawal over time. No signs of allodynia were observed. Cell therapy further enhanced such rewiring process. In conclusion, the repair with PRP and hESC is efficient and may be considered an approach to improve sensory-motor recovery following dorsal rhizotomy, fulfilling a critical gap in reparative procedures after this type of injury.

Disclosures: M.V. De Castro: None. **S. Kyrylenko:** None. **M. Santana:** None. **Â. Luzo:** None. **A. Oliveira:** None.

Poster

477. Spinal Cord Injury III

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Program #/Poster #: 477.28/Y11

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Swiss National Science Foundation 323530-164220
ALARME Foundation
International foundation for Research in Paraplegia
Dr. Miriam and Sheldon G. Adelson Medical Foundation
Wings for Life

Title: Activity signaling to induce axon sprouting and regrowth after complete spinal cord injury

Authors: *S. L. BARLATEY[1], M. A. ANDERSON[1], J. COTTET[1], L. ASBOTH[1], L. D. P. BAUD[1], J. BLOCH[2], M. V. SOFRONIEW[3], G. COURTINE[1,2]
[1]Ecole Polytechnique Federale De Lausanne, Geneve, Switzerland; [2]Neurosurg., Univ. Hosp. Lausanne CHUV, Lausanne, Switzerland; [3]UCLA Schl Med., Los Angeles, CA

Abstract: Neuro-prosthetic rehabilitation promotes the recovery of voluntary leg movements through the reorganization of residual reticulospinal projection pathways. However, restoring supraspinal control of movement after an anatomically complete SCI will require robust regrowth and sprouting of severed axons across the injury. Here, we studied various strategies to enhance sprouting and activate growth programs of reticulospinal neurons. Our ultimate goal is to restore anatomical connectivity across a complete SCI, and to promote the functional integration of these new axons through targeted neuroprosthetic rehabilitation programs. To promote regrowth and sprouting of severed reticulospinal axons across an anatomically complete SCI in mice, we are manipulating various factors including the lesion environment with hydrogels and growth factors, the establishment of chemical axon guidance, the activation of intrinsic growth programs in neurons, and activity-dependent pathways. These interventions are

delivered with a spatiotemporal profile that is consistent with the growth of axons during development. While we obtained regrowth of severed reticulospinal axons within a complete SCI, the axons did not grow across the lesion, indicating the importance of identifying complementary strategies to attract the axons caudal to the injury in the future.

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Poster

477. Spinal Cord Injury III

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Program #/Poster #: 477.29/Y12

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Errett Fisher Foundation

Title: Early activation and recruitment of endogenous stem cells for the treatment of spinal cord injury

Authors: *Z. ZABARSKY, T. D. LUO, X. MA, T. L. SMITH
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Abstract: Spinal cord injury (SCI) is a devastating neurologic event with complex pathophysiological mechanisms that currently has no effective therapies available. The spinal cord has endogenous neural stem/progenitor cells (NSPCs) and after injury, neuroinflammation prevents NSPC-mediated neuroprotection and repair. The majority of regenerative medicine strategies for SCI overlook native NSPCs and transplant exogenous cells into the injured spinal cord during the later stages of injury, when inflammatory-associated tissue loss has developed, with limited success. This research aims to use a philosophically different approach by employing a multimodal combinatory treatment of regenerative pharmacologics that not only support the endogenous stem cells directly, but to also provide a sustainable microenvironment for growth and repair through immunomodulation of the surrounding tissue.
Using adult female Sprague-Dawley rats, a moderate-to-severe contusion-based SCI was employed following laminectomy by an Infinite Horizons Spinal Cord Injury Impactor at the T9 level. After injury, animals were treated with 1) Pioglitazone, 2) Granulocyte Colony Stimulating Factor, 3) Both drugs in combination, or 4) Vehicle (DMSO) control. Animals were transcardially perfused with PBS followed by 4% paraformaldehyde to prepare spinal cord tissue for histological and immunohistochemical analysis. Functional recovery was assessed by the Basso, Beattie, Bresnahan (BBB) locomotor rating scale on 1, 3, 7, 14, 21, and 28 days post injury (DPI) by two blinded observers. Repeated measures ANOVA was performed to trend the change in BBB scores over time (n=8/group). Animals treated with both drugs had significantly

higher BBB scores at 1 ($p<0.001$), 3 ($p<0.001$), 7 ($p<0.05$), and 14 ($p<0.05$) DPI compared to vehicle treated controls.
Histological analysis and functional recovery assessments may reveal how effective the treatments can increase NSPC numbers, decrease overall tissue damage, and prevent motor function loss. Findings may provide a better understanding of how key cellular functions can influence the microenvironment and viability of NSPCs to repair the injured spinal cord and potentially support the advancement of acute critical care interventions for SCI patients.

Disclosures: Z. Zabarsky: None. **T.D. Luo:** None. **X. Ma:** None. **T.L. Smith:** None.

Poster

477. Spinal Cord Injury III

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: DOD grant W81XWH-13-1-0277/SC120066
PVA grant 3004
Craig H. Neilsen Foundation
Wings for Life Foundation

Title: Spinal cord injury perturbs circadian rhythms

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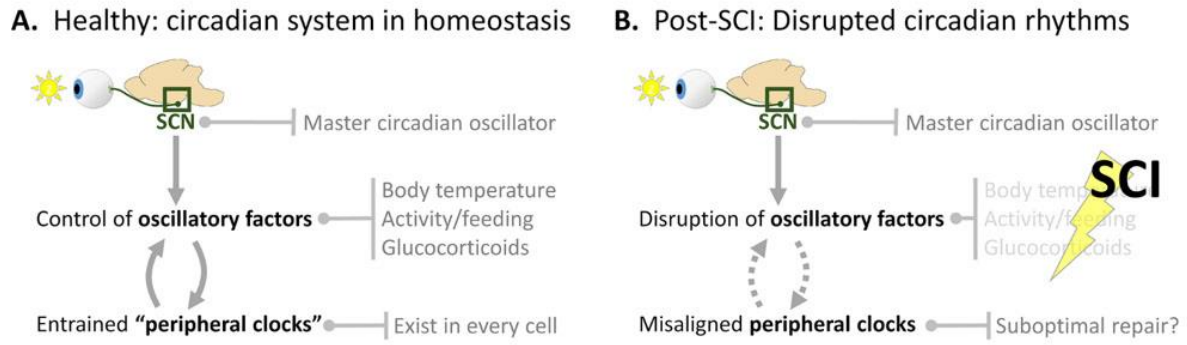
Abstract: Spinal cord injury (SCI) can disrupt many physiological functions. The circadian system helps maintain homeostasis throughout the body by regulating daily rhythms in physiology and behavior. Circadian rhythms likely exist in all cell throughout the body, yet whether SCI alters daily rhythms remains under-studied. Here, we hypothesized that SCI in rats would disrupt several prominent circadian outputs including glucocorticoids, core temperature, activity, and circadian gene expression. Female and male rats were subjected to clinically relevant thoracic (T-) 8 moderate-to-severe contusion SCI (or laminectomy sham surgery). Circadian measures - including rhythms of plasma corticosterone, body temperature and activity (using small implanted transmitters), plasma glucose, and gene expression - were studied prior to and after surgery. First, we found that SCI disrupted intraspinal and peripheral rhythms of clock and inflammatory gene expression. Circadian rhythms in peripheral cells are entrained by key “oscillatory factors”, including glucocorticoids, body temperature, and activity. SCI caused overall increases and disrupted rhythms of the major rodent glucocorticoid, corticosterone. Pre-

surgery and sham rats displayed expected rhythms in activity and body temperature, whereas rats with SCI had blunted daily rhythms in activity and body temperature. In parallel, SCI increased plasma glucose levels and liver expression of glucose metabolism genes. Our data show that moderate SCI in rats causes wide-ranging circadian dysfunction that is severe at acute time points and gradually recovers over time. Normalizing post-SCI circadian rhythms could enhance recovery of homeostasis and quality-of-life.



Disclosures: A.D. Gaudet: None. **L.K. Fonken:** None. **M.T. Ayala:** None. **E.M. Bateman:** None. **W.E. Schleicher:** None. **E.J. Smith:** None. **H.M. D'Angelo:** None. **S.F. Maier:** None. **L.R. Watkins:** None.

Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 478.01/Y14

Topic: D.03. Somatosensation: Pain

Support: National Natural Science Foundation of China Grant 31371122
National Natural Science Foundation of China Grant 31771158
Chinese Academy of Sciences Hundreds of Talents Program
Youth Thousand Plan
the Strategic Priority Research Program of the Chinese Academy of Sciences Grant XDB02010000

Title: Hyperalgesia mediated by mu-opioid receptors in spinal GABAergic neurons

Authors: *X. ZHANG, Y. SUN
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Abstract: Mu-opioid receptors (MORs), which is critical for analgesic effect of morphine, are highly expressed at the spinal level. MORs expressed in spinal excitatory neurons and projection

neurons play important roles in mediating analgesic effect of morphine. However, the functional role of MOR in spinal GABAergic neurons in nociception remains unknown. We investigated the role of MORs expressed in spinal GABAergic neurons in nociception using a new genetic approach, which enables selective expression of MORs in distinct neuronal populations. We found that selective activation of MORs expressed in spinal GABAergic neurons induced hyperalgesia, and evoked spontaneous nocifensive behavior. Consistently, blockade of endogenous activation of MORs expressed in spinal GABAergic neurons attenuated formalin-induced nocifensive behavior, which is likely mediated by suppression of spinal GABAergic synapses as shown in electrophysiological experiments. These results demonstrated that MOR-mediated disinhibition at the spinal level plays an important role in the development of hyperalgesia in inflammatory pain.

Disclosures: X. Zhang: None. **Y. Sun:** None.

Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 478.02/Y15

Topic: D.03. Somatosensation: Pain

Support: LABEX ANR-10-LABX-0034_Medalis
the Research Foundation Flanders (FWO Vlaanderen)
the Strategic Research Program – Growth Funding of the VUB and the Austrian Science Fund (FWF: I 2463-B21)

Title: A bifunctional biased mu opioid agonist - neuropeptide FF receptor antagonist as analgesic with improved acute and chronic side effects

Authors: *F. SIMONIN[1,2], A. DRIEU LA ROCHELLE[1,2], K. GUILLEMYN[3], M. DUMITRASCUTA[4], C. MARTIN[3], V. UTARD[1,2], R. QUILLET[1,2], S. SCHNEIDER[1,2], F. DAUBEUF[1,2], T. WILLEMSE[5], P. MAMPUYS[5], B. U. W. MAES[5], N. FROSSARD[1,6,2], F. BIHEL[1,2], M. SPETEA[4], S. BALLET[3]
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Abstract: Opioid analgesics, such as morphine and fentanyl, continue to be the cornerstones for treating moderate to severe pain. However, upon chronic administration, their efficiency is limited because of prominent side effects such as tolerance and dependence. One hypothesis for the occurrence of these side effects is that the chronic stimulation of the opioid system may trigger its endogenous counterparts, anti-opioid systems, producing hyperalgesia (opioid-induced

hyperalgesia, OIH) and analgesic tolerance. Previous data from our lab and others have shown that RF9, an antagonist of neuropeptide FF receptors (NPFF1R and NPFF2R), efficiently blocks opioid-induced hyperalgesia and tolerance when co-administered with fentanyl or morphine in rodents. In this study, we designed multi-target molecules that display mu-opioid receptor (MOR) agonist activity, as well as NPFF receptor antagonist properties. To this purpose, a set of unnatural peptide ligands was generated, which combines an already known high affinity mu-opioid receptor agonist together with the carboxyl-terminal RF-amide signature of NPFF. In vitro characterization of these compounds led to identification of KGFF03 and KGFF09 as G protein-biased MOPr agonists with full agonist or antagonist activity at NPFFRs, respectively. In agreement with their biased MOPr agonism, KGFF03/09 showed reduced respiratory depression in mice, as compared to the unbiased parent opioid agonist KGOP01. Chronic subcutaneous administration of KGOP01 and KGFF03 in mice rapidly induced hyperalgesia and analgesic tolerance, effects that were not observed upon chronic treatment with KGFF09. This favorable profile was further confirmed in a model of persistent inflammatory pain. In addition, we showed that KGFF09 induced less physical dependence compared to KGOP01 and KGFF03. Altogether, our data establish that combining, within a single molecule, the G protein-biased MOPr agonism and NPFFR antagonism, have beneficial effects on both acute and chronic side effects of conventional opioid analgesics. This strategy can lead to the development of novel and potent antinociceptive drugs with limited side effects upon acute and chronic administration.

Disclosures: F. Simonin: None. **A. Drieu La Rochelle:** None. **K. Guillemyn:** None. **M. Dumitrascuta:** None. **C. Martin:** None. **V. Utard:** None. **R. Quillet:** None. **S. Schneider:** None. **F. Daubeuf:** None. **T. Willemse:** None. **P. Mampuys:** None. **B.U.W. Maes:** None. **N. Frossard:** None. **F. Bihel:** None. **M. Spetea:** None. **S. Ballet:** None.

Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 478.03/Y16

Topic: D.03. Somatosensation: Pain

Support: Science Foundation Ireland and Alkermes Inc (14/SPP/B3051)

Title: Hyporesponsivity to morphine in the Wistar-Kyoto rat model of hyperalgesia associated with negative affective state

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Abstract: Background and aim: The role of the endogenous opioid system in pain-negative affect interactions and the influence of genetic background is poorly understood. Wistar-Kyoto (WKY) rats, a genetic model of negative affect that also exhibit hyperalgesia, show hyporesponsivity to systemically administered mu-opioid receptor (MOP) agonists. The ventrolateral periaqueductal grey (vlPAG) plays a key role in MOP-mediated antinociception. We compared the effects of systemic and intra-vlPAG administration of morphine (MOP agonist) on nociceptive responding to noxious thermal and inflammatory stimuli in WKY *versus* Sprague-Dawley (SD) rats and associated alterations in c-Fos expression in the nucleus raphe magnus (NRM) of the rostral ventromedial medulla (RVM) downstream of the vlPAG. Methods: Male WKY and SD rats (n=8-11/group) were allocated to groups across three experiments using within-subject design to investigate the effects of morphine (0.5-7.5 mg/kg, s.c.) in hot plate (HP) and formalin tests. In a subsequent study, the effects of intra-vlPAG administration of vehicle or morphine (1, 2.5, or 5 µg) on formalin-evoked nociceptive behaviour was investigated in male WKY and SD rats (n=6-7/group). Immunohistochemical staining of c-Fos in perfused brain sections was carried out. MOP expression in the vlPAG of the two strains was assessed using western immunoblotting. Data were analysed using repeated measures or two-way ANOVA followed by Student-Newman-Keuls *post hoc* test ($p<0.05$ significant). Results: In the HP test, the minimal effective dose of systemically administered morphine was 2 and 0.5 mg/kg in WKY and SD rats, respectively. Morphine significantly reduced formalin-evoked nociceptive behaviour in SD, but not in WKY, rats; the antinociceptive effects of morphine were attenuated by cyprodime (MOP antagonist). Plasma morphine levels did not differ between the two strains. Intra-vlPAG administration of morphine 1 µg reduced formalin-evoked nociceptive behaviour in SD, but not in WKY, rats; morphine 2.5 and 5 µg was antinociceptive in both strains. Intra-vlPAG administration of morphine dose-dependently increased c-Fos expression in the NRM of both strains, being more pronounced in SD than WKY rats. MOP expression in the vlPAG did not differ between strains. Conclusions: These data provide further evidence that WKY rats exhibit hyporesponsivity to the antinociceptive effects of MOP agonism. The results identify the vlPAG as a key locus for this hyporesponsivity in WKY versus SD rats and suggest that opioid-induced engagement of descending pain circuitry downstream of the PAG (within the NRM) is reduced in WKY rats versus SD counterparts.

Disclosures: M.I. Ferdousi: 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. **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. **S. Aggarwal:** 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. **K. Smith:** 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.P. 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. **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.

Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 478.04/Y17

Topic: D.03. Somatosensation: Pain

Support: NIH R01-DA015353

Title: Effects of intrathecal PZM-21, a biased mu receptor ligand in rats

Authors: *S. KOKUBU[1,2], K. EDDINGER[1], P. GMEINER[3], T. L. YAKSH[1]
[1]Univ. California San Diego, LA Jolla, CA; [2]Dokkyo Med. Univ., Tochigi, Japan; [3]Emil Fischer Ctr., Erlangen, Germany

Abstract: PZM-21 is a mu receptor preferring ligand that signals though Gi protein with minimal activation of ß arrestin, e.g. a biased ligand. Methods: Using male adult Sprague Dawley rats prepared with chronic lumbar intrathecal (IT) catheters, we focused on: i) effects of IT PZM21 on thermal escape, formalin evoked flinching; ii) effects of naloxone (a pan MOR antagonists) and naltrendole (a delta receptor preferring antagonist) on IT PZM-21 effects; iii) adverse motor effects; iv) effects of repeated bolus delivery on tolerance and cross tolerance with IT morphine and v) effects of continuous IT PZM21 infusion on thermal escape. Results. i) IT bolus morphine and PZM-21 resulted in a dose dependent increase in acute thermal escape latencies, with a 3-4 hr duration of action. Additionaly IT PZM-21 resulted in a robust dose

dependent suppression of Phase 1 and phase 2 formalin evoked flinching. ii) Effects were blocked by IP naloxone but not by naltrindole. iii) IT morphine resulted in a naloxone resistant Straub tail. In contrast to IT morphine, motor dysfunction was observed with PZM21 only at the highest supra-analgesics dose. iv) Following 4 daily IT bolus injections to assess tolerance and cross tolerance, morphine but not PZM21 treated animals showed a loss of analgesia as compared as compared to saline treated animals. Animals tolerant to IT morphine showed a normal response to IT PZM-21. Animals treated with 4 days of IT PZM-21 showed no loss of response to IT morphine. v) IT infusion of PZM-21 or morphine resulted in a significant increase in thermal escape with recovery to baseline, e.g. tolerance by day 7-10. Significance: These results show that PZM-21 is analgesic as a mu opioid agonist. In many ways it resembles morphine though time course of tolerance may be slightly different and there is a suggestions of an asymmetric cross tolerance after bolus delivery. However, continuous IT infusion of PZM21 at equi-analgesic doses to morphine resulted in a comparable loss of effect over time. (NIH NIDA 5 R01 DA015353; TY; NIMH Screening Program, Bryan Roth)

Disclosures: S. Kokubu: None. **K. Eddinger:** None. **P. Gmeiner:** None. **T.L. Yaksh:** None.

Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 478.05/Y18

Topic: D.03. Somatosensation: Pain

Support: National Institutes of Health (DA041711)
the N.G. and Helen T. Hawkins Endowment

Title: Mitogen-activated protein kinase signaling mediates opioid-induced presynaptic NMDA receptor activation, hyperalgesia and tolerance

Authors: *M. DENG, S.-R. CHEN, H. CHEN, Y. LUO, Y. DONG, H.-L. PAN
The Univ. of Texas MD Anderson Cancer Ctr., Houston, TX

Abstract: Opioid-induced hyperalgesia and analgesic tolerance can lead to dose escalation and inadequate pain treatment with μ-opioid receptor agonists. Opioids cause tonic activation of glutamate NMDA receptors (NMDARs) at primary afferent terminals, increasing nociceptive input. However, the signaling mechanisms responsible for opioid-induced activation of presynaptic NMDARs in the spinal dorsal horn remain unclear. In the present study, we determined the role of mitogen-activated protein kinase (MAPK) signaling in opioid-induced presynaptic NMDAR activation caused by chronic morphine administration. Whole-cell recordings of excitatory postsynaptic currents (EPSCs) were performed on dorsal horn neurons in rat spinal cord slices. Chronic morphine administration markedly increased the frequency of

miniature EPSCs, increased the amplitude of monosynaptic EPSCs evoked from the dorsal root, and reduced the paired-pulse ratio of evoked EPSCs. These changes were fully reversed by an NMDAR antagonist and normalized by inhibiting extracellular signal-regulated kinase 1/2 (ERK1/2), p38, or c-Jun N-terminal kinase (JNK). Furthermore, intrathecal injection of a selective ERK1/2, p38, or JNK inhibitor blocked pain hypersensitivity induced by chronic morphine treatment. These inhibitors also similarly attenuated a reduction in morphine's analgesic effect in rats. In addition, co-immunoprecipitation assays revealed that NMDARs formed a protein complex with ERK1/2, p38, and JNK in the spinal cord and that chronic morphine treatment increased physical interactions of NMDARs with these three MAPKs. Our findings suggest that opioid-induced hyperalgesia and analgesic tolerance are mediated by tonic activation of presynaptic NMDARs via three functionally redundant MAPKs at the spinal cord level.

Disclosures: M. Deng: None. **S. Chen:** None. **H. Chen:** None. **Y. Luo:** None. **Y. Dong:** None. **H. Pan:** None.

Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 478.06/Z1

Topic: D.03. Somatosensation: Pain

Support: CIHR MOP-123399
NSERC RGPIN-2015-05213

Title: Cdk5-mediated phosphorylation of the delta opioid receptor: A key process for the regulation of cell surface receptors

Authors: *F. BERGERON, S. BERTHIAUME, B. QUIRION, E. ST-LOUIS, V. BLAIS, J.-L. PARENT, C. LAVOIE, L. GENDRON
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Abstract: Under basal condition, the delta opioid receptor (DOP) is mainly located in intracellular compartments and is therefore hardly accessible to ligands. Interestingly, others and we have shown that the level of DOP at the cell surface can be increased. In particular, stimulation of DOP with an agonist, inflammatory pain, as well as prolonged treatment with morphine all increased the cell surface availability of DOP. The molecular mechanisms regulating the trafficking/targeting of DOP to the plasma membrane remain however poorly understood. We have previously shown that the cyclin-dependent kinase 5 (Cdk5) participates in the regulation of DOP-mediated analgesia. Here, we hypothesized that the retention of DOP in the endoplasmic reticulum (ER) can be decreased, and hence the level of DOP at the cell surface

increased, by targeting the interaction between p35, Cdk5 and DOP. When coexpressed in HEK293T cells, we found that both p35 and Cdk5 interact (co-immunoprecipitate) together in the presence or absence of DOP. Interestingly, both proteins were also found to individually interact with the receptor, but only when the other counterpart was absent. Indeed, the interaction with the receptor was lost when p35 and Cdk5 were expressed together. Once activated by its neuronal-specific activator p35, Cdk5 is thought to phosphorylate the T161 of a consensus sequence [(S/T)PX(K/H/R)] located within the second intracellular loop of DOP (ICL2). This threonine residue is important in the trafficking of DOP because when mutated to an alanine (T161A), a significant decrease in its surface expression was observed. Interestingly, the phosphorylation motif of Cdk5 (T161-K164) overlaps with the binding site of COPI (K164-K166), a coatomer complex involved in the retrograde transport of DOP from the Golgi to the ER. We believe that once the consensus sequence is phosphorylated by Cdk5, the association of COPI to DOP is compromised, allowing DOP to escape the Golgi and reach the plasma membrane. Supporting this idea, an increase of DOP at the cell surface was observed when the receptor is coexpressed along with the mu opioid receptor (MOP). This effect was however abolished when MOP was coexpressed with the T161A DOP mutant, further supporting that the Cdk5-mediated phosphorylation of T161 plays a key role in the morphine-induced trafficking of DOP. A better understanding of the mechanisms underlying this process may lead to the identification of a new pharmacological strategy to increase the levels of DOP at the cell surface, and hence the DOP-mediated analgesia for the treatment of pain.

Disclosures: S. Berthiaume: None. **B. Quirion:** None. **E. St-Louis:** None. **V. Blais:** None. **J. Parent:** None. **C. Lavoie:** None. **L. Gendron:** None.

Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 478.07/Z2

Topic: D.03. Somatosensation: Pain

Title: Morphine promotes breast cancer cell proliferation via mechanism independent of m-opioid receptor: An *in vitro* study

Authors: *R. RAMACHANDRAN[1], Y. ZHU[1], Y. HE[1], P. W. MANTYH[2], T. L. YAKSH[1]
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Abstract: Abstract:
Background: Systemic morphine results in significant pain relief in patients that are in advanced stage of cancer. However, extra analgesic effects of morphine in facilitating tumor development is a recent concern. Several pre-clinical studies have showed that morphine can enhance tumor angiogenesis and promote cancer growth reducing long time survival with few contradictory

studies. The present study therefore dissects the effects of morphine on cell proliferation using a rat mammary adenocarcinoma cell line (MTLn3).
Materials and Methods: MTLn3 cells were cultured in MEM-alpha growth media supplemented with 5% heat-inactivated fetal bovine serum and 0.5 % pen-strep. Cells were Incubated at 37°C in a humidified 5% CO_2 environment and grown to 70-90% confluence. To assess proliferation MTLn3 cells were seeded (1 x 10^4 cells/well) in a 12 well plate and incubated for 24 hrs, followed by 48 hrs incubation with test material. The cells were incubated with Morphine (3 nM - 30 μM), fentanyl (0.03 pM - 0.3 μM) , Naloxone (3 nM - 30 μM) and PZM 21 (3 nM - 30 μM) and cell proliferation assay was performed after 48 hrs by counting total number of cells using a hemocytometer by the observer blinded to the treatment.
Results: Morphine enhanced the proliferation of MTLn3 cells following 48 hrs incubation. A peak effect was observed with 0.03 μM morphine. This effect was not reversed by naloxone or naltrexone. Further, fentanyl did not promote cell proliferation. Moreover, PZM-21 a potent μ-opioid receptor agonist did not have any effect on proliferation.
Conclusion: These results show that morphine enhanced proliferation of breast cancer cells and that the tumor enhancing effects of morphine may independent of μ-opioid receptor. MAS related g-protein coupled receptor (MRGPR) may be of particular interest.

Disclosures: R. Ramachandran: None. **Y. Zhu:** None. **Y. He:** None. **P.W. Mantyh:** None. **T.L. Yaksh:** None.

Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 478.08/Z3

Topic: D.03. Somatosensation: Pain

Title: *Ex vivo* receptor occupancy at mu and kappa opioid receptors in rat brain

Authors: *S. C. CHEETHAM, A. NEEDHAM, L. JAGGER
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Abstract: The opioid system has been implicated in a number of behavioural and physiological responses including control of pain and mood. Opioids exert their pharmacological actions via mu (μ)-, kappa (κ)- and delta (δ)- opioid peptide receptors. This study investigated the *ex vivo* receptor occupancy of the μ-opioid receptor agonists, morphine and buprenorphine, and the κ-opioid receptor agonist, (-)-pentazocine, in various brain regions following peripheral administration in the rat. Male Sprague-Dawley rats (300±50 g) were administered vehicle, morphine [3, 10 or 30], buprenorphine [0.1, 0.3 or 1] or (-)-pentazocine [5, 10 or 20] and terminated 60 (morphine, buprenorphine) or 30 mins later ((-)-pentazocine). Doses in square brackets are [mg/kg ip]. Brains were removed. Coronal sections (20 μm) containing regions of

interest (cortex, striatum, hippocampus and periaqueductal grey (PAG)) were cut and incubated in buffer containing either [^{3}H]DAMGO (2 or 5 nM) or [^{3}H]U-69,593 (2.5 nM) for 10 or 90 mins, respectively. Non-specific binding was determined by 50 μM (-)Naloxone or 10 μM U-69,593 for [^{3}H]DAMGO or [^{3}H]U-69,593 autoradiography, respectively. Binding was terminated by aspiration and sections washed in buffer (3 x 5 mins). Radioactivity bound to the section was determined using a Beta-Imager. Results are expressed as % occupancy (determined from mean specific binding using 100 % for the vehicle group), n = 3-5 rats/group. Significant differences from control are denoted by $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$. Morphine [10 and 30] significantly occupied μ-opioid receptors labelled by [^{3}H]DAMGO in the cortex (49** and 61 %***), striatum (52** and 74 %***), hippocampus (48* and 56 %**) and PAG (33%*, top dose only). Buprenorphine [0.3 and 1] significantly occupied μ-opioid receptors in the cortex (92*** and 93 %***), striatum (87*** and 89 %***) and hippocampus (88 %***, both doses). The lowest dose of buprenorphine tested also significantly occupied μ-opioid receptors in the cortex (49 %*). (-)-Pentazocine [5, 10 and 20] significantly occupied κ-opioid receptors labelled by [^{3}H]U-69,593 in the striatum (54*, 44* and 55 %**). Morphine and buprenorphine significantly occupied central μ-opioid receptors in a dose-dependent manner. (-)-Pentazocine significantly occupied central κ-opioid receptors at the doses tested. This technique can be used to determine CNS penetration and receptor occupancy of novel drugs at μ- and κ-opioid receptors in rodent brain.

Disclosures: S.C. Cheetham: 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.; RenaSci is an organization providing 'fee for service' experimental services. **A. Needham:** 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.; RenaSci is an organization providing 'fee for service' experimental services. **L. Jagger:** 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.; RenaSci is an organization providing 'fee for service' experimental services.

Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 478.09/Z4

Topic: D.03. Somatosensation: Pain

Support: Nektar Theraputics

Title: NKTR-181: Relationship between mu-opioid receptor binding kinetics and *in vivo* pharmacodynamics

Authors: *L. VANDERVEEN, T. MIYAZAKI, S. K. DOBERSTEIN, J. ZALEVSKY
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Abstract: NKTR-181 is a novel mu-opioid receptor agonist with a slow onset of neuropharmacological effects in preclinical and human studies that is attributable, in part, to its slow rate of entry into the CNS. It is likely that mechanisms at the molecular level also contribute to NKTR-181's pharmacodynamic profile. In competitive receptor radioligand binding assays, NKTR-181 was found to have moderate binding affinity (K_d = 240 nM) to mu-opioid receptor (MOR) that was approximately 10-fold lower relative to oxycodone. *In vitro* receptor binding kinetic studies showed that NKTR-181 had an approximately 10-fold slower k_{on} but a similar k_{off} relative to oxycodone, demonstrating that on-rate defines the reduced affinity of NKTR-181 for MOR. The impact of association rate on receptor pharmacology was assessed by comparing the differential effects of NKTR-181 and oxycodone on kinetic signaling responses using *in vitro* functional assays, such as [^{35}S]GTPγS binding and cAMP. To establish the kinetics of MOR pharmacology in the CNS, *in vivo* pharmacodynamic studies were conducted that measure dopamine in microdialysis samples collected from the nucleus accumbens shell of awake rats. NKTR-181-dependent dopamine induction in the nucleus accumbens was more gradual compared to oxycodone following intravenous administration; however, the response was sustained for much longer. Together, these data suggest that the onset of NKTR-181 pharmacology is governed initially by its low concentration in the CNS, a result of slow CNS entry rate, coupled with slow association with its target receptor. The consequence is slow MOR occupancy that produces an initially modest response to NKTR-181 that develops into a substantial and sustained pharmacodynamic effect. In conclusion, receptor binding kinetics play a key role in understanding the cellular response and *in vivo* pharmacodynamic profile of NKTR-181.

Disclosures: L. VanderVeen: A. Employment/Salary (full or part-time):; Nektar Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nektar Therapeutics. **T. Miyazaki:** A. Employment/Salary (full or part-time):; Nektar Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nektar Therapeutics. **S.K. Doberstein:** A. Employment/Salary (full or part-time):; Nektar Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nektar Therapeutics. **J. Zalevsky:** A. Employment/Salary (full or part-time):; Nektar Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nektar Therapeutics.

Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 478.10/Z5

Topic: D.03. Somatosensation: Pain

Title: Phosphatidylethanolamine-binding protein reduces βarrestin2 recruitment to the mu opioid receptor, thus promoting opioid anti-nociception

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Abstract: The United States has roughly 100 million people suffering from chronic pain, which has been poorly managed by opioid treatment with attendant side effect and abuse liabilities. Recent efforts to create novel therapies that avoid these problems include making biased ligands at the mu opioid receptor (MOR) and targeting other receptors such as the cannabinoid system; however none have been truly successful. A likely reason for this is due to a lack of understanding of the mechanisms of ascending and descending pain pathways. Although the general mechanisms and circuits are well known, less is known about the micro-circuitry, cell types, receptor distribution and receptor signaling mechanisms within these pain pathways. Our lab has identified a novel regulator of MOR signaling, phosphatidylethanolamine-binding protein (PEBP), and characterized its role in MOR signaling and MOR mediated behavior. PEBP in its unphosphorylated monomeric form binds and inhibits Raf-1, and when phosphorylated by PKC it will dimerize, bind, and inhibit GRK2. Thus we hypothesized that inhibiting PEBP will increase free GRK2 and thus increase desensitization and decrease MOR analgesic effects. Indeed, when using a small molecule PEBP inhibitor, locostatin, injected in mice intrathecally (*it*) or intracerebroventricularly (*icv*), there was a 45.2% (*icv)* and 57.7% (*it*) decrease in morphine's antinociceptive effect in the tail flick assay. We next sought to identify which component of PEBP signaling was mediating the reductions in antinociception. We first examined PEBP's role in ERK signaling using siRNA to knockdown PEBP in two different cell lines, which showed no differences in MOR mediated ERK signaling. We also observed no differences in spinal cord ERK with PEBP inhibition. Next we sought to determine PEBP's role in βarrestin2 (βarr2) recruitment to the MOR, which is downstream of GRK2. Using two different assays we measured βarr2 recruitment to the MOR after knockdown or inhibition of PEBP. We observed a consistent 30% increase in βarr2 recruitment to the MOR, while PEBP activation with PMA led to a reciprocal decrease in βarr2 recruitment. We are currently utilizing a GRK2 inhibitor to directly link the behavioral and signaling changes due to PEBP inhibition to GRK2 activity at the MOR. Furthermore, we will investigate whether PEBP has a role in gating descending pain control: nociceptive input leads to PKC and thus PEBP activation, leading to

GRK2 sequestration and more effective MOR response to endogenous opioids. These insights will help meet the need to understand how distinct signaling regulators act within a circuit, potentially leading to improved future therapies for pain.

Disclosures: J.E. LaVigne: None. **C. Kim:** None. **K.A. Edwards:** None. **J.M. Streicher:** None.

Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 478.11/Z6

Topic: D.03. Somatosensation: Pain

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NIH T32DA035165
New York Stem Cell Foundation

Title: The neuroanatomical organization of delta and mu opioid receptors in CNS pain circuits

Authors: *D. WANG[1,2,3,4], V. L. TAWFIK[1,2,3,4], G. CORDER[1,2,3,4], S. A. LOW[1,2,3,4], A. FRANÇOIS[1,2,3,4], A. I. BASBAUM[6], G. SCHERRER[1,2,3,4,5]
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Abstract: Cellular interactions between delta and mu opioid receptors (DORs and MORs) are thought to regulate pain and opioid analgesic efficacy. However, the identity of the nociceptive neurons in which such interactions could occur *in vivo* remains elusive. Here, we used knockin reporter mice, as well as immunohistochemical, *in situ* hybridization, and electrophysiological techniques in wild type mice, to resolve the functional organization of DORs and MORs along pain neural circuits. In the spinal cord dorsal horn, we found that DORs and MORs are mostly segregated in different populations of lamina II excitatory interneurons, and that DOR-MOR co-expression is limited to subpopulations of lamina I projection neurons of the anterolateral tract. Similarly, DOR-MOR co-expression is rare in several brain regions that process nociceptive information and shape the different dimensions of pain experience, including the parabrachial nucleus, amygdala, and anterior cingulate cortex. Unexpectedly, we found that DOR-MOR co-

expression predominates in neuronal populations of motor circuits, in pre-motor neurons of the spinal cord ventral horn, and in cerebellum-projecting neurons of the pontine and lateral reticular brain nuclei. Collectively, these data provide the fundamental neuroanatomical basis for understanding the mechanism of action of endogenous and exogenous opioids and for developing improved opioid analgesics, an urgent need given the chronic pain and opioid epidemics.

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Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 478.12/Z7

Topic: D.03. Somatosensation: Pain

Support: NIDA R01 DA015438-10
NIH T32 DA007097-32

Title: Examining sex differences in analgesic tolerance to a peripherally-restricted opioid combination

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Abstract: The development of analgesic tolerance to opioid pharmacotherapies presents a persistent issue in the treatment of chronic pain, resulting in dose escalation and increased risk for dependence and respiratory depression. Recent studies have demonstrated the involvement of peripheral opioid receptors in the development of opioid tolerance to classical opioids like morphine and oxycodone. There have also been reports of differences in opioid analgesia, tolerance and addiction between males and females. Therefore, we studied whether peripherally-restricted opioid combinations would differentially induce tolerance in a rodent model of neuropathic pain. For these studies, we used loperamide (Lo), a peripherally-restricted mu-opioid agonist, in combination with oxymorphindole or N-benzyl-oxymorphindole (OMI, BOMI), which are partial and full agonists at the delta-opioid receptor, respectively. The Lo-OMI and Lo-BOMI combinations have been shown to synergistically reverse numerous pain states in mice, including neuropathic pain. After the induction of a neuropathic pain phenotype with spared nerve injury, male or female mice and rats were given once daily injections of saline, Lo-OMI, Lo-BOMI or morphine for 10 days, and daily mechanical sensitivity was monitored by an electronic von Frey apparatus. Initial experiments indicate that male mice do not develop

tolerance to either peripherally-restricted combination, but that female mice rapidly become tolerant to the analgesic effects of Lo-BOMI. From these results, we conclude that there is a sex difference in the development of peripherally-mediated opioid tolerance in mice, and that this phenomenon is dependent on the delta opioid component of a synergistic pair.

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Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 478.13/Z8

Topic: D.03. Somatosensation: Pain

Support: NIDA Grant DA041529

Title: Impact of advanced age and sex on μ opioid receptor expression, affinity, and signaling in the rat periaqueductal gray: Implications for analgesia

Authors: *E. FULLERTON[1], M. RUBAHARAN[1], M. C. KAROM[1], R. I. HANBERRY[1], A. Z. MURPHY[2]
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Abstract: An estimated 45-80% of the aging population (65 and above) suffers from chronic pain on a daily basis. Pain in the elderly is severely under-treated; it is currently estimated that 47-80% of community-dwelling and 16-27% of institutionalized individuals do not receive adequate treatment for their pain. While opiate-based analgesics are the standard for pain management, clinical studies indicate that the elderly are less sensitive to the pain-relieving properties of opiates. Remarkably, very little is known regarding the impact of advanced age on opioidergic signaling in the midbrain periaqueductal gray (PAG), a key neural site for opiate action. The present studies test the hypothesis that reduced efficacy of opioids observed in the aged population is due to changes in mu opioidergic expression, affinity, and signaling in the PAG. Using immunohistochemistry and autoradiography, we report decreases in both μ opioid receptor (MOR) expression and [^{3}H]-DAMGO binding in the ventrolateral PAG (vlPAG) in aged (16-20 months) vs. adult (2-3 months) rats. In addition, MOR protein expression and binding are consistently higher in males versus females, regardless of age. Furthermore, our behavioral studies show that the antihyperalgesic effect of morphine is significantly attenuated in aged male rats compared to adults; no shift in morphine ED_{50} values was observed in females. These analyses indicate that age and sex impact MOR expression in the PAG. Current studies are underway assessing the impact of age and sex on MOR binding affinity (using ligand binding

assays) and MOR signaling (using GTPγS assays). Collectively, the data provide novel insight into the impact of age and sex on the molecular mechanisms mediating opioid analgesia.

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Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

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Program #/Poster #: 478.14/Z9

Topic: D.03. Somatosensation: Pain

Support: NIH R01DA034749
NIH R01NS066792
NIH R03DA026734

Title: cMyc mediated the expression of EZH2 in an epigenetic manner in morphine tolerance in rats

Authors: K. TAKAHASHI[1], H. YI[2], D. IKEGAMI[4], Y. KASHIWAGI[1], S. LIU[1], D. LUBARSKY[1], *S. HAO[3]
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Abstract: The opioid epidemic has recently taken a vast toll on American society. Repeated opioid induces analgesic tolerance, dependence, or hyperalgesia. Morphine modulates mRNA expression of c-Myc in the kidney fibroblasts. Enhancer of zeste homolog 2 (EZH2), an epigenetic writer, is a histone methyl transferase subunit of a polycomb repressor complex. It is not clear about the role of c-Myc and EZH2 in the morphine tolerance (MT) state. In the present study, we hypothesized that c-Myc played an important role in MT through mediating EZH2 in an epigenetic manner in rats. MT was induced by repeatedly intrathecal morphine twice daily for 7 days. Mechanical threshold and thermal latency was measured using von Frey test and hot plate test. Intrathecally c-Myc antisense-oligodeoxynucleotide (AS-ODN) or GSK126 (a EZH2 inhibitor) was given before morning morphine once daily for 7 days. C-Myc or EZH2 proteins was measured using western blots and immunohistochemistry. Chromatin immunoprecipitation (ChIP)-qPCR and RT-PCR assays were used for the cMyc gene promotor enrichment and transcription. Chronic morphine induced MT at day 7. Immunohistochemistry shows that the expression of cMyc and EZH2 are localized in the neurons of the spinal cord dorsal horn in MT rats. The expression of cMyc and EZH2 was increased at the spinal cord dorsal horn in MT rats using western blots. Intrathecal cMyc-AS-ODN against or GSK126 reduced MT development in the von Frey test and hotplate test. ChIP-qPCR assay demonstrated that MT increased the

enrichment of cMyc bound at the EZH2 gene promotor area. The present findings suggest that cMyc and EZH2 are involved in spinal MT, and that cMyc mediated EZH2 expression in MT in an epigenetic manner.

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Poster

478. Pain: Opioid Receptor Pharmacology and Signaling Mechanisms

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 478.15/Z10

Topic: D.03. Somatosensation: Pain

Title: Acute fasting induces analgesia via activation of opioid system

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Abstract: Pain is considered to be both sensory and emotional experience. Since emotion is affected by homeostasis such as temperature, hunger, satiety and thirsty, the perception of pain is also likely to be regulated by homeostatic control. Feeding behavior is crucial for maintaining homeostasis and it is well investigated that pain perception is changed in eating disorder patients. Opioid system, especially is known to modulate pain as well as feeding homeostasis. However, little is known about the relationship between feeding homeostasis and pain. In the present study, we examined whether pain perception is affected by change of feeding homeostasis, with focus on opioid system. We found that 24h acute fasting suppressed formalin-induced paw licking behavior in the second phase. Intraperitoneal administration of opioid receptor antagonist (Naloxone, 10 mg/kg) inhibited acute fasting-induced analgesic effect. Taken together, our results suggest that acute changes in feeding homeostatic lead to analgesic effects, which are related to opioid receptor.

Disclosures: J. Lee: None. **Y. Kang:** None. **S. Oh:** None.

Poster

479. Pain: Non-Opioid Analgesics

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 479.01/Z11

Topic: D.03. Somatosensation: Pain

Support: NIH R01

Title: Glycine receptor-targeted analgesics for the treatment of chronic pain

Authors: *J. CAPOROSO, M. WELLS, P. TANG, Y. XU
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Abstract: Glycine receptors (GlyRs) are inhibitory ligand-gated ion channels that regulate signal transduction in the central nervous system. They are important targets for many anesthetics and analgesics, including Δ9-tetrahydrocannabinol (THC). The undesirable psychoactive effects of THC are independent of this glycinergic mechanism for analgesia. Using *in vitro* electrophysiology, we tested a group of top-ranked compounds from computational screening that were predicted to bind to the THC site in α3GlyR. The compound with the best potency and selectivity (MJPY1) was used as a scaffold to select analogs for *in vivo* optimization of the analgesic effects. MJPY1 and 13 analogs were tested for analgesic effects using CD1 strain mice with CFA-induced inflammation to a hind paw. Mice were treated with MJPY compounds and the analgesic effects were measured using a Hargreaves or Thermal Plate Preference apparatus. The lead compound MJPY1 and 7 of the analogs produced analgesia against inflammatory chronic pain in the Hargreaves test. One compound (MJPY2) showed even greater analgesia than MJPY1 in both behavioral tests. The effects of these compounds are observed within 30 minutes of treatment and last for at least 90 minutes. MJPY1 and MJPY2 were also examined for tolerance via the Hargreaves test with repeated doses: no tolerance or decrease in analgesia was observed for MJPY1 or MJPY2. Both compounds were also tested for mutagenicity via the Ames test and showed negligible activity. Qualitative behavioral observations suggest that none of the MJPY compounds produce any negative psychoactive effects. In conclusion, we have discovered a novel class of analgesics acting at the THC-binding site in GlyRs that produce analgesia without tolerance, mutagenicity, or psychoactive effects. More intensive testing is required to fully characterize the structure-activity relationship of these compounds and optimize their analgesic effects. The analgesic action of these novel compounds may have a significant impact on chronic pain management and help curb the use of popular analgesics with addictive side effects.

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Poster

479. Pain: Non-Opioid Analgesics

Location: SDCC Halls B-H

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Program #/Poster #: 479.02/Z12

Topic: D.03. Somatosensation: Pain

Support: NIH Grant R01 CA142115-07
NIH Grant P01 DA041307-01

Title: MAGL inhibition attenuates cancer-induced bone pain

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Abstract: Many types of cancer metastasize to the bone, but one of the most prevalent cancers that does is breast cancer. The localized destruction of the bone causes severe, chronic pain that leads to a significant reduction in quality of life and functional status. Bone cancer pain proves to be very difficult to manage due to its progressive nature and multi-modal etiology. The current treatment of cancer induced bone pain (CIBP) is opiate therapy but has drawbacks due to the severe side effect profiles including respiratory depression, hyperalgesia and addiction. Cannabinoids have long been known to inhibit neuropathic and inflammatory pain, but cannabinoids have undesirable psychotropic effects that have decreased interest for further drug development. The endogenous cannabinoids (eCB) system, though, has proven to be a viable target for novel analgesics. The eCB system synthesizes cannabinoid compounds from long chain fatty acids. The primary catabolic enzymes of these compound are MAGL and FAAH. Previous studies have demonstrated that inhibition of FAAH and MAGL leading to increased eCBs are effective as anti-nociceptive and anti-allodynic compounds in models of neuropathic pain. In our studies, we explored the effects of the MAGL inhibitor, MJN110, at varying doses on spontaneous pain behaviors in murine models of CIBP. Female BALB/cAnH mice (15-20g, 2 months old) underwent implantation of 80,000 66.1 breast adenocarcinoma cells into the right femoral cavity. Sham operated animals underwent the procedure, but were injected with cell media alone. We performed spontaneous pain behaviors, flinching and guarding, at baseline, 7, 10 and 14 days post-surgery. MJN110 or vehicle was administered as i.p. injection once daily from days 7 to 14. Changes in inflammatory cytokines were measured by ELISA, bone degradation was analyzed via radiographs and analysis of tumor burden were performed via H&E staining. All analysis was performed by blinded observer. Animals reliably displayed significant increase in spontaneous pain behaviors 7 days post-surgery as compared to sham surgical animals and to baseline. The administration of MJN110 significantly decreased the pain behaviors observed in a dose-dependent manner as compared to vehicle treated controls. Treatment with MJN110 caused a significant decrease in inflammatory cytokines (e.g. IL-1, IL-6, TNFa, MCS-F) within the bone microenvironment compared to the vehicle. Tumor burden and bone degradation were unaffected by MJN110. Modulation of the eCB system via MAGL inhibition significantly reduces spontaneous pain behaviors in a CIBP model and lowers inflammatory cytokines within the tumor microenvironment.

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Poster

479. Pain: Non-Opioid Analgesics

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Program #/Poster #: 479.03/Z13

Topic: D.03. Somatosensation: Pain

Support: 1R01GM123746-01

Title: Pre-emptive alphaxalone application as a potential method to decrease opioid consumption post-surgery

Authors: *Q. TAT[1], S. L. JOKSIMOVIC[2], K. KATHIRESAN[3], D. F. COVEY[4], S. M. TODOROVIC[1], V. JEVTOVIC-TODOROVIC[5]
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Abstract: When undertreated, post-operative pain severely impacts patient recovery, and can develop into chronic pain which can interfere with patient's quality of life. Hence, proper treatment for post-operative pain is crucial. Currently, most effective therapy for treating post-operative pain are opioid drugs. However, opioids are overprescribed and carry risk of many dangerous side effects, including respiratory depression, addiction and tolerance. Using an incisional pain model, we study the analgesic effects of neurosteroid anesthetic alphaxalone (ALPH), in an effort to seek a possible treatment to reduce the usage of morphine.
We generated an incisional pain model by performing skin and deep tissue incisions in adult female Sprague Dawley rats. For preemptive analgesia studies, we administered ALPH (60 µg or 180 µg) intrathecal (IT) 30 min prior to surgery, then assessed mechanical hypersensitivity 2h, 1 day, 2 days, 3 days, and 5 days post-incision. At the dose of 60 µg ALPH, the mechanical hypersensitivity post-surgery was decreased while the thermal hyperalgesia remained unaffected. An even more profound decrease in mechanical hypersensitivity post-surgery was found at the dose of 180 µg ALPH.
For post-surgical injection testing, we administered ALPH or morphine at 2h post-incision after pain development was confirmed. With a dose of 60 µg ALPH, the mechanical threshold remained the same, while doses of morphine (0.25 µg, 0.75 µg, and 1.5 µg) showed an increase in mechanical hyperalgesia threshold in a dose-dependent manner.
Our preliminary data strongly suggests that ALPH helps alleviate the mechanical hypersensitivity when applied prior to surgery. The use of neurosteroids like alphaxalone may provide superior perioperative analgesia and potentially diminish the risk for drug addiction resulting from opioid overuse.

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Poster

479. Pain: Non-Opioid Analgesics

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Program #/Poster #: 479.04/Z14

Topic: D.03. Somatosensation: Pain

Support: NIH Grant R01-NS093990

Title: Pharmacodynamic mechanisms underlying the antinociceptive actions of fingolimod (FTY720) in a mouse model of nerve injury-induced neuropathic pain

Authors: *L. J. SIM-SELLEY, G. DONVITO, V. MCLANE, P. KARLSSON, S. SPIEGEL, K. F. HAUSER, A. H. LICHTMAN, D. E. SELLEY
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Abstract: Modulation of the sphingosine-1-phosphate (S1P) system regulates nociception in models of acute and chronic pain. We showed that agonist actions of the S1PR prodrug FTY720 mediated analgesia to an acute thermal stimulus and that repeated FTY720 produced tolerance and desensitized S1P receptor (S1PR)-mediated G-protein activity. However, both agonism and functional antagonism have been proposed to underlie FTY720-mediated antinociception in chronic pain models. The present study assessed the effect of single or repeated dose FTY720 treatment in mice with chronic constriction injury (CCI) to determine whether repeated FTY720 acted as an agonist or functional antagonist in this model of neuropathic pain. Mice received sciatic nerve ligation or sham surgery. After one week of recovery, separate groups were administered daily injections (i.p.) of vehicle or FTY720 (0.01, 0.03, 0.1, 0.3, 1, 3 mg/kg) for 14 days. Mechanical allodynia was assessed with Von Frey filaments 1 h after injections on days 1, 7 and 14. After final testing, the lumbar spinal cord (L4-L6) and brain were collected for agonist-stimulated [^{35}S]GTPγS binding and sphingolipid analysis using LC-MS/MS. Repeated administration of FTY720 produced dose and time-dependent antinociception to mechanical allodynia in CCI mice, such that moderate doses were effective after 1-7 days, but low doses required 14 days of treatment. Repeated FTY720 treatment reduced [^{35}S]GTPγS binding stimulated by S1P or the S1PR1 agonist SEW2871 in the lumbar spinal cord in a treatment dose-dependent manner. [^{35}S]GTPγS autoradiography similarly revealed treatment dose-dependent desensitization of S1P, SEW2871 or FTY720-phosphate-stimulated activity in regions including the periaqueductal gray. CCI did not affect [^{35}S]GTPγS binding in vehicle-treated mice. Lipidomic analysis revealed elevated S1P, sphingosine, dihydro-S1P and ceramide in the lumbar spinal cord of CCI mice in both groups, indicating an injury-induced increase in de novo synthesis. FTY720 did not affect sphingolipid levels in either group. These results show that

repeated FTY720 treatment enhanced antinociception to CCI-induced mechanical allodynia despite producing S1PR desensitization, consistent with a functional antagonist mechanism.

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Poster

479. Pain: Non-Opioid Analgesics

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Topic: D.03. Somatosensation: Pain

Support: CIC UMSNH 26.10
CIC UMSNH 30.2

Title: Supra additive interaction between topiramate and ketorolac, locally administered in the rat formalin test

Authors: E. SANCHEZ-SERRANO[1], M. Y. GAUTHEREAU-TORRES[1], C. CERVANTES-DURAN[1], *L. F. ORTEGA-VARELA[2,3]
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Abstract: Combination therapy approaches to manage acute and chronic pain are commonly used. Here, we attempted to characterize a supra additive interaction between topiramate and ketorolac in the inflammatory pain model of formalin test. Female Wistar rats were used (200-300g), and injected with 50 µl of 1% formalin in the dorsal surface of the right hind paw. This substance causes a typical flinching pain-related behavior. The antinociceptive effect was determined by the administration of topiramate (10, 30, 100 and 300 µg/paw), ketorolac (25, 50, 100 and 200 µg/paw) and their combination; by local peripheral route. Isobolographic analysis was used in a fixed dose combination (0.5:0.5) to analyze the nature of the interaction of this combination; based on the ED_{30} of topiramate (391.34 ± 51.70 µg/paw) and ketorolac (53.06 ± 7.97 µg/paw). The combination of these two drugs significantly reduced the number of flinches in the second phase of the test. Theoretical ED_{30} of the combination ($ED_{30}T$) was 222.20 ± 64.99 µg/kg. Experimentally, the ED_{30} of the combination ($ED_{30}E$) had a significantly lower value: 60.41 ± 15.72 µg/paw; indicating the presence of supra additive effects (interaction index was 0.27). The results show that local peripheral administration of the combination can interact synergistically to reduce inflammatory pain in the formalin test, suggesting that combination could be useful in the treatment of inflammatory pain.

Disclosures: E. Sanchez-Serrano: None. **M.Y. Gauthereau-Torres:** None. **C. Cervantes-Duran:** None. **L.F. Ortega-Varela:** None.

Poster

479. Pain: Non-Opioid Analgesics

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 479.06/Z16

Topic: D.03. Somatosensation: Pain

Support: DA041229
DA009158
T32 DA024628
Harlan Research Summer Scholars program

Title: Evaluation of AM1710 as a broad spectrum analgesic and its impact on morphine tolerance and physical dependence

Authors: *A. LI[1], X. LIN[1], A. S. DHOPESHWARKAR[1], A. C. THOMAZ DOS SANTOS[1], L. M. CAREY, IV[1], Y. LIU[2], S. P. NIKAS[2], A. MAKRIYANNIS[2], K. MACKIE[1], A. G. HOHMANN[1]
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Abstract: AM1710, a cannabilactone CB2 agonist, has shown promising anti-allodynic efficacy in suppressing neuropathic pain without producing tolerance or unwanted side effects associated with CB1 receptors (Deng, *et al.* (2015) *Biological Psych* 77: 475-87). In this study, we characterized the signaling profile of AM1710 in vitro and further evaluated whether it behaved as a broad spectrum analgesic agent in vivo. We assessed efficacy of AM1710 in suppressing inflammatory nociception evoked by complete Freund's adjuvant (CFA) inflammation of the hind paw as well as neuropathic pain induced by either traumatic nerve injury produced by partial sciatic nerve ligation (PSNL) or toxic challenge with the chemotherapeutic agent paclitaxel. We also verified whether AM1710 behaves as a functional CB1 antagonist in vivo. In vitro, AM1710 inhibited forskolin-stimulated cAMP in a manner that was sensitive to pertussis toxin, indicating it was Gi/o protein-mediated. AM1710 also produced a long lasting activation of ERK1/2 phosphorylation in HEK cells expressing mCB2. However, significant species differences in the signaling profile of AM1710 were observed between HEK cells stably expressing mCB2 and hCB2. In vivo, AM1710 suppressed paclitaxel-induced neuropathic pain without producing tolerance. Prior history of AM1710 treatment (5 mg/kg/day x 12 day, i.p.) delayed, but did not eliminate, the development of morphine analgesic tolerance in paclitaxel-treated mice. AM1710 also attenuated morphine-induced physical dependence as measured by naloxone-precipitated opioid withdrawal. Moreover, AM1710 (10 mg/kg, i.p.) did not precipitate

CB1-receptor mediated withdrawal symptoms in mice rendered tolerant to Δ^9-tetrahydrocannabinol, suggesting that AM1710 does not behave as a CB1 antagonist *in vivo*. Furthermore, AM1710 (1, 3, 10 mg/kg, i.p.) did not suppress established mechanical allodynia induced by either CFA or PSNL. Similarly, prophylactic and chronic dosing with AM1710 (10 mg/kg, i.p.) showed no antiallodynic efficacy in the CFA model. Both models responded to the anticonvulsant agent gabapentin. Our results indicate that AM1710 is not a broad spectrum analgesic agent in mice. Our results also emphasize the importance of future medicinal chemistry efforts aimed at developing CB2 agonists that are efficacious at both rodent and human CB2 to better exploit their therapeutic potential for clinical translation.

Disclosures: A. Li: None. **X. Lin:** None. **A.S. Dhopeshwarkar:** None. **A.C. Thomaz Dos Santos:** None. **L.M. Carey:** None. **Y. Liu:** None. **S.P. Nikas:** None. **A. Makriyannis:** None. **K. Mackie:** None. **A.G. Hohmann:** None.

Poster

479. Pain: Non-Opioid Analgesics

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 479.07/Z17

Topic: D.03. Somatosensation: Pain

Support: JUST-Research Grant No: 2016/349

Title: Early and late anti nociceptive effects of sucrose on neonatal inflammatory pain; comparison to a non-steroidal anti-inflammatory drug

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Abstract: Management of neonatal pain is not only ethical but is also essential. Barriers to pain management in infants include lack of safe and effective medications and fear of adverse effects of conventional pain medications. Sweet solutions given intraorally had been shown to reduce pain behaviors and associated symptoms. Sucrose and other sweet inducing solutions are being increasingly used at the NICUs and immunization clinics. Sucrose for mild invasive procedures is effective and safe for those procedures that need to be repeated multiple times during the day. Only few studies examined the efficacy of sucrose for the management of inflammatory pain during infancy. In this study, CFA was used to induce inflammation in 5 day old rat pups; CFA also produce inflammation that last for more than a day thus can also a model for chronic pain. Sucrose or Ibuprofen (NSAIDs) was given to subset of pups shortly after CFA intraplantar injections. Thermal as well as mechanical pain sensitivity was assessed on subsequent days and also during adolescent and early adulthood. Sucrose and ibuprofen were both effective in preventing hyperalgesia and allodynia produced by CFA. Interestingly, sucrose was even more

effective than ibuprofen, and the analgesic effects continued further to adolescent and adult life of the rat. BDNF, an important factor in the consolidation of memory through enrichment of neurogenesis and synapses proliferation in the hippocampus was not affected by CFA, sucrose or ibuprofen before CFA when measured at the age of 8 weeks.

Disclosures: K. Nuseir: None. **A. Tasslaq:** None. **A. Altarifi:** None. **K.H. Alzoubi:** None.

Poster

479. Pain: Non-Opioid Analgesics

Location: SDCC Halls B-H

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Topic: D.03. Somatosensation: Pain

Support: Canadian Institutes of Health Research (CIHR) Grant
Fonds de recherche du Québec - Nature et technologie (FRQNT) Grant
Centre d'excellence de neurosciences de l'Université de Sherbrooke (CNS) Grant

Title: Treating pain with a cell-penetrating neurotensin type 1 receptor (NTS1) pepducin

Authors: *R. L. BROUILLETTE[1,2], É. BESSERER-OFFROY[1,2], C. MONA[1,2], S. LAVENUS[1,2], J. CÔTÉ[1,2], M. SOUSBIE[1,2], J.-M. LONGPRÉ[1,2], R. LEDUC[1,2], M. GRANDBOIS[1,2], É. MARSAULT[1,2], P. SARRET[1,2]
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Abstract: To date, the single most successful protein target class in drug discovery is a receptor family known as G protein-coupled receptors (GPCRs). In recent years, new and innovative approaches have been developed to better exploit their therapeutic potential, such as the design of cell-penetrating lipopeptides termed “pepducins”. These pepducins are composed of a peptide sequence mimicking one of the intracellular loops of a GPCR of interest, conjugated to an N-terminal palmitic acid. The lipid moiety effectively anchors the pepducinto the cell membrane and facilitates its translocation into the cell, where it functionally interacts with its cognate GPCR at the receptor-effector interface and modulates its signaling output. Thus, pepducins may behave as allosteric agonists or allosteric modulators of the receptors they target. We recently designed a series of pepducins derived from the intracellular domains of the human neurotensin type 1 receptor (hNTS1), a GPCR which mediates many of the physiological effects of the neurotensin (NT) tridecapeptide, including analgesia, hypotension and hypothermia. Here, we report the cellular and physiological actions of an ICL1-derived pepducin, named PP001. In CHO-K1 cells stably expressing hNTS1, we determined that high PP001 concentrations ($\geq 10^{-5}$M) partially inhibited NT orthosteric binding, while the non-palmitoylated control did not do so. Using BRET-based biosensors monitoring the pepducin’s ability to engage G protein-dependent

and G protein-independent signaling pathways, we further found that PP001 preferentially promoted GαoA and Gα13 activation over β-arrestin recruitment, and inhibited NT-mediated β-arrestin recruitment, thus acting as a biased allosteric agonist and negative allosteric modulator of NTS1.Additionally, PP001 administration enhanced hNTS1 homomerization in a BRET titration experiment. *In vivo*, we found that i.t. administration (275 nmol/kg) of PP001 significantly reduced the rat nociceptive behaviors in acute (tail-flick), tonic (formalin), and chronic (chronic constriction injury) pain models. Finally, in order to elucidate which residues are critical for these actions, we synthesized an Ala-scan of PP001, and monitored its effects on a CHO-hNTS1 cell monolayer by Electric Cell-substrate Impedance Sensing. In doing so, we determined a critical ARKK motif. Altogether, our results indicate that PP001 clearly participates in the cellular and physiological actions linked to NTS1 activation and may thus constitute a valuable tool to inform the design of novel NT-based drugs that could better cater to the needs of chronic pain patients.

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Poster

479. Pain: Non-Opioid Analgesics

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 479.09/AA1

Topic: D.03. Somatosensation: Pain

Support: NIH grant R01NS099338
NIH grant R44DA038968
research funds from Kalyra Pharmaceuticals, Inc.

Title: Analgesia and abuse potential of acetaminophen and a bioisostere acetaminophen analogue in mice

Authors: *T. L. YAKSH[1], N. A. REGEN[1], H. HOSHIJIMA[1], K. A. EDDINGER[1], K. D. BUNKER[2], C. D. HOPKINS[2]
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Abstract: Acetaminophen (*N*-acetyl-*para*-aminophenol: APAP) is one of the most commonly used over-the-counter analgesic drugs in the United States. Robust trials show that APAP is well tolerated, significantly decreases pain, and decades of clinical use reveal no abuse liability. In recent work, we have constructed an APAP-mimetic (D-112) built on a bioisostere of the APAP backbone and herein we examined its analgesic activity (formalin flinching) after intrathecal (IT) and intraperitoneal (IP) delivery. Additionally, re-enforcing properties of APAP and D-112

agents after IP delivery of approximately equi-analgesic doses were compared to morphine using the conditioned place preference (CPP) model.
Methods: In adult male C57BL6 mice, IP and percutaneous IT delivery of APAP and D-112 was undertaken and the effects upon formalin evoked flinching assessed. To define abuse potential, the effects of vehicle, morphine, APAP and D-112 were compared using the conditioned place preference (CPP) model.
Results: In these studies, both IP and IT dosing of either APAP (200 mg/kg and 100 µg/5 µL, respectively) or D-112 (30 mg/kg and 30 µg/5 µL, respectively) resulted in suppression of Phase 2 formalin flinching at doses that had no effect upon motor function. In the CPP model, IP delivery of morphine resulted in a significant place preference 1 or 5 days after the last drug place pairing. In contrast, APAP, D-112 or saline had no effect on drug place pairing selection.
Significance: Thus, D-112, like APAP, can produce a significant effect upon facilitated pain processing after systemic and spinal exposure but, in contrast to morphine, they do not support a place preference, suggesting a minimal abuse potential. (Work supported by NIH grants R01NS099338 (TY) and R44DA038968 (KB), and funds from Kalyra Pharmaceuticals.)

Disclosures: T.L. Yaksh: 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.; contracted research with Kalyra Pharmaceuticals. **N.A. Regen:** None. **H. Hoshijima:** None. **K.A. Eddinger:** None. **K.D. Bunker:** 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.; Kalyra collaborated on a research project with UCSD and provided funding.. **C.D. Hopkins:** None.

Poster

479. Pain: Non-Opioid Analgesics

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 479.10/AA2

Topic: D.03. Somatosensation: Pain

Title: Exercise dosing: A meta-analysis of existing exercise paradigms in the treatment of chronic pain

Authors: *A. POLASKI[1], A. L. PHELPS[2], M. C. KOSTEK[3], K. A. SZUCS[4], B. J. KOLBER[1]
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Abstract: Increasing evidence implicates exercise as a first line therapy for the treatment of nearly all forms of chronic pain. Physical activity has been shown to be associated with decreased symptoms of depression and anxiety, further suggesting that exercise could be

particularly advantageous in the context of chronic pain comorbid with psychiatric illness. However, knowledge of efficacious dosing respective to exercise type and pain condition is virtually absent in the literature. Therefore, understanding dose will provide insight into the mechanisms underlying treatment and the conditions themselves. The purpose of this analysis was to calculate the extent to which exercise treatment shows dose-dependent effects similar to what is seen with pharmacological treatments. Data was extracted and analyzed from existing clinical trials, focusing specifically on the dose of exercise intervention and the pain effect size in these studies. Dose was defined as the time exercising per week (minutes/week), frequency of exercise per week (# of sessions/week), intensity of the intervention (MET-minutes/week) and duration of intervention (in weeks). Univariate linear regression analysis was done to look at correlations between each component of exercise dose with pain effect. Results of multiple linear regression modeling of these data helped to predict interaction effects between different aspects of exercise dose. Overall, these results suggest the presence of a dose effect of exercise in pain, but also reinforce the need to explicitly test the question of dose in specific patient populations.

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Poster

479. Pain: Non-Opioid Analgesics

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 479.11/AA3

Topic: D.03. Somatosensation: Pain

Support: NIH Grant R01-NS070715

Title: Attenuated dopamine receptor signaling in nucleus accumbens core in a rat model of chemically-induced neuropathic pain

Authors: *D. E. SELLEY[1], M. F. LAZENKA[1], D. N. POTTER[2], L. J. SIM-SELLEY[1], W. A. CARLEZON, Jr[2], S. S. NEGUS[1]
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Abstract: Neuropathy is major source of chronic pain that can be caused by mechanically or chemically induced nerve injury. In a rat model of chemically-induced neuropathic pain, bilateral formalin injection into the hind paw produced mechanical hypersensitivity (allodynia) and depressed responding for intracranial self-stimulation (Leitl et al. Mol. Pain, 10:62, 2014). To determine whether dopamine receptor responsiveness was altered in mesolimbic brain regions in response to formalin-induced neuropathy, we examined dopamine D_1-like and D_2-like receptor ($D_{1/2}R$) signaling and expression in male Sprague-Dawley rats with bilateral formalin injection.

D_2R-mediated G-protein activation, measured by agonist-stimulated [^{35}S]GTPγS binding, was reduced in nucleus accumbens (NAc) core, but not in NAc shell, caudate-putamen (CPu) or ventral tegmental area (VTA) of formalin- compared to saline-treated rats. Likewise, decreased expression of D_2R long, but not short, isoform protein was observed in formalin-treated rats by immunoblot in NAc core, but not shell. In contrast, formalin treatment did not alter CB_1 cannabinoid receptor activity in NAc core, or any other region examined. D_1R signaling was also reduced in NAc core, but not in NAc shell or prefrontal cortex of formalin-treated rats, as assessed by agonist-stimulated adenylyl cyclase (AC) activity. However, D_1R protein levels in NAc or any other regions examined were unaffected by formalin treatment. Adenosine A_1 receptor-stimulated AC activity in NAc was unaltered by formalin treatment. Expression of other proteins involved in dopamine neurotransmission in NAc and VTA, including dopamine transporter and tyrosine hydroxylase, were unaffected by formalin treatment. These results reveal selective decreases in D_2R_L signaling and expression, and D_1R signaling, in NAc core of male rats with formalin-induced neuropathic pain, suggesting that reduced DA receptor signaling contributes to pain-depressed behavior.

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Poster

479. Pain: Non-Opioid Analgesics

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 479.12/AA4

Topic: D.03. Somatosensation: Pain

Title: Acupuncture alleviates cognitive impairment and pain via increased glutamate receptors and synaptic plasticity in the hippocampus in chronic neuropathic pain mice

Authors: *J.-H. JANG[1], Y.-K. KIM[1], E.-M. SONG[2], J.-Y. OH[1], J.-Y. PARK[3], M.-Y. SONG[2], H.-J. PARK[1]
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Abstract: Background and aims: Growing evidence reveals that neuropathic pain is frequently accompanied with emotional disorder, such as cognition. We investigated that specific acupoints of acupuncture have analgesic effects, and also improve cognitive dysfunction induced by neuropathic pain.
Methods: One week after the left partial sciatic nerve ligation (PSNL), acupuncture treatment on the acupoints Hwando (GB30)/Yanglingquan (GB34), Sinmun (HT7)/Baekhoe (GV20), or control points were performed for 4 weeks. We assessed the effect of repeated acupuncture on

mechanical and cold allodynia, and also evaluated cognitive impairment at the pre- and post-acupuncture.
Results: In the PSNL model, nociceptive behavior and cognitive impairment was increased in the 1 week after surgery. We found that the acupoints GB30/GB34 treatment significantly attenuated mechanical and cold allodynia in PSNL model, and also significantly attenuated cognitive impairment symptom (in the novel object recognition and Y maze). The acupoints GB30/GB34 treatment significantly increased expression level of N-methyl-d-aspartate receptor including the NR2B subunit and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor including the GluR1 subunit in the hippocampus in PSNL model. Moreover, we assessed the expression of the Ca^{2+}/calmodulin-dependent protein kinases II (CaMKII), presynaptic components synapsin-1 and postsynaptic density protein 95 (PSD-95) and found that CaMKII, synapsin-1 and PSD-95 were increased in hippocampus of PSNL mice after acupuncture treatment.
Conclusions: We suggested that GB30/GB34 acupuncture might be a good candidate for the comorbidity of pain and cognitive impairment through increased expression of glutamate receptors and synaptic plasticity in the hippocampus in chronic neuropathic pain.
Key words: Acupuncture, partial sciatic nerve ligation (PSNL), analgesia, cognitive disorder, emotional disorder

Disclosures: J. Jang: None. **Y. Kim:** None. **E. Song:** None. **J. Oh:** None. **J. Park:** None. **M. Song:** None. **H. Park:** None.

Poster

479. Pain: Non-Opioid Analgesics

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 479.13/AA5

Topic: D.03. Somatosensation: Pain

Support: SIP20180861

Title: New bioisosteres and hybrids of NSAIDs with antinociceptive properties

Authors: *M. DECIGA-CAMPOS[1], M. E. GONZÁLEZ-TRUJANO[2], G. NAVARRETE-VÁZQUEZ[3]
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Abstract: The therapeutic options that are currently on the market to deal with pain, inflammation and fever pathophysiology have a series of adverse drug reactions, such as damage

to the digestive, kidney and cardiovascular systems. For this reason, the search for new bioactive molecules with non-steroidal anti-inflammatory effects that produce minimal adverse effects continues. Drug discovery for pain medications aims to develop new NSAIDs with a good analgesic effect to side effect ratio. The aim of this study was to assess the anti-nociceptive and/or anti-inflammatory activities of synthesized molecules that were designed as bioisosteres and hybrids of paracetamol, ibuprofen and naproxen in a rat model. 4-(acetylamino)phenyl (2S)-2-(6-methoxy-2-naphthyl)propanoate (A), 4-(acetylamino)phenyl 2-(R,S)-(4-isobutylphenyl)propanoate (B), 2-(R,S)-(4-isobutylphenyl)-N-1H-tetrazol-5-ylpropanamide (C), (2S)-2-(6-methoxy-2-naphthyl)-N-1H-tetrazol-5-ylpropanamide (D), (2-(R,S)-N-hydroxy-2-(4-(2-methylpropyl)phenyl) propanamide) (E), and (2S)-N-hydroxy-2-(6-methoxy-2-naphthyl)propanamide (F) were synthesized as bioisosteres of the NSAIDs paracetamol, ibuprofen, and naproxen, respectively. All these compounds were characterized by spectroscopic and spectrometric analysis. Antinociceptive activity was evaluated using the formalin test in rats. Pharmacological responses of A, B (hybrids), and E (bioisostere) compounds demonstrated significant antinociceptive effects; thus these compounds were assayed in an inflammation test like carrageenan-induced paw oedema in rats. Complete molecular docking of cyclooxygenase and the A and B hybrids showed high docking scores, compared to the reference drugs. Our data demonstrate that compounds A, B, and E possesses antinociceptive and antiinflammatory activities resembling and improving those known for the traditional NSAIDs, paracetamol, naproxen and ibuprofen.

Disclosures: M. Deciga-Campos: None. **M.E. González-Trujano:** None. **G. Navarrete-Vázquez:** None.

Poster

479. Pain: Non-Opioid Analgesics

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 479.14/AA6

Topic: D.03. Somatosensation: Pain

Support: DGAPA-PAPIIT-IN204416

Title: Quercetin reduces the antinociceptive effect of diclofenac in a model of inflammatory pain

Authors: *R. VENTURA-MARTINEZ[1], A. BUSTAMANTE-MARQUINA[2], M. DECIGA-CAMPOS[2], M. Y. HERNANDEZ-ARAMBURO[3], R. RODRIGUEZ[1], G. E. ANGELES-LOPEZ[1], M. E. GONZALEZ-TRUJANO[3]
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Abstract: In this study, the antinociceptive effect of diclofenac, a non-steroidal anti-inflammatory drug used at clinical level, was determined in the absence and in the presence of quercetin, a bioflavonoid present in many food, in a model of arthritic pain type gout. For this, male Wistar rats (200 g) were used, in which the food was removed 12 hours before. In the day of the experiment, animals were administered with 50 µl of uric acid in the femoro-tibial-patellar articulation of the right hind paw of each rat. The index of functionality of each animal was determined every 30 min and when they presented a total dysfunction of the extremity administered with uric acid (approximately 2.5 h after); then, they were distributed in groups of 6 animals per group. Several treatments were administered in each group as follows: diclofenac (0.1, 0.31, 1 or 3.16 mg/Kg, p.o.) alone or in combination with quercetin (100 mg Kg, i.p.). In this model, the recovery of the index of functionality of each animal after treatment was considered as antinociceptive effect. Results showed that diclofenac induced an antinociceptive effect from the lower doses with a maximal effect of 69.7 ± 2.7% at dose of 3.16 mg/Kg; whereas, quercetin did not produce a significant antinociceptive effect (9.3 ± 3.2%). On the other hand, when diclofenac was administered together with quercetin its antinociceptive effect decreased to 39.0 ± 8.5% at the same dose. These results suggest that quercetin induces an interaction like antagonism on the analgesic effect of diclofenac, in which pharmacokinetic and/or pharmacodynamic mechanisms may be involved.
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Poster

480. Touch: Barrel Cortex I

Location: SDCC Halls B-H

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Program #/Poster #: 480.01/AA7

Topic: D.04. Somatosensation: Touch

Support: NRF-2017M3C7A1049051

Title: Exploration of effective connectivity of the mouse somatosensory neurons for whisker object localization using dynamic causal modeling

Authors: *K. JUNG[1,3], J. KANG[3], H.-J. PARK[1,2,3,4]
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Abstract: The computational modeling to estimate the effective connectivity among neuronal populations may unravel the encoding mechanism for the stimuli. The purpose of this study is to estimate effective connectivity among neuronal populations of the somatosensory cortex during an object localization task.
To investigate the encoding process during the task, we analyzed functional calcium imaging data of neuronal responses in the barrel cortex evoked by a single whisking, which was downloaded from a public database (https://crcns.org/data-sets/ssc/ssc-1) [1]. Calcium image data were measured while a mouse was performing a pole localization task. To estimate the effective connectivity among clusters of neurons, we used dynamic causal modeling (DCM) [2] with Jansen and Rit model [3] and a calcium image time series evoked by touching whiskers. We performed waveform sorting of valid neuronal responses in the barrel cortex using principal component analysis for time series of behaviorally successful trials. We visually identified 9 representative calcium signal modes evoked by whisker stimulation. Using time series of these modes, we estimated effective connectivity among these modes using DCM, a Bayesian method for inferring a causal architecture in the dynamic system. For the DCM, we used a convolution-based model for neural state transition model, which was initially proposed by Jansen and Rit. We also made an observation model for the calcium imaging, which maps neuronal state to calcium imaging data. The calcium imaging data with a given external input were used to fit both neural state transition model and calcium imaging observation model. Among several possible models with different inputs, we chose an optimal model after Bayesian model comparison. As a result, we found different effective connectivity between hit and error trials on the shared modes. The current method provides a method to explore the relationship between amplification and suppression of the canonical microcircuit in the cortex using DCM for calcium imaging data set. In this framework, we are further working on establishing more precise models for calcium imaging data and validation test using simulation studies.
[1] Simon Peron, et al., (2014). “Calcium imaging data from vibrissal S1 neurons in adult mice performing a pole localization task.” CRCNS.org.
[2] Friston, K. J., et al. (2003). "Dynamic causal modelling." Neuroimage 19(4): 1273-1302.
[3] Jansen, B. H. and V. G. Rit (1995). "Electroencephalogram and visual evoked potential generation in a mathematical model of coupled cortical columns." Biol Cybern 73(4): 357-366.

Disclosures: K. Jung: None. **J. Kang:** None. **H. Park:** None.

Poster

480. Touch: Barrel Cortex I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 480.02/AA8

Topic: D.04. Somatosensation: Touch

Support: ERC Grant No 633428

DFG (SFB 1089)

Title: Mathematical framework for testing wiring specificity in cortical connectomes

Authors: *D. UDVARY[1], V. J. DERCKSEN[2], R. EGGER[3], C. P. J. DE KOCK[4], B. SAKMANN[5], M. OBERLAENDER[1]
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Abstract: We present a mathematical framework for formulating and testing rules of synaptic organization on both sparse and dense connectomics data. Our approaches will make it possible to implement hypotheses of synaptic organization in terms of mathematically formulated rules. We generated a structurally dense model of the rat barrel cortex and formulated a null hypothesis rule that synaptic wiring is based on axo-dendritic overlap. This null hypothesis states that synapses form (1) proportional to the locally available pre- and postsynaptic target structures, (2) locally random and (3) globally independent. The rule predicts distributions of pair-wise connectivity that are non-Gaussian and non-Poisson. We show that (sparse) pair-wise connectivity measurements obtained with different experimental methods cannot reject the null hypothesis. The rule predicts a wide range of 2nd and higher order connectivity patterns. These predictions can be used in the future to reject the null hypothesis and to identify wiring specificity that cannot be explained by axo-dendritic overlap. The framework will make it possible to (1) interpret sparse or dense connectivity measurements in a rule-based context, (2) identify which structural features are predictive of synaptic connections, (3) quantify how well a connectivity rule is constrained by data and (4) provide unbiased statistical tools for determining which set of rules is most consistent with empirical data.

Disclosures: D. Udvary: None. **V.J. Dercksen:** None. **R. Egger:** None. **C.P.J. de Kock:** None. **B. Sakmann:** None. **M. Oberlaender:** None.

Poster

480. Touch: Barrel Cortex I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 480.03/AA9

Topic: D.04. Somatosensation: Touch

Support: JSPS KAKENHI Grant Number JP18K06487

Title: Gap junctions mediate the connectivity among different subtypes of parvalbumin-positive interneurons in layer 4 of the mouse barrel cortex

Authors: *N. SHIGEMATSU, T. FUKUDA
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Abstract: Layer 4 of the rodent barrel cortex receives excitatory inputs from barreloids in the thalamus. Distribution pattern of these inputs shows typical cortical columnar structure. Although there are many studies about excitatory neurons in this area, local circuits composed of GABAergic interneurons remain poorly understood. Parvalbumin (PV)-positive interneurons form dendritic gap junctions with one another, but the connectivity among gap junction-coupled dendrites remains uninvestigated in most neocortical areas.
In the present study we visualized PV neurons including gap junctions in layer 4 of the mouse barrel cortex using immunohistochemical methods. Barrels were visualized by immunolabeling of vesicular glutamate transporter 2 (VGluT2), the thalamocortical afferent marker, and were reconstructed three-dimensionally based on serial 3.3 μm-thick optical slices in CLSM images using Neurolucida software. Then we reconstructed dendrites of PV neurons and analyzed their positional relationship to barrels. PV neurons were classified into four groups depending on their dendritic morphologies and somatic locations as follows:
Type1. All dendrites were within a single barrel
Type2. Dendrites crossed barrel/ septa border, soma was located in a barrel cortex
Type3. Dendrites crossed barrel/ septa border, soma was located outside the barrels
Type4. All dendrites were within the interbarrel septa
Next we observed gap junctions between different types of PV neurons. The majority (33/38, 86.8%) of dendritic gap junctions were within 75 μm from at least 1 of 2 paired somata. Type1 PV neurons formed dendrodendritic gap junctions with Type2 and Type3 neurons, but never with one another.
From these results, we focused on the Type1 PV neuron because this type restricts their dendrites within one barrel but never make contacts with the same type through gap junctions inside a limited space of a single barrel. One of the major challenges is how single axon originating from a barreloid distributes boutons on the Type1 PV neurons residing in a single barrel. To visualize the individual axons, we injected biotinylated dextran amines (BDA), the anterograde tracer, into the mouse ventral posteromedial thalamic nucleus (VPM). PV and BDA were visualized by immunohistochemical methods and serial optical slices were taken in CLSM. PV neurons and the BDA-labeled axons in one barrel were reconstructed by the same method as described above. We observed the appositions of BDA-labeled boutons against Type1 PV neurons and discussed the structural relationship between the boutons and the targeted PV neurons.

Disclosures: N. Shigematsu: None. **T. Fukuda:** None.

Poster

480. Touch: Barrel Cortex I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 480.04/AA10

Topic: D.04. Somatosensation: Touch

Support: Marie Sklodowska-Curie Grant No 702726

Title: Neuronal responses of the rat barrel cortex to highly predictable multi-whisker deflection patterns

Authors: *M. A. GOLDIN, D. E. SHULZ
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Abstract: Processing of sensory information depends on the nature of the input but is also determined by previous stimulation history. A violation of an expectation can trigger neuronal responses that show the preparedness of the nervous system for an expected input. Within the predictive coding hypothesis (Friston 2005), these expectancy signals are determined by the mismatch between sensory input and a prediction coming from higher cortical areas. However, in a primary sensory cortex it still needs to be determined if these signals can appear in a pre-attentive manner. In this work, we used the rat whisker system to study the effect of repetitive spatio-temporal patterns of stimulation that provide a strong predictability in space and time. We used a dedicated multi-whisker stimulator that delivers controlled micrometric displacements to the 24 caudal whiskers of the snout of the rat (Jacob et al. 2010), while simultaneously recording multiple single units and local field potentials (LFP) in the primary somatosensory cortex of animals anesthetized with isoflurane. We designed stimulation patterns converging into a whisker and made our measurements in its corresponding cortical column across all layers using multielectrode silicone probes. Complete patterns were used during a training phase while truncated patterns were given as tests in a pre- and post-test phase. Random occurrences of truncated sequences with a 10 % chance were also present during the training phase to follow the evolution of the putative expectancy signals. We found that LFP signals become stronger after training together with many single units responses to the truncated stimulations. These preliminary results show that the stimulus history can reconfigure the activity in the barrel cortex in a manner that responses to truncated inputs resemble those to the full pattern of stimulation.

Disclosures: M.A. Goldin: None. **D.E. Shulz:** None.

Poster

480. Touch: Barrel Cortex I

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Topic: D.04. Somatosensation: Touch

Support: NSF MRI PHY153264

NIH NINDS U01 NS0905905
NIH NINDS R35 NS097265

Title: Neural coding of vibrissa set-point in layer 5 cortical neurons measured in basal dendrites and spines by two-photon imaging with adaptive optics

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Abstract: Active sensing by rodents involves multi-sensory coding and integration at the cellular level. In mouse vibrissa cortex, layer 5 pyramid neurons receive distinct inputs from multiple separated brain regions (Petreanu et al. *Nature* 2009) including, either directly or via interneurons, efference control input from vibrissa motor cortex (Hill et al. *Neuron* 2011; Petreanu et al. *Nature* 2012; Xu et al. *Nature* 2012). This suggests that layer 5 pyramid neurons are a computational hub that integrates and processes multiple inputs for subsequent output, including subcortical premotor regions. Further, layer 5 pyramid neurons can be directly activated by thalamus through inputs to their basal dendrites (Constantinople et al. *Science* 2013). This leads to the hypothesis, that layer 5b neurons, through inputs to the basal dendrites, can function as a "single computational layer" for input to and output from cortex. We have begun to address this hypothesis in the context of control on vibrissa set-point during active sensing. We use adaptive optics with a vascular-based wavefront sensing method to achieve near diffraction-limited two-photon imaging in cortical layer 5b (depth ~ 800 μm). This permits us to measure calcium dynamics throughout jRGECO1a-labelled layer 5b pyramidal somata, dendrites, and spines. In preliminary work, we observe robust signals to changes in the set-point during freely whisking, in response to air flow, and in response to active touch. We will test the hypothesis that layer 5b neurons function as a "single computational layer" in terms of concurrent measures of neuronal input and output.

Disclosures: R. Liu: None. **M. Deschênes:** None. **D. Kleinfeld:** None.

Poster

480. Touch: Barrel Cortex I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 480.06/BB1

Topic: D.04. Somatosensation: Touch

Support: Swiss National Science Foundation
University of Zurich, Forschungskredit Candoc

Title: Comparison of mesoscale dynamics in layer 6 and layer 2/3 of mouse neocartex during texture discrimination

Authors: *D. LORENZO MERCADO[1,2], A. GILAD[1], Y. GALLERO-SALAS[1,2], F. HELMCHEN[1,2]
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Abstract: The complexity of the mammalian neocortex is reflected in one of its most prominent anatomical features: its laminar organization in six horizontal layers. Each one of these layers is presumed to engage in information processing differently. Especially the role of layer 6 (L6) in mesoscale cortical dynamics and during behavior is not well understood. In mouse primary visual cortex it has been shown that the activity of L6 cortico-thalamic pyramidal cells suppresses the activity of neurons in superficial layers during visual stimulation. Whether such a modulatory effect of L6 on layer 2/3 (L2/3) occurs during sensory processing and short-term memory in a discrimination task is not known. Here, we used wide-field calcium imaging in head-restrained mice to measure task-related activity patterns across the entire dorsal cortex in one hemisphere. We selectively targeted L6 and L2/3 by using the Ntsr1-Cre and Rasgrf2-2A-dCre transgenic mouse lines, respectively, crossed to a GCaMP6f reporter line. The mice were trained to perform a 'go/no-go' texture discrimination task, where they sensed and differentiated with their whiskers between two presented textures: rough (P100), and soft (P1200) sandpaper. After the sensation period, the mice have a >2 s response delay, during which they maintain task-relevant information to finally report their response: lick in order to obtain a reward for the 'go' texture (hit), or refrain from licking in order to avoid a white noise punishment for the 'no-go' texture (correct rejection). We found that it is possible to perform wide-field calcium imaging with indicator expression in deep cortical layer 6. We observed mesoscale calcium signals that were clearly correlated with the task and trial types. As preliminary finding, we found in three L6-CaMP6f mice higher activity in posterior association areas during the delay period in correct rejection trials than in hit trials. This observation is opposite to what we previously found for L2/3 activity. Our results thus appear consistent with a modulatory effect between L6 and L2/3 for the maintenance of short-term memory in the mouse cortex during sensory discrimination.

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Poster

480. Touch: Barrel Cortex I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 480.07/BB2

Topic: D.04. Somatosensation: Touch

Support: DFG research group on Barrel Cortex Function (BaCoFun)

Title: A comprehensive study of layer 6A synaptic microcircuits in rat barrel cortex using paired patch-clamp recordings

Authors: *G. QI[1], D. YANG[1], D. FELDMEYER[1,2,3]
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Abstract: Neocortical layer 6A (L6A) is the principal source of cortico-thalamic feedback which is involved in the top-down control of attention and gain modulation. Principal cells (PCs) in this layer fall into three distinct groups with different axonal projection patterns, namely cortico-thalamic (CT), cortico-cortical (CC) and cortico-claustral (CCl) neurons. In addition, diverse types of L6A GABAergic interneurons exist. L6A synaptic microcircuits are not as well investigated as those in other cortical layers. Here we studied the electrophysiological and morphological properties of L6A synaptic connections using paired patch-clamp recordings and simultaneous biocytin labeling in the somatosensory (barrel) cortex of rats. L6A excitatory-excitatory (E-E) connections (n=44) had a low efficacy with a mean EPSP amplitude of 0.4 ± 0.3 mV. In response to paired presynaptic APs, EPSPs showed either weak depression or facilitation with a mean paired-pulse ratio (PPR) of 1.3 ± 0.7. Presynaptic neurons were predominantly CC (n=38/44) with rest being either CCl (n=3) or CT (n=3) cells. When presynaptic neurons were CT cells the connections showed strong short-term facilitation. Four E-E pairs between CC cells were reciprocally coupled. In addition, connections between L6A PCs located in two neighbouring columns were also recorded. Notably, in nearly all (n=5/6) transcolumnar connections, presynaptic neurons are CC cells and postsynaptic neurons are CT cells. L6A excitatory-inhibitory (E-I) connections (n=20) had an average EPSP amplitude of 0.6 ± 0.7 mV and a PPR of 2.2 ± 2.2. Presynaptic neurons were predominantly CC cells (n=15/20) and postsynaptic neurons both fast spiking (FS) (n=10) and non-FS (n=10) interneurons. L6A inhibitory-excitatory (I-E) connections (n=15) had a mean IPSP amplitude of 0.7 ± 1.1 mV and a PPR of 0.9 ± 0.3. Pre- and postsynaptic neurons were predominantly FS interneurons (n=12/15) and CC cells (n=13/15), respectively. Nine E-I/I-E pairs between CC cells and FS interneurons were reciprocally connected. For connections between CC cells and interneurons, FS and non-FS interneuron connections showed depression and facilitation, respectively while for connections between CT cells and interneurons, all (n=5/5) showed facilitation regardless of interneuron type. In conclusion, L6A synaptic connections are mainly formed by CC cells and their synaptic connectivity does not markedly decline with increasing inter-soma distance. L6A E-I/I-E connections are mainly between CC cells and interneurons; their short-term synaptic plasticity and hence neurotransmitter release probability depends on pre- and postsynaptic neuron types.

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Poster

480. Touch: Barrel Cortex I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 480.08/BB3

Topic: D.04. Somatosensation: Touch

Support: SC3GN122657

Title: Exploring the role of microglia and the perineuronal net as effectors of plasticity during barrel cortex development

Authors: A. C. BARRIENTOS[1], J. E. MUNOZ[3], *J. C. BRUMBERG[4,2]
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Abstract: Organisms rely on touch to make sense of their environment and adapt to it. To better understand how tactile experience shapes the brain, it is necessary to study the interaction of the cellular and molecular constituents in the primary somatosensory cortex (S1) during critical period development. Using the mouse barrel cortex as a model system, we examined two key components in neural development and plasticity: Microglia (MG) and the Perineuronal Net (PNN). In early post-natal development, MG fine-tune the cortical grand wiring diagram in an experience-dependent manner by strengthening synapses while also removing weak or dying synapses. Mature PNNs emerge at the closure of developmental critical periods, “cementing in” past alterations, thereby restricting plasticity into adulthood. Previous work from the laboratory has shown that sensory deprivation via whisker trimming leads to activation of MG, and a reduction in PNN density across cortical laminae. To determine whether extrinsic manipulations that trigger MG activity during S1 critical period development would yield similar effects on the PNN comparable to sensory deprivation, we altered the physiological state of MG with pharmacological agents through random assignment of IP injections of saline (control), minocycline (a MG inhibitor) and lipopolysaccharide (LPS; an inflammatory agent) to C57BL/6 mouse litters. Pups received injections every third day until post-natal day 30. We examined MG density, morphology and PNN density using immunohistochemical and histochemical staining and stereology (Neurolucida, StereoInvestigator). We hypothesized that LPS-treated mice would show greater activated MG and fewer PNNs relative to minocycline- and saline-treated mice. Preliminary work indicates that minocycline and LPS treatment led to significant differences in the morphology of the MG. In general MG soma contours and process features varied between the two groups. We found no significant differences in PNN density. This suggests that MG activity may not be sufficient to effect alterations in PNN density. Perhaps other cellular mechanisms interact with PNNs to modify them or destroy them during cortical development.

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Poster

480. Touch: Barrel Cortex I

Location: SDCC Halls B-H

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Program #/Poster #: 480.09/BB4

Topic: D.04. Somatosensation: Touch

Support: Rutgers Brain Health Institute Pilot Grant (DJM, JMT)
NIH R01 NS034865 (JMT)
NIH R01 NS094450 (DJM)

Title: Opposing influence of distinct cortical inputs on striatal circuitry and behavior

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Abstract: The striatum is the main input nucleus of the basal ganglia and receives excitatory afferents from neocortex and thalamus. It is largely unknown 1) how corticostriatal inputs from specific cortical areas influence striatal projection neurons and interneurons and 2) whether afferent input from sensory and motor cortical areas have distinct effects on behavior. Here, we interrogated the synaptic connectivity of corticostriatal inputs from primary somatosensory (S1) and motor (M1) cortex and determined their roles in modulating behavior. Channelrhodopsin-2 (AAV1.CamKIIa.hChR2(H134R)-eYFP.WPRE.hGH) was expressed in either S1 or M1. Ex vivo whole-cell recordings were carried out in identified D1 and D2 receptor-expressing medium spiny neurons (MSNs) and parvalbumin (PV)-expressing fast spiking interneurons. Optogenetic activation of either S1 or M1 axon terminals in the striatum revealed marked differences in postsynaptic potential (PSP) amplitude recorded in each of the neuron types depending on the afferent stimulated. Optogenetic activation of S1 terminals elicited larger PSPs in PV interneurons compared to D1 or D2 MSNs, while activation of M1 terminals elicited large and non-preferential responses in all three neuron types. We examined how this circuitry relates to behavior in a sensory-guided discrimination task. Thus, we tested the hypothesis that discrete corticostriatal input biases responding towards facilitation or suppression based on the relative balance of PV and MSN innervation. Head-fixed mice were trained to perform a Go/No-Go task using their whiskers to discriminate between two textures for a water reward. Activation of S1 projections decreased responding, while M1 projections increased responding to Go and No-Go

trials. Given the preferential functional innervation of PV interneurons by S1 inputs, we further tested in PV-ChR2 mice whether direct activation of striatal PV interneurons during the discrimination task induced similar effects to S1 stimulation. Strikingly, activation of PV interneurons decreased responding during Go and No-Go trials. These effects were not observed in open field and rotarod tasks, suggesting that the observed differences in responding were due to task-specific rather than general motor effects of optogenetic stimulation. Overall, we show that S1 and M1 corticostriatal projections induce behavioral suppression and facilitation, respectively. These effects are likely mediated through differential functional innervation of striatal circuitry by these cortical regions.

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Poster

480. Touch: Barrel Cortex I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 480.10/BB5

Topic: D.04. Somatosensation: Touch

Title: Functional connectivity of diverse long-range inputs to the primary somatosensory cortex

Authors: *S. NASKAR, J. QI, S. LEE
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Abstract: The mammalian neocortex is divided into specialized areas that communicate with one another through long-range projections, enabling sensory processing, sensorimotor integration and motor control. However, it is not clear whether there are specific rules that govern circuit mechanisms for cortico-cortical communication. A previous study has demonstrated that excitatory inputs from primary motor cortex (M1) strongly recruit vasointestinal peptide (VIP)-expressing GABAergic interneurons (IN) in primary sensory cortex (S1). The recruitment of VIP INs results in disinhibition of pyramidal neurons by inhibiting somatostatin (SST)-expressing GABAergic INs. A similar circuit has been observed in other primary sensory areas, including visual and auditory cortices. We asked whether the VIP interneuron-mediated disinhibition constitutes a canonical circuit motif for cortico-cortical interactions. Using retrograde viral tracing methods, we first identified the major input areas to the superficial layers of S1. These areas include primary vibrissa-related motor cortex (vM1), secondary somatosensory cortex (S2), contralateral primary somatosensory cortex (cS1), perirhinal cortex (Prh) and posteromedial thalamic nucleus (POm). Based on this anatomical study, we then investigated the functional connectivity from these major input areas to the different neuronal elements in the superficial layers of S1 using optogenetics and whole-cell patch clamp recordings in *ex vivo* preparations. We found that, in contrast to the VIP IN-

mediated disinhibitory circuits from vM1 to S1, long-range projections from different areas preferentially engage specific sets of GABAergic neurons in the superficial layers of S1. For example, projections from S2 and cS1 strongly recruit fast-spiking parvalbumin (PV)-positive neurons. Regardless of the input areas, SST neurons received the weakest long-range inputs. Our results imply that sensory-related feedback information is transmitted to S1 by engaging PV IN-mediated feedforward inhibition, while motor-related feedback information propagates to S1 through VIP IN-mediated disinhibition. Thus, primary sensory cortex may parse information from diverse feedback projections by means of input area-dependent, preferential recruitment of specific types of GABAergic interneurons.

Disclosures: S. Naskar: None. **J. Qi:** None. **S. Lee:** None.

Poster

480. Touch: Barrel Cortex I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 480.11/BB6

Topic: D.04. Somatosensation: Touch

Support: NIH R01 NS045130
Fulbright Graduate Study Award
Carney Institute for Brain Science Graduate Research Award

Title: Persistent gamma spiking in nonsensory fast-spiking cells predicts perceptual success

Authors: *C. I. MOORE, H. SHIN
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Abstract: Gamma oscillations (30-55Hz) are mediated by fast-spiking interneurons (FS) and are believed to serve as a 'template' for temporal coordination of stimulus 'content,' thereby enabling sensory perception. In general support of this view, a prior study found that optogenetic stimulation of FS in the primary somatosensory 'barrel' neocortex (SI) at gamma frequency (40 Hz), starting before and continuing during the sensory input ('peristimulus'), could benefit tactile detection. The view that peristimulus gamma contributes to sensory encoding through temporal alignment of spiking poses a conundrum: How can an oscillation serve as a template for sensory encoding when the stimulus itself drives the mediators of the rhythm (FS), and perturbs its maintenance? Here we found that FS in SI that are not driven by sensory stimuli ('nonsensory FS') show a strong peristimulus gamma in their spiking, and the strength of its expression robustly predicts threshold-level perception. Using tetrode recordings during vibrissa detection in mice, we recorded 197 well-isolated FS. On detected 'hit' trials, nonsensory FS (N = 121) showed persistent spiking at gamma (~25ms peak in inter-spike interval (ISI) distribution) that began before and continued, unperturbed, after vibrissa deflection. These nonsensory FS were

also intrinsically more periodic, with higher regularity in their ISIs than sensory FS (as assessed by coefficient of variation). Within nonsensory FS, a subset (N=60) had distinct peak in the ISI distribution in the gamma range (18.18-33.33ms), and they also showed higher regularity. Nonsensory FS spiking showed only weak coupling with the gamma band local field potential (LFP), while sensory FS showed significantly stronger coupling. This dissociation may explain why prestimulus LFP power negatively predicted detection. A key implication of these results is that a distinct subgroup of interneurons, that is not 'distracted' by sensory input, is the carrier of perceptually-relevant oscillations.

Disclosures: C.I. Moore: None. **H. Shin:** None.

Poster

480. Touch: Barrel Cortex I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 480.12/BB7

Topic: D.04. Somatosensation: Touch

Support: Wellcome Trust Doctoral Training Programme Grant

Title: *In vitro* investigations of predictive coding in the mouse somatosensory system

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Dept. of Physiology, Anat. and Genet., Univ. of Oxford, Oxford, United Kingdom

Abstract: According to the logic of predictive coding, sensory representations fundamentally consist of two main pieces of information: i) internal predictions about the expected patterns of sensory stimulation, formed on the basis of experience and ii) prediction error signals stemming from comparisons between predictions and feedforward inputs which sensory systems are purportedly hard-wired to perform. Here, we present a series of experiments aiming to capture sensory prediction error signals *in vitro*, in the activation patterns of mouse somatosensory cortex exposed to optogenetic stimulation patterns with divergent statistical properties. Moreover, we set out to test the possible anatomical and spectral segregation of the predictive and error signals, based on proposals that prediction errors may be selectively affiliated with gamma-oscillatory activity generated by the superficial cortical layers. In the first series of experiments, S1 slices expressing channelrhodopsin under the CaMKII promoter are exposed to 4 sec. trains of sinusoidally modulated light (10 Hz) which linearly ramps up in amplitude over time. We examine the cortical LFP response during a small fraction of trials (5%) which feature an oddball pulse of an amplitude which exceeds the average at that time-point by 64%, and compare this to conditions under which the same oddball pulse is the statistically dominant type of stimulus (80% frequency). The experiments reveal that, on average, power in the gamma-band (60-150Hz) increases and peak gamma frequency shifts towards higher values (up to 120 Hz) as light

amplitude increases over the course of a stimulus train, and during exposure to the high-amplitude oddball. However there is no evidence that these aspects of oscillatory activity are significantly influenced by whether the oddball stimulus represents the statistical norm versus anomaly. In the second series of experiments, individual barrel columns are exposed to temporally varying (50Hz) custom-made random-dot light mosaics generated using a digital micro-mirror device, designed to engage distinct cell populations in a prescribed sequence. With the use of dual electrode recordings for simultaneous sampling of the superficial and deep layers of the barrel column during stimulation, we are in the process of characterising the oscillatory dynamics of sensory responses to normal versus oddball stimulation patterns.

Disclosures: S. Deleniv: None. **E. Mann:** None.

Poster

480. Touch: Barrel Cortex I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 480.13/BB8

Topic: D.04. Somatosensation: Touch

Support: R21

Title: Exploring circuit plasticity deficits in fmr1 mice during tactile learning

Authors: S. WALKER[1], *S. A. HIRES[1], A. MCGEE[2]
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Abstract: Fragile X Syndrome (FXS) is the most inheritable cause of mental impairment and autism, typically caused by transcriptional silencing of the *Fmr1* gene and the loss of expression of FMRP (fragile X mental retardation protein). FMRP is known to regulate the translation of numerous messenger RNAs, many of which encode synaptic proteins and regulate plasticity. In humans, FXS can be characterized by impaired cognition, hypersensitivity to sensory stimuli, autistic behaviors, and defects in synaptic plasticity. No treatment to reverse the collective pathology has been found, and there is a fundamental gap in our knowledge of how FXS causes mental impairments through alterations in neural circuitry. Mice lacking a functional *Fmr1* gene exhibit several phenotypes similar to FXS and can be used to help us understand what links learning impairments to specific changes in neural circuit organization. We hypothesize that impairment in learning tactile learning assays is driven by reduced synaptic structural plasticity and hypersensitive touch responses in the somatosensory cortex. In this investigation, we perform juxtacellular loose-cell recordings of single neurons in targeted barrels of S1 while the mice perform head-fixed localization tasks with a single whisker. We pair high-speed tracking of whisker positions with the activity of neurons in the corresponding barrel during localization to quantify the force and direction selectivity of excitatory neurons in layers 2-4 of S1 in *Fmr1* and

wild type control mice. We quantify the extent to which tactile discrimination and cortical representation of afferent sensory activity in somatosensory cortex are abnormal in *Fmr1* mutant mice.

Disclosures: S. Walker: None. **S.A. Hires:** A. Employment/Salary (full or part-time):; University of Southern California, Department of Biological Sciences, Neuroscience. **A. McGee:** None.

Poster

480. Touch: Barrel Cortex I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 480.14/BB9

Topic: D.04. Somatosensation: Touch

Support: ERC Grant #633428

Title: *In vivo* structure and function of pyramidal tract neurons and their long range inputs

Authors: *J. M. GUEST, D. UDVARY, M. SEETHARAMA, M. OBERLAENDER
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Abstract: Pyramidal tract neurons (PTs) represent the major output cell type of the neocortex. We have previously shown on the example of the rat barrel cortex that a functional property of PTs is to broadcast cortically processed sensory information to downstream targets and that PTs relay this information in target related manner. In order to further explain the role of PTs in sensory information processing, we found it is necessary to investigate how this specific neuronal cell type receives sensory information. Therefore this study aims to focus on the structure and function of long range inputs of PTs using the example of the rat barrel cortex. We show that by injecting different subcortical regions with an anterograde virus expressing channel rhodopsin coupled with single cell attached in vivo recordings, allows for both mapping long range inputs to PTs and gives access to their electrophysiological responses during optogentic stimulation of these mapped inputs. By reconstructing the full dendritic morphology of individual recorded PTs and quantifying the number of synapses according to long range input region, we report for the first time the relationship between the 3D distribution of synapses along the dendrites of PTs according to input region and their electrophysiological responses to optogenetic stimulation of these different long range inputs.

Disclosures: J.M. Guest: None. **D. Udvary:** None. **M. Seetharama:** None. **M. Oberlaender:** None.

Poster

480. Touch: Barrel Cortex I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 480.15/BB10

Topic: D.04. Somatosensation: Touch

Support: 1U01NS103558

Title: *In vivo* performance of GPCR-based genetically encoded norepinephrine indicators in mice

Authors: *J. ZOU[1], J. FENG[3], J. KIM[1], J. YAO[1], Y. LI[3], S. A. HIRES[2]
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Abstract: Norepinephrine is an important neuromodulator playing roles in regulation of arousal, memory formation and focused attention. While the importance of norepinephrine is largely appreciated, the fine details on when and where the norepinephrine is released when it functions are still unknown. This is mainly due to the lack of tools with high spatial and temporal resolution to identify norepinephrine release. Recently two G-protein-coupled receptor activation-based norepinephrine indicators (GRAB-NE2.1 and GRAB-NE2.2) with different affinity to norepinephrine were developed. In vitro responses are highly specific to norepinephrine with a δF/F ~200%. Here, we assess these indicators' suitability for imaging norepinephrine dynamics in awake, behaving mice. We packaged these GRAB-NE variants in AAV, and determined optimal injection parameters for expression in mouse barrel cortex. Both GRAB-NE2.1 and GRAB-NE2.2 show strong and dense expression in neurons of S1 cortex. We then characterized the response of these 2 variants of GRAB-NE in 6 mice. We quantify the speed and magnitude of responses to following stimulation paradigms: direct chemical activation of GRAB-NE in S1, chemical stimulation of Locus Coeruleus, and whisker-mediated object localization.

Disclosures: J. Zou: None. **J. Feng:** None. **J. Kim:** None. **J. Yao:** None. **Y. Li:** None. **S.A. Hires:** None.

Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 481.01/BB11

Topic: D.05. Olfaction and Taste

Title: Neuronal mechanisms driving kin recognition in zebrafish larvae

Authors: *S. KUMAR, I. DUBOVA, S. CHALASANI
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Abstract: Many animals have evolved machinery to distinguish between their kin from non-kin facilitating altruism in the young and preventing inbreeding in adults. Despite this, less is known about the underlying neuronal pathways driving these behaviors. The transparent vertebrate, zebrafish larva, with large progeny sizes and robust behaviors is ideally suited for a comprehensive analysis of kin recognition. We designed a novel behavioral paradigm and found that larvae that are at least 7 days post-fertilization are able to recognize their kin. Additionally, we used pharmacology to reveal that these animals recognize their kin using olfactory cues. Furthermore, we identified a cluster of neurons in the telencephalon of the 7-day old zebrafish larvae that is specifically activated by kin, but not non-kin cues. Together, our results show that zebrafish larva engages distinct neural pathways to identify kin using olfactory information and generating robust behavior.

Disclosures: S. Kumar: None. **I. Dubova:** None. **S. Chalasani:** None.

Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

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Program #/Poster #: 481.02/BB12

Topic: D.05. Olfaction and Taste

Support: SNF grant 31003A_135196
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HFSP LT000278/2012-LXXX
EMBO ALTF 994-2010
Novartis Research Foundation

Title: Remapping of odor representations in the zebrafish forebrain by inhibitory network plasticity

Authors: *T. FRANK[1], N. R. MOENIG[1], S.-I. HIGASHIJIMA[2], R. W. FRIEDRICH[3]
[1]Friedrich Miescher Inst., Basel, Switzerland; [2]Okazaki Inst. for Integrative Biosci., Okazaki-Shi, Japan; [3]Friedrich-Miescher-Institute For Biomed Res., Basel, Switzerland

Abstract: Intelligent behavior depends on the ability to associate high-dimensional sensory representations with low-dimensional, behaviorally relevant qualities such as valence. Learning of associations involves plasticity at excitatory synapses but it remains poorly understood how this process reorganizes information flow in networks. Moreover, it remains unclear whether learning also modifies inhibitory subnetworks. To address these questions we trained adult zebrafish in an appetitive odor discrimination task and analyzed odor representations in a specific compartment of telencephalic area Dp, the homolog of olfactory cortex. Associative conditioning enhanced the intensity and selectivity of responses to the positively conditioned odor (CS+). Moreover, conditioning reorganized coding space such that the direction of maximal variance represented the appetitive value of odors. Hence, associative conditioning remapped odor space onto a behaviorally relevant axis of valence. Variations in coding space were highly correlated to behavioral variations among individuals. Optogenetic hyperpolarization of interneurons attenuated the representation of the CS+, reversed odor remapping, and reduced inter-individual variations in coding space. These results reveal an individualized odor-to-valence map that is reorganized during learning by plasticity of inhibitory subnetworks.

Disclosures: T. Frank: None. **N.R. Moenig:** None. **S. Higashijima:** None. **R.W. Friedrich:** None.

Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

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Program #/Poster #: 481.03/BB13

Topic: D.05. Olfaction and Taste

Support: NSF 1555891
NSF 1555862
NSF 1555916
NSF 1555933

Title: Optimal encoding of odor concentration for olfactory navigation is approximated by the Hill nonlinearity

Authors: *J. D. VICTOR[1], S. D. BOIE[1], E. G. CONNOR[2], J. P. CRIMALDI[2], G. B. ERMENTROUT[3], K. I. NAGEL[4]
[1]Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY; [2]Civil, Environmental, and Architectural Engin., Univ. of Colorado, Boulder, CO; [3]Mathematics, Univ. of Pittsburgh, Pittsburgh, PA; [4]Neurosci. Inst., NYU Langone Med. Sch., New York, NY

Abstract: Olfactory navigation is a sensorimotor behavior that is critical to the survival of a wide range of organisms. It is made computationally challenging by the turbulent nature of

natural olfactory plumes. Evolutionarily successful organisms accomplish olfactory navigation by making navigation decisions on a moment-by-moment basis. These decisions are necessarily based on a limited knowledge of the odor plume. Limitations arise not only because measurements are restricted to sensor's locations, but also because the sensors have limited accuracy and bandwidth. Our focus here is how these limited resources are best used. We take an information-theoretic approach: how can odor concentration be encoded into a fixed number of bits in a way that maximizes information about location within a plume? Recently, we showed that for single samples, little is gained by increasing the resolution for odor concentration beyond 3 to 4 bits (8 to 16 levels). Here, we ask how these levels are best used, i.e., how can the range of odor concentrations be segmented into a set of coding levels, to maximize information about location. To answer this question, we developed a dynamic-programming algorithm to determine this optimal segmentation. The algorithm was then applied to spatiotemporal odor distributions obtained via planar laser-induced fluorescence measurements of real plumes. We analyzed five plumes, with realistic advection speeds (5 to 20 cm/s), with and without a nearby boundary or obstacle, and nine sampling-point grids within each plume. Across conditions, the optimal segmentation strategy emphasized resolution at the higher odor concentrations, indicating that while infrequent, high concentrations provide a disproportionate amount of location information. Next, we compared this coding strategy to histogram-equalization (HE). HE, in which the range is divided into segments of equal probability, is optimal for reconstructing a sensory input, but not necessarily for other tasks. Compared to HE, the optimal coding strategy for navigation devoted more resources to discriminating among the high odor concentrations. Finally, we considered a process in which odor concentration is first transformed by a Hill nonlinearity associated with receptor binding, and then the fraction of bound receptors is linearly encoded. This results in near-optimal allocation of coding levels, provided that the binding constant is near the mean odor concentration at the sampling points. These findings suggest that the saturation nonlinearity associated with the biophysics of the earliest stage of olfactory information processing plays an important computational role in navigation.

Disclosures: J.D. Victor: None. **S.D. Boie:** None. **E.G. Connor:** None. **J.P. Crimaldi:** None. **G.B. Ermentrout:** None. **K.I. Nagel:** None.

Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 481.04/BB14

Topic: D.05. Olfaction and Taste

Support: Grants in Aid from the Ministry of education, Science, Sports and Culture of japan, 14599003 (Principal Investigator), Analysis of molecular mechanisms of caspases during development (1/4/2002-31/3/2004)

Title: Olfactory function is impaired in Olfaxin-deficient mice

Authors: *S. ISLAM[1,2], M. UEDA[1,3], E. NISHIDA[1], M. WANG[1], M. ITOH[1], K. NAKAGAWA[1], T. ANA[1], T. NAKAGAWA[1]
[1]Gifu Univ. Grad. Sch. Med., Gifu, Japan; [2]BCSIR laboratories Chittagong, Chittagong, Bangladesh; [3]Inst. for Developmental Research, Aichi Human Service Ctr., Achi, Japan

Abstract: We found that Olfaxin is involved in odor preference and olfactory memory influencing the expression of NMDAR subunits.
PRUNE2, one of Bcl-2/adenovirus E1B 19 kDa-interacting proteins (BNIPs), plays critical roles in several cellular processes such as cellular transformation, apoptosis, neuronal differentiation, and synaptic function through the BNIP2 and Cdc42GAP homology (BCH) domain. *PRUNE2* has five isoforms: PRUNE2: BCH motif-containing molecule at the carboxyl terminal region 1 (BMCC1)-1; C9orf65: BMCC1-2; BMCC1: BMCC1-3; BNIP2 Extra Long (BNIPXL): BMCC1-4; and Olfaxin/BMCC1s. Olfaxin share 56.3% amino acid identity with Caytaxin. Olfaxin and Caytaxin are alike in their glutamatergic terminal localization, kidney-type glutaminase (KGA) interaction, and caspase-3 substrate. Olfaxin is predominantly expressed in mitral and tufted cells in the olfactory bulb (OB), while Caytaxin is localized in cerebellar granule cells, whose deletion causes Cayman ataxia. At the present, the role of Olfaxin in glutamatergic neuron is largely unknown.
In order to characterize Olfaxin, we generated a *Prune2* gene mutant mice ($Prune2^{Ex16-/-}$; knock out [KO] mice) using the CRISPR/Cas9 system, which deletes the exon 16 containing start codon of *Olfaxin* mRNA. Although four of five Prune2 isoforms including PRUNE2, BMCC1, BNIPXL, and Olfaxin/BMCC1s contain Ex 16, homozygous KO mice were born at the expected Mendelian ratios and morphological change was not observed in the brain. Olfaxin mRNA and protein were deficient in OB and piriform cortex. Using video recording and an automated tracking system, we measured time spent sniffing in the door preference test by urinary scents of the opposite-sex and nonsocial odor stimuli (almond extract), as well as in the odor-aversion test. We observed the impairment of odor preference and olfactory memory in KO mice. Interestingly, the switching of NMDAR2A/NMDAR2B subunits composition in the piriform cortex was affected in KO mice, coinciding with decrease of BDNF expression and increase of Kv 4.2 expression at postnatal day 14 in KO mice.
Since 87% of amino acids are identical between mouse and human Olfaxin, investigation of the role of human Olfaxin will be really interesting because impairment of odor perception is confirmed in patients with early-stage Alzheimer's disease.

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Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 481.05/BB15

Topic: D.05. Olfaction and Taste

Support: NSF BRAIN 1555880
NIDCD Grants R01 DC011286
R01 DC014723

Title: Mouse detection of fluctuating odors based on odor plume properties

Authors: *A. GUMASTE[1,2], E. CONNOR[3], J. CRIMALDI[3], K. NAGEL[4], J. VERHAGEN[2,1]
[1]Neurosci., Yale Univ., New Haven, CT; [2]John B Pierce Lab., New Haven, CT; [3]Dept. of Civil, Envrn. and Architectural Engin., Univ. of Colorado, Boulder, CO; [4]Neurosci. Inst., NYU Langone Med. Sch., New York, NY

Abstract: Odor-based navigation is critical to animal survival as animals depend on olfactory cues to locate food sources, find mates, and avoid predators. Odors in nature are often carried by turbulent air flow, producing plumes with complex spatiotemporal structure. In large naturalistic environments, odor plumes become filamentous and characterized by odor fluctuations with highly varying intermittency. Such complex odor information must be actively sampled through sniffing, integrated by the olfactory system, translated into odor identity, and ultimately, drive behavior. However, little is known about how animals actively sample fluctuating odor stimuli to detect relevant stimulus properties and how this sniff-dependent odor sampling is encoded by olfactory sensory neurons. In a collaborative effort, we have designed a go-nogo task that implements turbulent odor plumes, characterized by Planar Laser Induced Fluorescence (PLIF), as stimuli. More specifically, we have trained water-regulated OMP-GCaMP6f mice to discriminate between static and dynamic odor sequences as well as between dynamic odor sequences with varying plume statistics. If animals lick following the presentation of a S+ stimulus (in some instances a static odor), they receive a water reward, however if they lick following the presentation of a S- stimulus (in some instances a dynamic odor), they receive an aversive salt solution. As animals are performing the task, we simultaneously record sniffing responses as well as image neural activity of mature olfactory sensory neurons in the dorsal olfactory bulb. Using this behavioral paradigm, we have been able to expand the current understanding of the sniffing strategies implemented by animals to detect fluctuating stimuli and the extent to which animals can detect certain properties (mean, variance, and intermittency) of dynamic odor plumes. Additionally, we have explored how neural encoding of fluctuating stimuli depends on sniffing patterns.

Disclosures: A. Gumaste: None. **E. Connor:** None. **J. Crimaldi:** None. **K. Nagel:** None. **J. Verhagen:** None.

Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

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Program #/Poster #: 481.06/BB16

Topic: D.05. Olfaction and Taste

Support: NIDCD (Grant 1R01DC015827)
NSF (Grant 1652647)

Title: Sensorimotor transformation in odor modulation of locomotion

Authors: *L. TAO, S. OZARKAR, J. BECK, V. BHANDAWAT
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Abstract: Odors affect many aspects of an animal's behavior including its locomotion. Different odors activate different patterns of olfactory receptor neurons (ORNs). Understanding the strategy by which an animal searches its environment and how this search pattern is affected by the different patterns of ORNs activated will give insight into the sensorimotor transformations along the olfactory system. *Drosophila* is an excellent model organism to study this transformation because of its relative simplicity, the availability of genetic tools and because odors have a marked effect on its locomotion. In this study we employ optogenetic stimulation, *in vivo* physiology, quantitative behavioral analysis and computational modeling to uncover the principles underlying odor modulation of locomotion.

This study focuses on 7 ORN classes out of ~60 in the flies that were previously shown [1] to be activated by apple cider vinegar, a food odor and a potent attractant which has a marked effect on a fly's locomotion. We created a circular arena 8 cm in diameter; within this arena a central 2.5 cm circular region was irradiated with red light. Different combinations of the 7 ORN classes were activated by genetically controlling which ORNs expressed red-light activated channelrhodopsin - *Chrimson*. Using the instantaneous head position of the flies and the measurement of light intensity in the arena, we were able to recreate the light stimulus in an electrophysiological rig to measure the spike responses in the ORNs to measure ORN input. The fly's behavior was modeled using a 2-layered Hierarchical Hidden Markov Model (HHMM) which was fit to instantaneous kinematics of the fly's locomotion.

We found that a fly's locomotion in our arena is characterized by 6-12 locomotor features such as stop, slow walking with sharp turn, fast left turn etc., which describes its locomotion over a few hundred milliseconds to seconds. Odors do not alter the locomotor features employed by the fly; rather they modulate the frequency with which each locomotor feature is employed by the fly. Activation of different ORN classes affects different locomotor features differentially

suggesting a modular organization between ORN activation and its effect on locomotion.
References
1. Jung, S. H., Hueston, C. & Bhandawat, V. Odor-identity dependent motor programs underlie behavioral responses to odors. *Elife* 4, doi:10.7554/eLife.11092 (2015).

Disclosures: L. Tao: None. **S. Ozarkar:** None. **J. Beck:** None. **V. Bhandawat:** None.

Poster

481. Olfaction: Perception and Behavior

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 481.07/BB17

Topic: D.05. Olfaction and Taste

Support: NIH U01NS090498

Title: Simple readout models of spatio-temporal olfactory activity predict behavioral responses

Authors: *E. CHONG[1], M. MORONI[2,3], M. ADAME[4], S. PANZERI[2], D. RINBERG[1]
[1]NYU Neurosci. Inst., New York, NY; [2]Inst. Italiano Di Tecnologia, Rovereto, Italy; [3]Ctr. for Mind and Brain Sci. (CIMeC), Univ. of Trento, Trento, Italy; [4]Div. of Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: Odorants evoke precise spatio-temporal patterns of activity in the olfactory bulb (OB). Previous studies suggest that fine spatial or temporal features in these patterns can potentially encode odor information. However, it remains unclear how olfactory perception is structured on OB patterns. Specifically, how does perception vary along individual and combined feature dimensions? To test this, we developed a novel experimental framework using optogenetic stimulation patterns as 'artificial odors'. This allowed us to achieve fine, parametric manipulation of OB patterns that was not previously possible using conventional odorant manipulations. We first trained mice on a two-alternative-forced choice task to discriminate target patterns from non-target patterns. After mice were well trained (>80% accuracy), we performed perturbations on target patterns and quantified animals' target recognition.
Our results reveal that both small spatial or temporal perturbations in the target pattern impaired target recognition, in line with several prevailing hypotheses of the olfactory code. Furthermore, spatial components occurring earlier in time have a greater impact on target recognition than later-occurring components, supporting a previously-found 'primacy' code for odors.
Unpredicted by previous hypotheses, perceptual distances are linear or graded in proportion to the size of perturbation. We quantified these results by building logistic regression models, and tested the possibility of higher-order structure in patterns which are revealed by non-linear interaction effects between perturbations. Finally, a combined process model can account for the behavioral data.

Disclosures: E. Chong: None. **M. Moroni:** None. **M. Adame:** None. **S. Panzeri:** None. **D. Rinberg:** None.

Poster

481. Olfaction: Perception and Behavior

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 481.08/CC1

Topic: D.05. Olfaction and Taste

Support: NSF1555916 (Urban)

Title: Strategies for odor source localization in mice

Authors: *A. E. PAPALE[1], A. LIU[2], J. HENGENIUS[3], K. PATEL[4], B. ERMENTROUT[3], N. N. URBAN[1]
[1]Dept. of Neurobio., [2]Sch. of Med., [3]Dept. of Mathematics, [4]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Navigation across an odor landscape to locate a food source is a critical foraging behavior for mice. To study this behavior, we developed an odor source localization task where mice forage for a small food reward placed at an odor spot on a large open field table. We then examined search and approach behavior as they navigated toward the odor source. Hungry mice were trained to associate a methyl salicylate (wintergreen) odor stimulus with a food reward. After training, mice were able to successfully locate odor sources above chance levels, even in the absence of a food reward at the odor source. Data show that mice reliably display several behaviors as they approach the odor source. At greater than 20cm away, mice orient toward the source during successful trials. Within 20cm, mice display progressively increasing dwell times closer to the source, increased 'casting' behavior, defined as the absolute curvature of the nose, and, finally, decreases in velocity. Velocity decreases during approach were only seen during successful trials, suggesting the possibility of a speed-accuracy trade-off in search behavior. While modeling suggests that success rate and search time should be concentration-dependent, we did not find any effects of concentration on these variables. Planned future studies will test for concentration-dependent effects using a wider range of concentrations, and with different solvents for the methyl salicylate odor. We have also developed an automated odor source localization task that does not require baiting the odor source with a food reward, allowing for greater numbers of trials per session. Preliminary analysis of the automated task supports our conclusions about odor source localization strategies in mice. Together, these results suggest that mice proficiently use olfactory sensory cues to locate an odor source, and their approach behaviors vary systematically as a function of distance from the odor source.

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Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 481.09/CC2

Topic: D.05. Olfaction and Taste

Support: Grants: NIDCD R01 DC014367

Title: Retro- and orthonasal olfaction interaction in rats

Authors: *R. HE[1,2], L. M. KAY[1,2]
[1]Psychology, The Univ. of Chicago, Chicago, IL; [2]Inst. of Mind and Biol., Chicago, IL

Abstract: Odorants entering orthonasally are frequently related to external environments, whereas retronasal odorants are integrated with taste and orosensory stimuli to generate flavor perception. We aim to examine whether the two olfactory routes give rise to similar perceptual qualities and interact during a learning process. Rats were pre-conditioned to odorized solutions retronasally with a customized lick spout and a vacuum nearby, which removed orthonasal odorants away from the animal's nares. We then tested the animals in an orthonasal Go/No-Go odor discrimination task but failed to find significant improvements in learning rate and overall performance for the retornasally pre-exposed odors. The negative result is consistent with the hypothesis that an odorant may generate qualitatively different percepts. Local field potential recordings in the olfactory bulb, the olfactory tubercle and the piriform cortex show odor-evoked oscillation power in beta and gamma band for both routes. However, preliminary power spectral density and coherence analysis indicate different temporal patterns of oscillatory events and coherence structure, suggesting that retro and orthonasal learning may be supported by different olfactory network configurations, perhaps leading to different perceptual quality.

Disclosures: R. He: None. **L.M. Kay:** None.

Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

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Topic: D.05. Olfaction and Taste

Support: NIH Grant R00-DC-012803

NIH Grant R01-DC-016364

Title: Nasal breathing modulates functional connectivity of the bed nucleus of the stria terminalis

Authors: *G. LANE[1,2], G. ZHOU[2], T. NOTO[2], J. JIN[4], G. ARABKHERADMAND[3], N. ARORA[2], C. ZELANO[2]
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Abstract: Nasal breathing, which is synonymous with olfactory sampling, impacts local field potential (LFP) oscillations in both olfactory and non-olfactory limbic brain regions, including the amygdala, which is heavily connected to olfactory structures. In the human amygdala, nasal (not oral) inhalation enhances delta and theta range (1-8 Hz) amygdala LFPs. Furthermore, electrical stimulation of the amygdala causes respiratory arrest, but only during nasal, not oral, breathing. These findings suggest a key role for the amygdala in respiratory control that is unique to the nasal breathing route, raising the possibility that the amygdala plays a role in complex sniffing behaviors. In order for sniffing to occur, autonomic respiratory centers must be overridden, allowing conscious control over nasal respiration. The amygdala may impact autonomic breathing via the bed nucleus of the stria terminalis (BNST), an extended region of the amygdala with extensive anatomical connections to the brainstem. Here, we set out to test the hypothesis that breathing route (nasal/oral) alters the intrinsic functional circuitry of the BNST. Resting functional magnetic imaging data were collected from 17 subjects who performed 15 min of both nasal and oral breathing. Seed-based whole-brain functional connectivity maps were calculated for each condition using the BNST as a region of interest. Preliminary analyses suggest that the BOLD time series in BNST and the pons are more strongly correlated during nasal compared to oral breathing (whole-brain corrected $p < 0.05$). These findings suggest that interactions between autonomic respiratory centers and limbic regions may contribute to the neural mechanisms underlying nasal breathing, sniffing and emotional processing. This study was supported by National Institutes of Health Grants (NIDCD) R00-DC-012803 and R01-DC-016364 (to C.Z.).

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Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 481.11/CC4

Topic: D.05. Olfaction and Taste

Title: The effect of aroma inhalation on cortical oscillation recorded by magnetoencephalography

Authors: *S. YAMAMOTO[1], T. YANAGISAWA[2], R. FUKUMA[2], A. TANIYAMA[2], M. SAKAUE[2], K. MAEDA[2], H. KISHIMA[2]
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Abstract: *Background*
Aroma inhalation has been found to change cortical oscillation, while the linalool which is contained in lavender essential oil (LEO) has been found to inhibit glutamate binding in the cerebral cortex. Based on these findings, we hypothesized that aroma inhalation has two effects on cortical oscillation: the odor effect and the pharmacological effect.
Previous research suggests that different essential oils target specific areas of the brain, Whereas previous analyses used electroencephalography, we used magnetoencephalography (MEG), which has higher spatial resolution than electroencephalography, to analyze which finely parcellated areas of the brain are affected by aroma inhalation in more detail.
Method
The participants were 17 healthy volunteers. Each of them inhaled three kinds of aroma (LEO, grapefruit essential oil [GEO], and synthetic lavender fragrance oil [SLFO]) in random order as a cross-over trial. Each participant's mood was evaluated using a Short Form of the Profile of Mood States (POMS), which measures six different dimensions of mood, before and after inhaling each essential oil, and MEG signals were recorded while participants were at rest. Cortical currents were estimated on 15,000 vertices by the minimum norm method. The mean power spectrum was calculated for six frequency bands (δ: 1–3 Hz, θ: 3–8 Hz, α: 8–13 Hz, β: 13–25 Hz, low γ: 25–50 Hz, and high γ: 70–110 Hz) in 360 regions of interest (ROIs) based on the Human Connectome Project.
Results
POMS scores for confusion and vigor were significantly lower after inhalation of GEO compared to LEO. The POMS score for confusion was significantly lower after inhalation of GEO compared to SLFO.
According to a one-way ANOVA, each aroma had a different effect on cortical oscillation. In ROI-based analysis, the effects of LEO and SLFO on beta frequency band power spectrum were significantly different at the left perientorhinal cortex and the left temporal fusiform cortex ($p < 0.05$, paired t-test, FDR corrected). We found no ROIs that had a significant correlation with the POMS scores.
Discussion
Both odors and pharmacological agents affect brain activity. The same odors may have different effects on cortical oscillation, possibly due to their specific pharmacological effects.
We could not find the enough supporting evidence to show that specific areas of the brain are related to certain mood dimensions. This is because mood may be related to activity of the deep part of the brain (such as the limbic system), the signals of which are difficult to record with MEG.

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Poster

481. Olfaction: Perception and Behavior

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Program #/Poster #: 481.12/CC5

Topic: D.05. Olfaction and Taste

Support: Israel Science Foundation (770/17)

Title: Functional magnetic resonance imaging of awake behaving mice performing a go/no-go odor discrimination task

Authors: *E. BERGMANN[1], A. RESULAJ[2], G. YONA[1], D. RINBERG[3], I. KAHN[1]
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Abstract: Brain research in animal models, and specifically in mice, provides powerful techniques for precise molecular and cellular manipulations. In contrast, human brain research, which is usually limited to non-invasive imaging methods, focuses on brain-wide network level neural correlates of perceptual and cognitive processes. A fundamental challenge in neuroscience is developing experimental platforms that allow brain-wide network characterization of the mouse brain to support parallel research across species, and to identify new targets for cellular- and systems-level investigations in mice. The current event-related fMRI study combines a temporally precise odor-delivery system, a non-invasive sniff recording methodology and MRI-compatible instruments for water-delivery and lick detection, in order to characterize brain-wide responses in head-fixed mice performing a go/no-go odor discrimination task. Leveraging the high relevance of olfaction to rodent behavior, we were able to train mice on this task in the relatively short period of 4-7 daily sessions and collect hours of data per animal. Using fMRI we identified odorant-specific localized activations in the olfactory bulb, both for the go and no-go odorants, demonstrating topographical organization. In addition, it revealed that correct responses in go trials (‘hits’) are accompanied by activation of the premotor cortex, which precede an extensive recruitment of multiple brain regions including somatosensory and association (prelimbic, anterior cingulate and retrosplenial) cortices, sub-cortical reward areas (nucleus accumbens, ventral tegmental area), caudoputamen, hippocampus and thalamus. Collectively, these results show the engagement of cortical and sub-cortical systems in goal-directed behavior, and establish the feasibility of whole-brain functional imaging of the behaving mouse. Future examinations will utilize the precise control enabled by this setup in combination with molecular tools to uncover the neural correlates of perception and cognition in the mouse brain in order to map the information pathways from nose to muscle.

Disclosures: E. Bergmann: None. **A. Resulaj:** None. **G. Yona:** None. **D. Rinberg:** None. **I. Kahn:** None.

Poster

481. Olfaction: Perception and Behavior

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Program #/Poster #: 481.13/CC6

Topic: D.05. Olfaction and Taste

Support: NIH/NIDCD R01DC006213
NIH/NIMH T32 MH017168
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Title: State-dependent olfactory information processing

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Abstract: For most animals, including humans, external stimuli typically lead to sensory perception in the wake state, but not during sleep states. Such state-dependent gating of information flow likely involves the thalamus for most sensory modalities; however, olfactory information, originated in olfactory sensory neurons (OSNs) and transmitted to the olfactory bulb, can reach the olfactory cortices such as the piriform cortex and subsequently the orbitofrontal cortex without the relay of the thalamus. Previous studies suggest that gating occurs in the piriform cortex as odor-evoked responses are reduced during the anesthesia-induced slow-wave state or natural sleep, but interpretation of these studies may be confounded by either the use of anesthesia or different odor stimulations due to state-dependent changes in breathing patterns. To ensure consistent peripheral inputs under different brain states, we used an optogenetic approach by expressing channelrhodopsin-2 (ChR2) in all mature mouse OSNs (OMP-ChR2) or a subset of OSNs (M72-ChR2). We optically stimulated these neurons while recording local field potentials (LFPs) and single-unit activities from olfactory areas in freely behaving mice that naturally switch between brain states. In contrast to previous studies, we surprisingly found similar or larger stimulation-evoked responses in the piriform and orbitofrontal cortices for M72-ChR2 (n=4) or OMP-ChR2 (n=10) mice, respectively, during the sleep state compared to the wake state. Additionally, natural odor stimulations delivered directly into the nasal cavity show similar results. These findings suggest that rather than reduced information flow into the olfactory cortex, the lack of smell perception during sleep is likely due to other mechanisms, which are currently under investigation.

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Poster

481. Olfaction: Perception and Behavior

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Program #/Poster #: 481.14/CC7

Topic: D.05. Olfaction and Taste

Support: NSF Grant 1555916

Title: The behavior of biologically-inspired olfactory navigation algorithms in realistic turbulent odor environments

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Abstract: Olfaction provides animals with vital navigational cues that allow them to avoid threats, find mates, and forage for food. However, the spatial scales of animal navigation are dominated by turbulent fluid flow that produces olfactory stimuli with high spatiotemporal variability. This prevents animals from using gradient ascent methods to localize odors. Experimental evidence suggests that mice use spatiotemporal sniff-to-sniff concentration comparisons during lateral head movements to decide which direction to move in odor trail-following and odor point-finding behavioral tasks. Models provide a means of representing such hypotheses and testing their predictions against data. To that end, we have developed agent-based models A) of the spatiotemporal head "casting" strategy, B) of navigation driven by simultaneously-measured left-right concentration comparisons (representative of arthropod antennal olfaction), and C) of a nonbiological algorithm that navigates using statistical features of a turbulent odor plume (intermittency of concentration fluctuations) to perform both trail-following and source localization tasks. We assess the models' navigation behavior in stochastic simulated odor environments representative of turbulent mixing and in real turbulent plume data obtained by planar laser-induced fluorescence (PLIF). We evaluate each model's performance on trail-following and spot-finding tasks in the stochastic simulated environments and plume source-finding in the PLIF plume. Despite the implicit gradient estimation approaches of the biological models (A, B), we find that they localize sources even in stochastically fluctuating environments. Finally, we compare the behaviors of biologically-inspired (A, B) and nonbiological (C) models with experimental mouse data. We find that, though the spatiotemporal casting strategy (A) conforms most closely to mouse behavior, the left-right spatial strategy (B) outperforms both remaining models on source localization and trail-following tasks.

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Poster

481. Olfaction: Perception and Behavior

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Program #/Poster #: 481.15/CC8

Topic: D.05. Olfaction and Taste

Support: KAKRNHI16K14557
KAKRNHI16H02061

Title: Behavioral state-specific responses of ventral tenia tecta neurons

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Abstract: Ventral tenia tecta (vTT) is an area of the olfactory cortex located in the ventromedial part of the olfactory peduncle in mice. vTT neurons receive olfactory sensory signals from axons of tufted and mitral cells in the olfactory bulb. However, little is known about the anatomical connections among other olfactory cortical areas and other brain regions and functional roles of vTT in odor-guided behavior. First, we performed anterograde and retrograde tracing from vTT and observed that vTT has reciprocal connections with many olfactory areas, including anterior olfactory nucleus and anterior and posterior piriform cortex. We also found that vTT received direct inputs from medial prefrontal cortex. These results suggest that vTT neurons can be driven not only by the olfactory bulb afferent input that conveys odor information but also by association fiber inputs and top-down inputs from many olfactory areas and medial prefrontal cortex. To address the question whether vTT neurons encode behavior-specific signals during odor-guided behavior, we recorded spiking activity of vTT neurons when the mice changed their behaviors between food seeking and eating. For this purpose, mice were trained to associate some odors with sugar reward. After the learning, the mice quickly approached the presented sugar with one of the associated odors on a dish and showed eating behavior. We also conditioned these mice to associate a different odor with aversive consequence after eating. After the learning, the mice approached the sugar with the odor on the dish but then left the dish without eating behavior. Many neurons in vTT showed either increased or decreased in their firing rates during the sequence of approaching and eating behaviors. We also recorded spiking activity of vTT neurons when the mice performed an odor-guided Go/No-Go discrimination task. Because this task can separate the timings of presentation between odors and reward, we can

elucidate whether vTT neurons encode behavioral states or not. Many neurons in vTT changed their firing rates not only during odor exposure but also during approaching, anticipating, and getting reward. These results suggest that many vTT neurons receive behavior-specific signals from the higher centers during odor-guided behaviors.

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Poster

481. Olfaction: Perception and Behavior

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Topic: D.05. Olfaction and Taste

Support: NIDCD Grant R01 DC011286
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NSF BRAIN 1555880

Title: Odor plume source navigation algorithms evaluated in an Arduino robot using pair of spatially separated sensors

Authors: *G. CORONAS-SAMANO[1,2], A. GUMASTE[1,2], R. AXMAN[1], J. HENGENIUS[3], B. G. ERMENTROUT[3], J. P. CRIMALDI[4], J. V. VERHAGEN[1,2]
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Abstract: How animals track odors in their environment has become a challenging question. Olfactory navigation is a critical and complex process by which animals can locate food, detect predators and find mates. In order to study strategies of odor navigation, we modified an Arduino robot with two optimized active gas sensors for odor detection, one light sensor to confirm odor source acquisition and three proximity sensors to avoid hitting the walls in the arena. The robot was placed in a plastic acrylic box (1x1x0.3m) with a laminar air flow rate of 5cm/sec and a turbulent odor plume of an iso-kinetically released odorant. We designed four algorithms as follows: A) the robot turned in the direction of higher odor concentration with constant forward movement, B) as A but also backward movement when the odor concentration was below the baseline, C) the heading was based on the odor concentration gradient change over time and D) as A but constant rotating movement when odor concentration was below the baseline. Every code was tested 10 times under eight different starting positions and four different configurations of the gas sensors (based on distance and angles between them). The control of the plumes and the robot tracking behavior was setup using Noldus Ethovision. Finally, we compared the robot's

data with previous experiments from our lab testing c57bl/6 mice under the same experimental conditions, as well as in silico behavior of models closely approximating the environment and algorithms.

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Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 481.17/DP06/CC10

Topic: D.05. Olfaction and Taste

Title: Behavioral state affects response to stimuli of competing valence

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Abstract: Reproduction and self-preservation are two fundamental, innately driven needs acted upon by natural selection. Animals must make adaptive decisions based upon sensory input and internal states to engage in behaviors that satisfy these critical needs. Such behaviors are often mutually exclusive: for instance, engaging in mating behaviors may expose one to predation; fleeing or hiding from unfamiliar bodies or environments may preclude propagation of the next generation. How animals make such adaptive decisions at the behavioral and neurophysiological levels is not well understood. Here we have utilized the zebrafish model organism to understand the neurobiology of competing reproductive and self-preserving needs. We developed a novel behavior assay to probe the competition of these needs. We then leveraged the optical accessibility of our model system to perform in vivo multiphoton neural activity imaging with genetically encoded calcium indicators to discover neural substrates mediating these behaviors and their control. We found that animals decisively choose just one behavioral outcome as opposed to indecision or a mix of outcomes, and that a trace of this choice can be directly observed from the animals' neural activity patterns. These results demonstrate how animals perform adaptive behaviors when presented with conflicting survival needs, which may represent an evolutionarily optimal strategy.

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Poster

481. Olfaction: Perception and Behavior

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Program #/Poster #: 481.18/CC11

Topic: D.05. Olfaction and Taste

Support: NIH T90DA043219

Title: Linking olfactory codes to behavior using holographic optogenetics

Authors: *J. V. GILL[1,2], G. M. LERMAN[2], S. SHOHAM[3], D. RINBERG[2]
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Abstract: A fundamental goal of neuroscience is to understand how the activity of specific neuronal circuits supports behavior. Determining which aspects of neural activity are used by downstream circuits to guide behavior requires simultaneously manipulating activity while monitoring behavioral readout. The mouse olfactory system is emerging as an ideal model for investigating spatiotemporal coding, given its ease of access for recording and manipulation, as well as its behavioral relevance for the animal. Recent studies have revealed that fine temporal scales are essential to olfactory information processing, but it is unknown which precise features of this code are behaviorally accessible. Recently, we developed a system for simultaneous large-scale 2-photon calcium imaging and holographic stimulation in the olfactory bulb of awake, behaving mice, permitting recording and manipulation of groups of neurons with high spatiotemporal resolution. With this system we have measured odor-evoked activity in broad populations of mitral and tufted cells (MTCs), the projection neurons of the olfactory bulb, and demonstrated the use of this system for closed-loop optogenetic feedback, mimicking natural, stimulus-evoked activity temporally patterned across an intrinsic biological rhythm (respiration). This resolution permits a series of theory-driven experiments to establish the basic rules of MTC code readability by higher brain areas. Specifically, we ask what features of spatiotemporal neuronal activity in the olfactory bulb are *detectable* and *discriminable* by downstream circuits to guide behavior. Initial results of these experiments indicated that mice can detect synchronous optogenetic activation of <20 neurons with high accuracy, suggesting exquisite sensitivity. Further experiments explore how this sensitivity changes as a function of timing, cell type and the odor tuning of targeted neurons.

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Poster

481. Olfaction: Perception and Behavior

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Topic: D.05. Olfaction and Taste

Support: NIH NIDCD R01 DC013779
NIH NIDCD F31 DC016485

Title: Learning-dependent and -independent enhancement of olfactory bulb odor responses following olfactory fear conditioning in awake mice

Authors: *J. M. ROSS, M. L. FLETCHER
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Abstract: The olfactory bulb (OB) glomerular layer is the first site of sensory input to the central nervous system and contributes to cortical processing of olfactory stimuli and subsequent behavioral output. Previous work from our lab in anesthetized animals suggests that olfactory fear learning induces plasticity observed at the post-synaptic glomerular level of the OB, presumably affecting downstream processing; however, there is a paucity of data regarding the extent to which this occurs in awake mice. In addition, associative fear learning often produces fear toward the conditioned stimulus (CS) as well as to similar, unlearned stimuli, a process referred to as generalization. How fear learning affects early sensory processing in awake mice of both learned and unlearned stimuli in relation to behavioral fear responses to these stimuli remains unclear. To address this, odor-evoked glomerular activity patterns were assessed in awake transgenic mice expressing the genetically encoded calcium indicator, GCaMP, in excitatory post-synaptic OB cell populations. Mice were subjected to simple, classical fear conditioning by paired presentations of an odor with foot shock. Before and after associative conditioning, glomerular representations to a panel of similar and dissimilar odorants were imaged, allowing us to investigate glomerular activation to the trained stimulus as well as neutral, untrained stimuli. The results demonstrate that odor-shock pairing non-specifically enhances glomerular odor representations in a learning-dependent manner and increases representational similarity between the CS and non-conditioned odors, potentially priming the system towards generalization of learned fear. Additionally, CS-specific glomerular enhancements remain even when associative learning is blocked; suggesting two separate mechanisms lead to enhanced glomerular responses following odor-shock pairings. As wide-field glomerular imaging encompasses a combination of responses, it is still unclear how these enhanced responses reflect somatic output. Current work is focused on investigating this question using 2-photon imaging of mitral cell activity in awake animals. Future directions include elucidating the mechanisms of fear learning induced OB glomerular potentiation. All

together, these studies will further our understanding of learning-induced plasticity at the initial stages of olfactory sensory processing and how neuromodulation influences this plasticity and shapes behavioural generalization in awake animals.

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Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

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Topic: D.05. Olfaction and Taste

Support: Funded by a CNS Translational Team Science Award from the University of Colorado School of Medicine. PI, Law and Co-PI, Restrepo and NIH grant NS099577

Title: NRG1-IV mice outperform control mice in focused go-no go olfactory discrimination

Authors: *D. RAMIREZ-GORDILLO[1], D. RESTREPO[2], A. J. LAW[3]
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Abstract: Schizophrenia is a complex neuropsychiatric disorder characterized by impaired concentration, working memory, perception and social dysfunction. Several factors including environment and genetics play a role in the development of schizophrenia. Increased expression of alternative transcript IV of Neuregulin 1 (NRG1-IV) has been associated with a increased genetic risk for schizophrenia (Law et al, 2006; Proc Natl Acad Sci U S A. 2006 Apr 25;103(17):6747-52). A novel transgenic NRG1-IV model of schizophrenia risk exhibits abnormal behaviors including impaired sensorimotor gating, discrimination memory and social behaviors (Papaleo et al. J. Neurosci. 36:4859, 2016). Here we conducted a preliminary study of behavioral performance and neural oscillations in the prefrontal cortex and the CA1 region of the hippocampus in NRG1-IV male mice and their littermate controls, using awake behave recording. Mice learned to associate one of two odorants with reward in the associative learning go-no go task. Subsequently, NRG1-IV mice and litter mate controls received double tetrode implants targeted to the medial prefrontal cortex and the CA1 region of the hippocampus. All mice learned to differentiate different pairs of odorants in the go-no-go task. A receiver operating characteristic (ROC) analysis showed that there was difference in the power of local field potential (LFP) oscillations as the mice became proficient in discriminating between two odorants. Unexpectedly, when mice discriminated between low concentrations of mixtures of odorants, the NRG1-IV outperformed the control littermates in odorant discrimination. These novel observations suggest a key role of NRG1-IV in associative learning and the development

of fronto-hippocampal circuitry. How this relates to procedural or sensorimotor learning in schizophrenia, requires further study.

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Poster

481. Olfaction: Perception and Behavior

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Program #/Poster #: 481.21/CC14

Topic: D.05. Olfaction and Taste

Title: Modeling the physicochemical basis of diverse human olfactory percepts

Authors: *J. J. KOWALEWSKI[1], A. RAY[1,2]
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Abstract: The neurophysiological basis of human auditory and visual perceptual content is better defined than olfaction. While olfactory circuits encode molecular identities that drive reflexive behaviors for many species, human olfaction appears filtered by culture, language and individual experience. Traditional olfactory research is limited by the low throughput of human subjects testing. There is subsequently a key role for modern computation and simulation. Using a dataset of 480 odorants, rated by the general public along 21 perceptual qualities, we identified approaches that could improve upon models where the perceptual quality proved challenging to predict by an initial effort to use machine learning algorithms trained on physicochemical features to predict select perceptual qualities. Molecular features that optimally predicted percepts for a completely different sample of trained professionals also mapped onto those selected for semantically similar percepts on the general public data. Given the expectation that odor language and culture should limit such comparisons, we tested models cross-study. A model predicting “sweet” for the professional survey could be used to predict “sweet” from the general public. Yet the perceptual space is large and incompletely understood. We therefore developed an approach to map optimal molecular features onto 147 different odor percept ratings. Clustering based on network density reverse engineered much of the perceptual space. Models using these features were predictive out of sample. Where models failed or succeeded, adding human odorant receptor activities from heterologous assays improved predictions with molecular features alone. These data emphasize human olfactory perception is more structured than thought. Our approach can subsequently be applied to assemble very large theoretical spaces in which algorithms can traverse, offering testable hypotheses for how molecular structure and receptor activity might map onto diverse perceptual qualities.

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Poster

481. Olfaction: Perception and Behavior

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Program #/Poster #: 481.22/CC15

Topic: D.05. Olfaction and Taste

Title: Labels transform the human olfactory perceptual space

Authors: *S. CORMIEA, J. FISCHER
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Abstract: We continually encounter odors in daily life, but we are notoriously bad at identifying their sources. There are few odors we can readily identify and many that we struggle to give any label at all. A correct label seems to transform an odor – to snap its perceptual features into sharper focus. Just how distinct and reliable is our perception of an odor prior to identifying it? And how does learning an odor's identity change its perceptual qualities? One barrier to addressing these long-standing questions has been the challenge of efficiently characterizing a perceptual space for everyday odors. Here, we present a novel method for mapping human olfactory perceptual space. We employ this approach to test whether assigning labels to everyday odors alters their perceived similarity. In three sessions, participants reported the similarity of sets of stimuli by dragging and dropping icons into a circular arena on a computer screen. In Session 1, the stimuli consisted of sixteen unlabeled odors from common food products (e.g. onion, carrot, grapefruit, vanilla), delivered in opaque squeeze bottles. Subjects sniffed the odors and then arranged the icons on the screen, placing similar-smelling items close together and different-smelling items far apart. In Session 2, participants performed the same task, but this time with labels on the bottles identifying the sources of the odors. In Session 3, participants performed the arrangement task based on the odor labels alone, reporting how similar they imagined the odors would smell. To control for any learning that might take place over repeated sessions, we also tested a separate set of participants on each of the three sessions in isolation. For each session, we computed an individual perceptual similarity space for each participant based on his/her collected responses. We found that the spaces were reliably correlated across participants, demonstrating shared structure in how participants perceived the relationships among the odors (leave-one-out correlation analysis; $p<0.001$). Further, the addition of labels in Session 2 altered the perceptual space in a reliable way that could not be fully accounted for by a linear combination of the spaces obtained for the odor-only arrangements (Session 1) and the label-only arrangements (Session 3). These results demonstrate an interaction between the

perceptual qualities of odors and the labels assigned to them: labels systematically shift the perceived similarities of odors from one reliable space to another.

Disclosures: S. Cormiea: None. **J. Fischer:** None.

Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 481.23/CC16

Topic: D.05. Olfaction and Taste

Support: R01 DC016364
R00 DC012803

Title: Perception and neural representation of dichorhinic odor stimuli in humans

Authors: G. ARABKHERADMAND, G. LANE, J. GOTTFRIED, G. ZHOU, *C. ZELANO
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Abstract: Unlike most sensory modalities, olfactory connections from periphery to cortex are mostly ipsilateral. While some cross-talk likely occurs across hemispheres, little is known about the extent of such connections in humans. Here we used psychophysics and functional neuroimaging to ask two questions about human olfaction: 1. Do ensemble patterns in olfactory regions reflect ipsilaterally- or contralaterally-delivered stimuli?, and 2. How does this inform the neural underpinnings of conscious perception of odors? 15 human subjects participated in an odor identification task. The odor stimulus was either monorhinic (same odor to both nostrils) or dichorhinic (different odor to each nostril). Following odor presentation, subjects were asked to select from one of four choices indicating what they smelled: odor A only, odor B only, both, or "other". When presented with dichorhinic stimuli, subjects responded with equal frequency that they smelled either odor A only or odor B only. By examining fMRI ensemble patterns in response to trials where subjects received a dichorhinic mixture but perceived only a single component of that mixture, we were able to ask if the non-perceived odor was still encoded in ipsilateral cortex and how far along the olfactory hierarchical pathway the subliminal odor representation was maintained. Preliminary analysis of data from 15 subjects suggests that subliminal odor representations persist to the level of anterior olfactory nucleus but not in any other subregions of primary olfactory cortex. Interestingly, in orbitofrontal cortex, odor patterns appear to reflect the perceived odor only, even on the side of the brain ipsilateral to the nonperceived odor. While still preliminary, these data suggest that odors are primarily coded ipsilaterally, and that OFC may play a role in conscious perception of odor.

Disclosures: G. Arabkheradmand: None. **G. Lane:** None. **J. Gottfried:** None. **G. Zhou:** None. **C. Zelano:** None.

Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

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Program #/Poster #: 481.24/DD1

Topic: D.05. Olfaction and Taste

Support: R00-DC-012803
R01-DC-016364

Title: Respiration induces phase synchronization of olfactory network in humans

Authors: *G. ZHOU[1], T. NOTO[1], S. SCHUELE[1], J. ROSENOW[1], J. JIN[2], G. ARABKHERADMAND[1], G. LANE[1], C. ZELANO[1]
[1]Dept. of Neurol., Northwestern Univ., Chicago, IL; [2]Psychology, Stony Brook Univ., Middle Island, NY

Abstract: The olfactory system is an important alerting system that detects life-endangering stimuli in rodents as well as in humans. In real life situations, the perception of a smell can come to awareness without active sniffing, which suggests that olfactory brain areas monitor the contents of ongoing autonomic breaths. Previous studies have demonstrated that natural nasal breathing entrains local field potential oscillations in both olfactory and non-olfactory brain regions. Furthermore, odor stimulation can also induce phase synchronization between piriform cortex and hippocampus. Whether this synchronization occurs during natural breathing, in the absence of odor, is unknown. Given the role of the hippocampus in memory encoding during ongoing sensory sampling, we hypothesized that natural breathing could modulate its coupling with primary olfactory regions, such as piriform cortex. In this study, fifteen minutes of resting local field potential data were recorded from 7 epilepsy patients. Functional connectivity between piriform cortex and hippocampus was examined with inter-trial phase locking value (PLV). We found rhythmic modulations in coupling between piriform cortex and hippocampus occurring in phase with natural breathing such that low frequency band PLV (1-8 Hz) increased following inhalation and decreased during exhalation. This finding suggests that resting-state coupling between piriform cortex and hippocampus is tied to the natural respiratory cycle, which might be an energy-efficient implementation of the olfactory alerting system.

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Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

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Program #/Poster #: 481.25/DD2

Topic: D.05. Olfaction and Taste

Support: National Institute on Deafness and Other Communication Disorders grant R01DC015426

Title: Identity prediction errors in human midbrain are computed based on abstract state representations

Authors: *J. SUAREZ[1], T. KAHNT[2]
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Abstract: Adaptive behavior requires the ability to update associations between predictive stimuli and outcomes. Errors induced by mismatches between expected and received outcomes (prediction errors, PE) are thought to provide a computational basis for updating these associations and have been linked to the activity of dopaminergic midbrain neurons. Model-free PE's are defined as discrepancy between the expected and received outcome value. However, recent evidence suggests that midbrain neurons also respond to value-neutral violations in outcome identity. Such identity PE's could be used to update the associative structure of the task environment and may play an important role in model-based learning and decision-making. However, it is unknown whether the brain computes identity expectations and errors in the form of abstract state representations or based on the perceptual identity of the outcome. If PEs are computed based on the perceptual similarity of expected and received outcomes, unexpected outcomes that are dissimilar to expected ones should elicit larger PE's compared to perceptually similar outcomes. If PE's are computed in an abstract space, neural responses should be independent of the perceptual similarity between expected and received outcomes. To test this, we designed a Pavlovian task involving value-matched food odors from two food categories (two sweet and two savory) as outcomes. During fMRI data acquisition, subjects (N=19) performed an outcome prediction task based on learned associations between visual cues and food odors. Unexpectedly to the subjects, associations were changed throughout the task to elicit both between-category and within-category PE's. We found that fMRI activity in the midbrain, dlPFC, and piriform cortex (PC) was significantly correlated with PE's derived from a computational model of identity learning. However, responses to between- vs within-category PE's did not differ in these areas, indicating that PE's do not scale with the perceptual similarly of the outcome. This suggests that PE's are computed based on abstract state representations rather than a space defined by perceptual similarity. Encoding expectations in abstract spaces

allows for sensitive error signals that can detect and update perceptually small mismatches between expected and received outcomes.

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Disclosures: J. Suarez: None. **T. Kahnt:** None.

Poster

481. Olfaction: Perception and Behavior

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 481.26/DD3

Topic: D.05. Olfaction and Taste

Support: CRSNG
FRQS
Parkinson Canada
UQTR research chair

Title: Electrophysiological response to trigeminal stimuli in patients with Parkinson's disease

Authors: *C. TREMBLAY[1], R. EMRICH[2], A. HAEHNER[2], A. CAVAZZANA[2], T. HUMMEL[2], J. FRASNELLI[1,3]
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Abstract: Olfactory dysfunction is a highly sensitive pre-motor symptom of Parkinson's disease (PD). In order to use olfactory testing to screen for PD, it is important to differentiate olfactory dysfunction associated with PD from other olfactory dysfunctions. One potential avenue to do so is the measurement of the trigeminal sensitivity. While there is evidence that patients with olfactory dysfunction show a reduced trigeminal sensitivity compared to controls, previous studies suggested that the trigeminal system does not seem to be impaired in PD. Our objective was, therefore, to measure peripheral (from the mucosa, negative mucosal potential, NMP) and central (event-related potential, ERP) electrophysiological responses to the trigeminal stimulus carbon dioxide in patients with Parkinson's disease and compare them to patients with non-parkinsonian olfactory dysfunction and to healthy controls. Our results show that patients with non-parkinsonian olfactory dysfunction show longer NMP latencies and amplitudes than controls and patients with Parkinson's disease. Moreover, PD patients show larger ERP components than patients with non-parkinsonian olfactory dysfunction. This was despite the fact that olfactory function was significantly diminished in both groups of patients compared to controls. These

results suggest a specific pattern of chemosensory impairment in patients with Parkinson's disease.

Disclosures: C. Tremblay: None. **R. Emrich:** None. **A. Haehner:** None. **A. Cavazzana:** None. **T. Hummel:** None. **J. Frasnelli:** None.

Poster

481. Olfaction: Perception and Behavior

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Program #/Poster #: 481.27/DD4

Topic: D.05. Olfaction and Taste

Support: Volkswagen Stifstung, Niedersächsisches Vorab

Title: Structural plasticity of mushroom body-related dopaminergic neurons in dependence of the nutritional value of food

Authors: *B. COBAN, H. POPPINGA, T. RIEMENSPERGER, A. FIALA
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Abstract: The experience of food with high or low nutritional value can influence behavior, e.g. food-related memory formation and feeding prevalence. The neuronal basis of these alterations that are dependent on the flies' dietary remain unclear. In this study, we use d*rosophila melanogaster* to address the question how the caloric value of the animals' dietary affects behaviors such as olfactory associative learning and food uptake. In particular, we investigated functional and structural changes in neuronal connectivity between dopaminergic neurons (DANs) and intrinsic mushroom body neurons (Kenyon cells).
In order to analyze the effects of long-term feeding experience, three days old adult flies were kept on either hypocaloric, isocaloric or hypercaloric food for seven days. Subsequently, we have quantified the flies' food uptake using a capillary feeder assay (CAFE assay), and we have analyzed the flies' appetitive olfactory learning and short-term memory. Our results show that the calorie restriction causes an increased food uptake and enhancement in appetitive learning, while aversive olfactory conditioning remained unaffacted when the flies were starved for 6 hours before the experiment.
The mushroom body (MB) is a key brain structure involved in associative learning and memory formation. The reinforcing effects of rewarding sugar stimuli or punitive signals are mediated by modulatory DANs innervating distinct compartments of MB. We investigated if modulatory DANs undergo structural rearrangement dependent on the dietary of the flies by measuring the intensity of reconstituted split GFP ("GRASP") across putative synaptic contacts between DANs and Kenyon cells. We found that DANs innervating specifically the γ3 compartment of the MB undergo structural remodeling in dependence of the nutritional value of food, whereas DANs

innervating the other compartments remain unmodified. Upon calorie restriction γ3 DAN innervations onto Kenyon cells decreased significantly. Furthermore, we have investigated if there is any functional change in γ3 DANs which can perhaps be causative for their restructuring. Thus, we have measured intrinsic calcium activity of the cells over a long-term period in a cumulative way using the GFP- based Ca^{2+} indicator CaLexA. We found an increase in the activity of the γ3 DANs upon restriction of the caloric food value. In summary, the caloric value of food re-structures brain connectivity in that it shapes the contacts between specific DANs and Kenyon cells.

Disclosures: B. Coban: None. **H. Poppinga:** None. **T. Riemensperger:** None. **A. Fiala:** None.

Poster

481. Olfaction: Perception and Behavior

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Program #/Poster #: 481.28/DD5

Topic: D.05. Olfaction and Taste

Support: NSFC 31772683

Title: Sublethal dose of thiacloprid impairs honeybees olfactory learning ability by damaging nervous system

Authors: *Y. LIU[1], Z.-W. JING[2]
[1]Inst. of Apicultural, CAAS, Beijing, China; [2]Res. Ctr. for Eco-Environmental Sciences, CAAS, Beijing, China

Abstract: The dramatic loss of bees is a major concern worldwide and has been related to the use of neonicotinoid insecticides which mainly impair nerve cells of bee brain and can cause their behavior abnormalities. Thiacloprid was declared less toxic to bees and used increasingly in the last years. However, little is known about how bees are affected by sublethal dose of thiacloprid. We treated *Apis mellifera L.*with sublethal concentrations of thiacloprid (0.2, 0.6, 1,2 ppm) and determined the effect on behaviors, neuronal apoptosis,and synaptic units in the mushroom bodies. Learning and Memory were significant impaired by 0.2 ppm thiacloprid at 12 d which can induce nerve cell apoptosis in the brain of honeybees. We also found that the synaptic units density in the calyces of mushroom decreased after exposed to sublethal dose of thiacloprid.Here, we provide evidence that thiacloprid damages nervous system and thus impairs the olfactory learning ability.

Disclosures: Y. Liu: None. **Z. Jing:** None.

Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 482.01/DD6

Topic: D.06. Auditory & Vestibular Systems

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Title: Cellular cartography of the organ of Corti based on tissue clearing <and> machine learning

Authors: *S. URATA, T. IIDA, Y. MIZUSHIMA, C. FUJIMOTO, Y. MATSUMOTO, T. YAMASOBA, S. OKABE
Univ. of Tokyo, Tokyo, Japan

Abstract: Spatial organization of hair cells in the organ of Corti, the mammalian auditory sensory epithelium, is a critical parameter that affects sensitivity and ability of frequency discrimination of mammalian hearing. Frequency discrimination is achieved by spatial tuning to specific frequencies along the longitudinal axis of the organ of Corti. The basic tuning pattern is simple, with higher frequencies on the base of the cochlear spiral and lower frequencies on the apex. However, multiple structural, mechanistic, and cell biological factors influence the real shape of the tonotopic map. Therefore, complete understanding of auditory perception requires imaging technology that enables accurate re-construction of the intact, three-dimensional structure of the organ of Corti. Here we report a tissue clearing-based analytical pipeline for the construction of a single-cell resolution map of the organ of Corti. A newly developed clearing method enabled imaging of the entire cochlea, with resolution sufficient to detect intricate subcellular structures of hair cells. We combined the tissue clearing method with machine learning-based pattern recognition. This analytical pipeline enabled high-fidelity detection and determination of total hair cell positions along the entire longitudinal axis of the organ of Corti. We applied this method to samples along the normal course of development and those with noise exposure. The pattern of hair cell damage revealed distinct impacts of aging and noise on hair cell pathology. Thus, our method of cellular mapping is highly effective in system-level phenotyping of the organ of Corti under both physiological and pathological conditions.

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Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

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Program #/Poster #: 482.02/DD7

Topic: D.06. Auditory & Vestibular Systems

Support: This research was funded by Otonomy, Inc.

Title: Development of intratympanically administered neurotrophic factor BDNF for the treatment of speech-in-noise hearing difficulties (cochlear synaptopathy)

Authors: *B. E. JACQUES, N. TSIVKOVSKAIA, R. FERNANDEZ, X. WANG, A. JONES, T. ALTMANN, J. HOU, F. PIU
Otonomy Inc., San Diego, CA

Abstract: Recent evidence from both preclinical and clinical studies indicates that a loss or dysfunction of the ribbon synapses that connect inner hair cells in the cochlea with spiral ganglion neurons (SGNs), whose axons form the cochlear nerve, contributes to hearing impairment. This ribbon synaptopathy is proposed as an underlying pathology in age-related and noise-induced hearing dysfunction and has been hypothesized to explain speech-in-noise hearing difficulties that occur despite normal audiometric thresholds. The application of exogenous neurotrophins, such as Brain-Derived Neurotrophic Factor (BDNF) or Neurotrophin-3 (NT-3), as well as selective high affinity monoclonal antibodies (mAbs) with agonist activities at the Trk receptors, has been investigated as a therapeutic approach based on their ability to provide trophic support to spiral ganglion neurons in the cochlea. In recent studies, BDNF, NT-3 and several Trk agonist mAbs were found to promote survival, neurite extension and synapse restoration in ex-vivo cochlear cultures. The in vivo pharmacokinetic and efficacy profile of OTO-413, a thermosensitive sustained-exposure formulation of BDNF developed for intratympanic round window delivery, was determined in a rat model of noise-induced cochlear synaptopathy. This delivery method provided significant and dose-dependent sustained-exposure of BDNF to the inner ear for several weeks, as determined by ELISA. The evaluation monitored several functional (ABR, wave 1 amplitude) and histological (ribbon synapse counts, hair cell viability) parameters. Following noise-exposure, BDNF administration statistically improved all measures of cochlear synaptopathy throughout the one-month duration of the study. Overall, OTO-413, a sustained-exposure formulation of BDNF, was effective in alleviating noise-induced cochlear synaptopathy in-vivo and demonstrated a suitable pharmacokinetic profile, thereby constituting an attractive and novel therapeutic approach for the treatment of cochlear synaptopathy-associated hearing loss and the preservation of cochlear neurons.

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Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 482.03/DD8

Topic: D.06. Auditory & Vestibular Systems

Support: ANPCyT PICT 2014-0319
ANPCyT PICT 2016-2155
NOHR

Title: Enhancement of the medial olivocochlear system prevents hidden hearing loss

Authors: *L. E. BOERO[1,2], V. C. CASTAGNA[2], J. D. GOUTMAN[1], A. B. ELGOYHEN[1,2], M. E. GÓMEZ-CASATI[2]
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Abstract: Hearing loss is a major public health problem, given that its impact on human communication and quality of life is devastating. Noise exposure has gained relevance as one of the most important sources, although the underlying causes of noise-induced hearing loss are still unknown. Recently, it has been demonstrated that acoustic trauma (AT) producing only transient auditory threshold shifts also produces long-term structural damages to the inner ear, such as a

reduction in the number synapses between inner hair cells (IHCs) and afferent neurons. This has been called hidden hearing loss (HHL) because it is not apparent in an audiogram. Medial olivocochlear (MOC) efferent neurons form a negative feedback gain-control system that inhibits amplification of sounds by the action of acetylcholine on a9a10 cholinergic nicotinic receptors at the base of outer hair cells (OHCs). It has been proposed that activity of the MOC fibers can ameliorate AT effects.
Here we explore the role of the MOC system in HHL by comparing the performance of two different mouse models after AT: an a9 nicotinic receptor subunit *knock-out* (*Chrna9* KO) which lacks cholinergic transmission between efferent neurons and OHCs, and a gain of function *knock-in* (*Chrna9L9'T* KI) bearing an a9 point mutation that leads to enhanced MOC activity. Animals of either sex were exposed to 1-16 kHz noise of 100 dB SPL for 1 hour. This sound pressure levels produced in WT mice transient auditory brainstem responses (ABRs) threshold shifts, a decrease in neural response amplitudes and loss of ribbon synapses, indicative of cochlear synaptopathy. In *Chrna9* KO ears, we also found cochlear synaptopathy but the ABR threshold shifts were permanent. In contrast, the *Chrna9L9'T* KI was completely resistant to the same acoustic exposure protocol. These results show a positive correlation between the degree of HHL prevention and the level of cholinergic activity. Notably, enhancement of the MOC feedback promoted new afferent synapse formation, suggesting that it can trigger cellular and molecular mechanisms to protect and/or repair the inner ear sensory epithelium.
Additionally, we were interested in elucidating if AT could affect the capacity of IHCs to release glutamate. Patch-clamp recordings were performed on IHCs in an ex-vivo cochlear preparation of exposed and control mice. Glutamate release from IHCs was estimated by monitoring cell membrane capacitance with a lock-in amplifier. We found an increase in capacitance changes and Ca2+ currents in noise exposed animals. These results suggest presynaptic overcompensation after acoustic overexposure.

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Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

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Program #/Poster #: 482.04/DD9

Topic: D.06. Auditory & Vestibular Systems

Support: National Institute of Health NIDCD R01 DC000141

Title: Auditory signal envelope processing by the organ of Corti of the guinea pig cochlea

Authors: G. BURWOOD, 97239[1], A. FRIDBERGER[2], R. WANG[3], *A. L. NUTTALL[1]
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Medicine, Cell Biol., Linköping Univ., Linköping, Sweden; [3]Dept. of Bioengineering, Univ. of Washington, Seattle, Seattle, WA

Abstract: The structure and function of the mammalian cochlea permits the perception of speech and music via the envelope of the otherwise complex acoustic signal. Much of this ability is clearly due to post-sensory processing, as cochlear implant users may understand speech with sparse frequency coding provided by their electrode arrays. The organ of Corti itself may possess the ability to relay envelope information, which is not necessarily reflected in the tuning and motion of the basilar membrane. Using optical coherence tomography vibrometry and electrophysiological measures of the intact guinea pig cochlea, we determined the ability of the cochlea to "extract" the signal envelope of a three tone complex at several stimulus intensities. Each tone complex possessed an f1, f2 and f3 subsequently separated by 50Hz, producing a quadratic difference tone of 50Hz. Varying the phase of the f2 had the effect of reducing the amplitude of the envelope component, and this effect was less pronounced at higher stimulus intensities. Based upon these observations of round window cochlear microphonic and mechanical motion of the organ of Corti, it is likely that envelope information is produced by cellular mechanosensory pathways that introduce distortion due to their non-linear nature. Such tissue displacement non-linearities could feasibly permit envelope information to be transduced by the auditory nerve, enabling the interpretation of complex acoustic signals.

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Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

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Topic: D.06. Auditory & Vestibular Systems

Support: NIH NIDCD R01 DC014685
NSF CMMI-1661413

Title: Outer hair cell motility can suppress the organ of Corti vibrations

Authors: *J.-H. NAM, T. JABEEN, J. BECKER
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Abstract: The organ of Corti (OoC) vibrates differently depending the existence of outer hair cell motility. The OoC micro structures vibrate roughly in-phase when passive. In contrast, they vibrate out-of-phase when outer hair cell motility contributes to the vibrations. Theories are divergent on how this difference in OoC vibration modes is related to the cochlear function such as sound amplification or tuning. We used isolated cochlear turns to investigate the vibration

patterns of the OoC when mechanical and electrical stimulations are applied simultaneously. Fresh cochleas were harvested from young gerbil (15-20 days old). To expose a targeted section of the OoC, the bones and tissues of the cochlea were removed so that approximately a single turn of the cochlear coil left. The cochlear turn was attached to a custom-designed micro-chamber. The micro-chamber has two ports for fluid circulation and two ports for pressure application and release (analogous to oval and round windows in the cochlea). It also has a slit on which the cochlear turn is attached. While acoustical pressures and electrical currents were delivered, the vibration amplitudes of the OoC complex were measured along the transverse and radial directions using a laser interferometer. The mechanical stimulations were applied with different time delays (phases) from the electrical stimulations. The measurement data was compared with computer model simulations of the OoC complex. At the measurement location (approx. 8 mm from the basal end), the vibration amplitudes were greater at the tectorial membrane than at the basilar membrane for both stimulation methods. We observed both constructive and destructive interactions between the mechanically and electrically agitated vibrations. This suggests that the outer hair cells' electromotility can not only amplify the OoC vibrations, but also suppress them. The computer model predicts that both constructive and destructive interactions exist under physiological cochlea.

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Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

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Program #/Poster #: 482.06/DD11

Topic: D.06. Auditory & Vestibular Systems

Support: NIBIB 5 R 01 EB018297

Title: A computational model for the effects of auditory nerve heminode disruption on hearing

Authors: *M. BUDAK[1], K. GROSH[2], V. BOOTH[3], M. R. ZOCHOWSKI[4], G. CORFAS[5]
[1]Biophysics, [2]Mechanical & Biomed. Engin., [3]Mathematics & Anesthesiol., [4]Physics, [5]Kresge Hearing Res. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: Hidden hearing loss (HHL) is an auditory neuropathy characterized by normal hearing thresholds but reduced amplitude of the sound-evoked auditory nerve (AN) compound action potential (CAP). It has been proposed that in humans HHL leads to speech discrimination and intelligibility deficits, particularly in noisy environments. Animal models originally indicated that HHL can be caused by moderate noise exposures or aging, and that loss of inner hair cell (IHC) synapses could be its cause. However, Wan and Corfas (2017) provided evidence that transient loss of cochlear Schwann cells also causes HHL in mice. In this animal model, HHL

occurs early in the demyelination process and persists for the animal's lifespan even after Schwann cells regenerate and axons remyelinate. The only histological finding in the mice after Schwann cell regeneration is a permanent disruption of the heminode at the AN peripheral terminals, i.e. while in the normal ear all heminodes are located at the same distance from the hair cell, in the remyelinated animals the heminodes are disorganized and some unmyelinated segments are observed. We constructed a reduced biophysical model for a population of IHCs with 15 postsynaptic AN fibers to elucidate the role the disruption of heminode position has on the transmission of action potential. We then used a probabilistic model to simulate neurotransmitter release from the IHC's synapses in response to different sound levels. Neurotransmitter released at the IHC-AN synapse causes brief axonal depolarizations in the biophysical models. By varying the position of heminodes in the different axons to model the pathology seen after remyelination, we found that the amplitude of simulated sound-evoked AN CAPs is lower and has a greater delay when the heminodes are disorganized, i.e. they are placed at different distances from the hair cell rather than at the same distance as seen in the normal cochlea. Thus, our model confirms that heminodal disruption causes desynchronization of AN spikes leading to a loss of temporal resolution and reduction of the sound-evoked AN CAP.

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Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 482.07/DD12

Topic: D.06. Auditory & Vestibular Systems

Support: CT Institute for the Brain and Cognitive Sciences
American Hearing Research Foundation

Title: To explore the function of C1QL1 protein in cochlea and sound perception

Authors: *J. BISWAS[1], R. PIJEWSKI[2], B. THOMPSON[2], R. MAKOL[2], T. MIRAMONTES[2], A. BURGHARD[2], T. C. SUDHOF[3], D. KIM[2], D. OLIVER[2], D. C. MARTINELLI[2]
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Abstract:
Hearing requires functional inner and outer hair cells of the cochlea. The inner hair cells (IHCs) transduce noise signals to the brain through afferent synapses whereas the electromotile outer hair cells (OHCs) provide sound amplification hence enhancing cochlear sensitivity. The OHCs are susceptible to damage as a result of noise exposure, ototoxic medications, or aging. This is

concerning because hair cells do not regenerate resulting in sensorineural hearing loss. C1QL1 is a presynaptically released secreted protein which promotes synapse maintenance in CNS. Our experimental finding demonstrates the cochlear expression of *C1ql1* selectively in OHCs. To determine the functional relevance of *C1ql1*, a novel conditional knock out (cKO) allele for *C1ql1* in OHCs was developed, allowing a unique opportunity to study the synaptic physiology of OHCs. Using a series of auditory tests, like DPOAE (Distortion Product Otoacoustic Emission), ABR (Auditory Brainstem Response), and AMFR (Amplitude-Modulation Following Response), we observed that cKO mice have lower thresholds for hearing compared to control littermates suggesting that they have enhanced OHC electromotility and improved hearing for low-level sounds compared to wildtype (WT) mice. Moreover, cKO mice startled more than control mice in a test for the acoustic startle response further suggesting their altered hearing abilities. Our findings show that the presence/absence of *C1ql1* affects the OHC's physiological response to acoustic stimuli through a yet-to-be-determined mechanism and makes it a prospective drug target for auditory therapeutics.

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Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

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Topic: D.06. Auditory & Vestibular Systems

Support: PICT 2016-2155 (to JDG)
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NIDCD R01 DC001508 (to PAF and ABE)
NIDCD R01 DC015309 (to PAF)
Firca-NIH 1R03TW009403-01 (to JDG and Elisabeth Glowatzki

Title: Compartmentalization of antagonistic Ca^{2+} signals in developing cochlear hair cells

Authors: *M. J. MOGLIE[1], P. A. FUCHS[2], A. B. ELGOYHEN[1,3], J. D. GOUTMAN[1]
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Abstract: During a critical developmental period, cochlear inner hair cells (IHCs) fire sensory-independent action potentials, crucial for the normal maturation of the auditory pathway. During each action potential, IHCs operate as a presynaptic terminal and Ca^{2+} influx through voltage-

dependent channels triggers the release of glutamate onto afferent dendrites of the auditory nerve. At the same developmental stage, IHCs are the postsynaptic target of efferent cholinergic neurons from the brainstem. This efferent synapse combines the entry of Ca^{2+} through cholinergic α9α10 receptors with the activation of nearby SK2, Ca^{2+}-dependent potassium channels to hyperpolarize the IHC. Thus, efferent Ca^{2+} signals are inhibitory, opposing IHC transmitter release. The aim of our work was to investigate the mechanisms that allow segregation of excitatory versus inhibitory Ca^{2+} effects within the limited diffusional space of the IHCs synaptic pole.
Electrophysiological recordings combined with swept–field confocal Ca^{2+} imaging experiments revealed the existence of multiple Ca^{2+} entry hotspots per IHC upon efferent fiber electrical stimulation. They were concentrated in the basal pole of the IHC in close apposition and intermingled with the afferent hotspots encountered following IHC depolarization. Using serial section electron micrographs we were able to perform IHC reconstructions at a nanometer scale. We estimated an average distance between efferent hotspots and closest afferent neighbors of 1.62 ± 1.11 µm. The intimate localization of antagonist Ca^{2+} entry sites encountered suggests that during normal operation of developing IHCs, efferent Ca^{2+} spread could potentially occur over other synapses. Finally, in order to evaluate a possible efferent to afferent crosstalk, recordings from afferent boutons were performed. Despite the close proximity, even high frequency (80 Hz) electrical stimulation of efferent fibers failed to evoke an increase in the frequency of postsynaptic excitatory currents. On the contrary, locally applied saturating concentrations of ACh elicited Ca^{2+} signals capable of cross-activating afferent release. Electrophysiological and Ca^{2+} imaging experiments in IHCs showed that physical barriers imposed by efferent synaptic cisterns, Ca^{2+} extrusion mechanisms and strong Ca^{2+} buffering prevent efferent to afferent synaptic crosstalk during synaptic activation of cholinergic release. Thus, efferent fibers maintain its inhibitory signature and operate at low frequencies to modulate spontaneous action potential firing in the developing IHC.

Disclosures: M.J. Moglie: None. **P.A. Fuchs:** None. **A.B. Elgoyhen:** None. **J.D. Goutman:** None.

Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 482.09/DD14

Topic: D.06. Auditory & Vestibular Systems

Support: NIDCD R01 DC006685

Title: Spontaneous calcium transients in the mouse utricular macula during the first postnatal week of development

Authors: H. A. HOLMAN[1], L. POPPI[3], Y. WAN[2], *R. D. RABBITT[1]
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Abstract: Prior to the onset of hearing, inner hair cells in the developing cochlea fire spontaneous calcium action potentials, evoking glutamate release from ribbon synapses and modulating firing rates of type I spiral ganglion neurons. This spontaneous activity involves an interplay between calcium transients in supporting cells and hair cells, and is essential to the development of hearing and maturation of tonotopy in the brainstem and higher auditory centers (1-3). In the present work we examined the hypothesis that spontaneous calcium transients are also present during early postnatal development in hair cells and supporting cells in the mouse vestibular organs. All animal experiments were approved by the University of Utah Institutional Animal Care and Use Committee. A transgenic mouse with the calcium indicator GCaMP5G and constitutive reporter tdTomato (4) was crossed with a Gad2-IRES-Cre- driver line (5). GCaMP5G imaging of the utricle was performed ex vivo using a swept field confocal microscope (Prairie) with a 60x water immersion objective (Olympus). Spontaneous G5 (ΔF/F) fluorescence modulation was recorded at a 100ms frame rate over successive optical sections.Results. GCaMP5G imaging revealed spontaneous calcium transients restricted almost exclusively to type I hair cells at birth (P1). By postnatal day 3 (P3) calcium transients in hair cells diminished, while extensive calcium transients developed in supporting cells. Transients in supporting cells at P3 were at the apical end where direct contacts are made with type I hair cells. Spontaneous transients diminished as calyces developed to envelop type I hair cells. Results confirm the hypothesis that spontaneous calcium transients are present in developing utricular hair cells and juxtaposed supporting cells. The temporal sequence of activity suggests that spontaneous calcium transients in type 1 hair cells and neighboring supporting cells likely modulates activity in calyx-bearing vestibular afferents during the first postnatal week, and may play a key role in the maturation of vestibular neural circuits. References: N. X. Tritsch et al.,Nature 450, 50-55 (2007). S. L. Johnsonet al., Proc Natl Acad Sci U S A 110, 8720-8725 (2013). D. H. Sanes, V. Siverls, J Neurobiol 22, 837-854 (1991). J. M. Geeet al., Neuron 83, 1058-1072 (2014). H. Taniguchiet al.,Neuron71, 995-1013 (2011).

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Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 482.10/DD15

Topic: D.06. Auditory & Vestibular Systems

Support: Grant E19 of the Interdisciplinary Centre for Clinical Research (IZKF) at the University Hospital of the Friedrich-Alexander-Universität Erlangen-Nürnberg
DFG Grant EN349/10-1

Title: Expression of group II metabotropic glutamate receptors at ribbon synapses of inner hair-cells

Authors: *R. ENZ, L. KLOTZ
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Abstract: Glutamate is the most important excitatory neurotransmitter in the central nervous system, acting on ion-channel associated (ionotropic) and G-protein coupled (metabotropic) glutamate receptors. In contrast to the post-synaptically localized group I metabotropic glutamate receptors mGluR1 and mGluR5, the localization of pre-synaptic receptors belonging to group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR7 and mGluR8) in hair-cells of the cochlea is largely unknown. General expression of mGluR7 and mGluR8 in inner and outer hair-cells was observed, but a synaptic localization was not investigated in detail. Therefore, we analysed expression and synaptic localization of mGluRs in the cochlea. Reverse-transcription PCR detected mRNA encoding for all known mGluR types in the adult mouse, including common splice-variants, except for the retina specific mGluR6. The sub-cellular distribution of corresponding receptor proteins was analysed in cochlear wholemounts of adult gerbils and mice. Tissue was co-stained with immunesera recognizing various mGluR types and antibodies directed against the C-terminal binding protein CTBP2, a marker for synaptic ribbons localized in pre-synaptic hair-cell terminals. Using confocal microscopy, antibodies binding a conserved epitope in mGluR2 and mGluR3, or immunesera recognizing mGluR4 or mGluR8 resulted in a punctate label in both species, indicating synaptic localization of these receptors. While mGluR4 and mGluR8 were not co-localized with CTBP2, we observed a close proximity between mGluR2/3 and the pre-synaptic ribbon at inner hair-cells synapses. Finally, stimulated emission depletion (STED) microscopy described the distribution of mGluR2/3 relative to the pre-synaptic ribbon in more detail. In summary, we detected expression of all mGluR types, except mGluR6 in the mouse cochlea. MGluR2/3, mGluR4 and mGluR8 showed a punctate appearance, but only mGluR/3 were localized close to pre-synaptic ribbons of inner hair-cells in gerbil and mouse. There, mGluR2/3 might be involved in inhibitory feedback loops that control the amount of glutamate released into the synaptic cleft, thus protecting hair-cells against noxious stimuli. Interestingly, mGluR2 and mGluR3 are both absent from ribbon synapses formed by photoreceptors of the retina. Thus, our data suggests that different sensory neurons need a tailor-made regulation of their neurotransmitter systems.

Disclosures: R. Enz: None. **L. Klotz:** None.

Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 482.11/DD16

Topic: D.06. Auditory & Vestibular Systems

Support: NIH NIDCD Grant R15 DC014843
NSF Grant IOS #1456866

Title: Adaptation of spontaneous and evoked activity in the Zebrafish lateral line

Authors: *D. FROLOV[1,2], E. ISKO[2], S. A. SHORT[2], T. F. SOMMERS[2], J. G. TRAPANI[2]
[1]Univ. of Massachusetts Amherst, Amherst, MA; [2]Amherst Col., Amherst, MA

Abstract: Adaptation dynamically excludes irrelevant or unchanging stimuli from sensory processing. The posterior lateral line (PLL) of zebrafish larvae is an accessible hair-cell (HC) sensory system for the study of adaptation. During mechanical stimulation of hair cells of the zebrafish lateral line while recording action potentials (spikes) from individual afferent neurons, we delivered paired-pulse stimuli with varying stimulus window length and inter-stimulus intervals (ISIs). We observed substantial adaptation between the responses to the first and second pulse. We quantified paired-pulse ratios (PPR) for first spike latency (FSL) and spike rate (SR). By varying the length of ISIs, we calculated time constants of recovery (τ) of adaptation. Preliminary results suggest that adaptation of FSL and SR recovers at different rates, which we hypothesize result from differential replenishment of two distinct vesicle pools at synaptic ribbon. To support this hypothesis, we expanded our dataset across a broader range of physiologically relevant ISIs. Examination of the entire time course of recovery for FSL and SR adaptation showed that FSL fully recovers before SR, consistent with our initial hypothesis. These two forms of adaptation were next shown to be mechanotransduction-independent via paired-pulse stimulation of hair cells with Channelrhodopsin-2. To further probe the role of the synaptic vesicle pools in spike train adaptation, we examined recovery of spontaneous spikes after single-pulse stimuli. First spontaneous spike latency (FSSL) recovery rates were longer than for evoked activity, suggesting a different mechanism of vesicle replenishment at the presynaptic ribbon. The synaptic architecture of the PLL is similar to mammalian vestibular synapses, highlighting its use as model system for the understanding of vestibular encoding.

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Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

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Topic: D.06. Auditory & Vestibular Systems

Support: Otonomy, Inc.
Canadian Institute of Health Research (CIHR) to HUS

Title: Effect of Trk receptor monoclonal antibodies and recombinant neurotrophins on neuron survival, neurite morphology, and synaptogenesis in rat *ex vivo* models relevant to hearing loss

Authors: *S. SZOBOTA[1], P. D. MATHUR[1], S. SIEGEL[1], H. SARAGOVI[2], A. C. FOSTER[1]
[1]Otonomy, Inc., San Diego, CA; [2]Lady Davis Institute-Jewish Gen. Hosp., Montreal, QC, Canada

Abstract: Hearing loss is the most common sensory disorder, affecting approximately 15% of adults in the US. Loss of spiral ganglion neurons (SGNs) and their synaptic connections with the cells of the inner ear plays a major role in decreased speech-in-noise discrimination and other forms of hearing loss. One treatment that has been investigated is the application of BDNF and NT-3, neurotrophins that provide trophic support to SGNs through activation of TrkB and TrkC receptors, respectively. Monoclonal antibodies (mAbs) with agonist activities also have the potential to activate TrkB or TrkC, while providing the potential advantage of biostability. Recombinant BDNF, NT-3, and mAbs were generated and their selectivity for TrkB or TrkC and cross-reactivity between human and rat Trk receptors were evaluated by AlphaLISA and Biacore. Agonist activity was detected as increased phosphorylation of Erk1/2, PLC-gamma, and AKT in Western Blot and AlphaLISA using cell lines that stably express Trk receptors. The ability of BDNF, NT-3, and mAbs to activate native cochlear Trk receptors and promote neuron survival was determined by counting surviving neurons in 96-well cultures containing dissociated rat SGNs that were fixed, immunostained, and imaged on the PerkinElmer Operetta. The most active molecules were then tested in SGN explants and organotypic cochlear cultures from postnatal rats to examine their ability to stimulate neurite growth and synaptogenesis. Effects on neurite length and branching were analyzed using Harmony software neurite detection features (PerkinElmer).
The mAbs selectively bound to either TrkB or TrkC with low nanomolar affinity and activated downstream signaling in TrkB or TrkC -expressing cell lines. The degree of agonism of the different mAbs varied, ranging from partial to full, relative to BDNF and NT-3. Survival of dissociated SGNs was increased significantly with BDNF, NT-3 and mAbs, compared to control cultures. Treatments also increased the number of primary neurites and total neurite tree length. In explanted SGNs, neurotrophic factors increased the number of neurites, the number of branch

points, and the number of extremities. In explanted cochlear cultures, selected treatments increased the number of PSD-95 puncta and neuron fiber density.
BDNF, NT-3, and the Trk agonist mAbs evaluated are potent activators of neurotrophin signaling in several ex vivo models that are relevant to hearing loss. Their ability to promote survival, neurite extension, branching, and synapse restoration make them attractive therapeutic candidates for the treatment of hearing loss.

Disclosures: S. Szobota: A. Employment/Salary (full or part-time):; Otonomy, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Otonomy, Inc. **P.D. Mathur:** A. Employment/Salary (full or part-time):; Otonomy, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Otonomy, Inc. **S. Siegel:** A. Employment/Salary (full or part-time):; Otonomy, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Otonomy, Inc. **H. Saragovi:** F. Consulting Fees (e.g., advisory boards); Otonomy, Inc. **A.C. Foster:** A. Employment/Salary (full or part-time):; Otonomy, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Otonomy, Inc..

Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 482.13/DD18

Topic: D.06. Auditory & Vestibular Systems

Support: NIH NIDCD R01 DC014261

Title: Investigating FOXO3's role in cochlear preservation and hearing recovery in a mouse model of noise-induced hearing loss

Authors: *H. BEAULAC[1], P. WHITE[2]
[1]Neurosci. Grad. Program, Univ. of Rochester Sch. of Med. and Den, Rochester, NY; [2]Univ. of Rochester Sch. of Med. and Dent., Dept. of Neurosci., Rochester, NY

Abstract: Approximately 16% of global cases of adult-onset hearing loss are attributable to excessive, occupational noise exposure. An individual’s susceptibility to noise-induced hearing loss (NIHL) and the severity of their condition depend on interactions between underlying genetic networks and the environment. We have previously established that the forkhead transcription factor FOXO3 is required for hearing recovery and outer hair cell (OHC) preservation after noise exposure (Gilels et al. 2017). The present study used immunohistochemistry and RNA sequencing to assess changes in protein and RNA expression in

the cochleae of adult mice with Foxo3 deletion ($Foxo3^{KO/KO}$) and their wild type (WT) littermates prior to and following noise exposure. Hearing threshold shifts were induced using a 105 dB unilateral octave-band noise centered between 8-16 kHz, exposed for 0.5 hours. $Foxo3^{KO/KO}$ and WT mice, including both control and noise-exposed individuals, were sacrificed at 0.5, 4, and 24 hours post-noise onset (HPN) (n=4 cochleae per condition). Both males and females were used, all were between the ages of P60-90, and all were FVB/nJ strain. Preliminary findings show that OHC numbers are comparable in both genotypes prior to noise but rapidly decline along the organ of Corti at 0.5 HPN, continuing through 24 HPN in the $Foxo3^{KO/KO}$. This loss does not appear to result from programmed cell death in response to noise or from increased oxidative stress in the absence of FOXO3. At 0.5 HPN in the $Foxo3^{KO/KO}$, increased pJNK activity is concentrated at the Deiter cells, inner hair cell, and nerve terminals. Disruption of OHC morphology is visible in the mid basal cochlear turn, and they appear to be progressively phagocytosed. Increased pJNK expression was present in the inner hair cell and nerve terminals, but not seen in the Deiter cells of WT littermates following noise. FOXO3 primarily regulates via transcription and its absence may result in altered gene expression. Both genotypes' cochleae were collected at 0, 4, and 24 HPN (n=6-7) for mRNA extraction. Changes in cochlear gene expression between WT and $Foxo3^{KO/KO}$ mice were examined using RNA-sequencing. Gene Ontology was used to perform enrichment analysis on our derived gene set. Clusters of genes associated with mechanical cell integrity and those with FOXO3 binding sites were investigated. Our preliminary findings show that FOXO3 is important in the preservation of OHCs and hearing maintenance prior to any stress incursion. We are continuing to examine how this major cell survival regulation is possible with the goal of identifying noise susceptibility genes modulated by FOXO3.

Disclosures: H. Beaulac: None. **P. White:** None.

Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

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Topic: D.06. Auditory & Vestibular Systems

Support: NIH grant R21DC015636 (ABC)

Title: Noise-induced damage to auditory hair cells and their synapses in the zebrafish lateral line

Authors: *K. J. LAWTON, P. M. URIBE, B. K. VILLALPANDO, A. B. COFFIN
Washington State Univ., Vancouver, WA

Abstract: Noise-induced hearing loss is a prevalent issue in modern human society, with few therapeutic options. Larval zebrafish are a tractable model for studying acoustic trauma *in vivo*,

due in part to their externally located lateral line system. The zebrafish lateral line is comprised of discrete clusters of hair cells which are both experimentally accessible and share cellular homology with mammalian systems. Previous work in our lab successfully used this system to identify potential otoprotective drug targets for pharmacologically-induced ototoxicity. We now extend the utility of this model system to understand the mechanisms of noise-induced hearing loss, via an acoustic trauma system developed in our lab. To induce acoustic trauma, we created a novel noise damage device to deliver a broadband underwater acoustic stimulus that targets lateral line hair cells. Using this method, we sought to characterize the timing and extent of noise-induced hair cell damage. For the present experiments, larval fish were exposed to noise stimulus parameters that induced partial hair cell loss in both the anterior and posterior lateral line. Noise-induced hair cell death was assessed via direct counts of surviving hair cells at several time points post-noise exposure. After 24 hours, hair cell survival was comparable to controls, but by 48 hours, noise-damaged fish showed a 40% reduction in hair cell number. As an initial step towards understanding intracellular signaling cascades underlying noise-induced cell death, we wished to identify the timing of initiation of key cell death events. For this we used TUNEL staining of apoptotic cells following noise exposure. We observed an increase in the number of TUNEL+ hair cells at 48 and 72 hours post-noise exposure, consistent with the timing of reduced hair cell survival. This increase is not seen in surrounding non-hair cells, indicating that noise-induced damage is specific to hair cells. In mammals, noise-induced auditory damage is also known to occur at the level of the synapse, even in the absence of hair cell death, so we asked if this synaptopathy also occurs in the zebrafish lateral line. We assessed synaptic integrity between hair cells and their afferent fibers following noise exposure using immunohistochemistry to colocalize the hair cell ribbon synapse protein RibeyeB and the post-synaptic density protein MAGUK. We found an increase in orphaned ribbons in noise damaged fish, indicating that fish exhibit noise-induced synaptopathy. This research can inform how noise induces damage at the level of hair cells and their afferent synapses in an *in vivo* model, with potential to identify targets for otoprotective drug development.

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Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 482.15/EE2

Topic: D.06. Auditory & Vestibular Systems

Title: Treatment of severe noise-induced hearing loss by oral SENS-401 is not affected by concomitant prednisolone administration

Authors: *J. DYHRFJELD-JOHNSEN, M. PETREMANN, C. ROMANET, C. TRAN VAN BA, P. LIAUDET, V. DESCOSSY
Sensorion SA, Montpellier, France

Abstract: Off-label use of corticosteroid therapy is not recommended in the current practice guidelines for sudden sensorineural hearing loss (Stachler et al., 2012) and recent meta-analysis concluded no significant treatment effect (Crane et al. 2015). However, as no approved pharmaceutical treatment currently exists for sudden sensorineural hearing loss (SSNHL), corticosteroids remain an accepted standard-of-care (SoC).
SENS-401 is small molecule, orally administered clinical drug candidate in development for the treatment of sudden sensorineural hearing loss which has demonstrated efficacy in a number of preclinical studies, including improvement of ABR threshold recovery, improvement of DPOAE amplitude recovery and enhanced survival of outer sensory hair cells (Petremann et al., 2018). We here evaluate whether co-administration of prednisolone at human equivalent dose (HED) in a rat model of severe SSNHL affects otoprotective treatment with SENS-401.
Following baseline bilateral ABR recordings, 7-week old awake and behaving male Wistar rats were exposed to 120 dB octave band noise (8-16 kHz) for 2 hours on a slowly rotating platform in a sound-attenuating cubicle. After ABR recordings 24h after acoustic trauma, rats were randomized to receive either oral SENS-401 13.2 mg/kg twice daily for 28 days with placebo intraperitoneal injection for 14 days (n=9) or SENS-401 for 28 days in combination with 8.3 mg/kg prednisolone sodium sulfate intraperitoneally once daily for 14 days (n=10) before final ABR recordings on D29 after acoustic trauma. Results of treatment with SENS-401 alone or in combination with prednisolone at HED were compared for the ear most severely affected by acoustic trauma. At 24h, ABR thresholds ranged from 84-94 dB SPL, with no significant difference in acute ABR threshold shifts between animals randomized to receive SENS-401 or SENS-401 + prednisolone (67±5.9 dB vs 69.5±5.7, p=0.402, two-tailed t-test). At D29, the mean ABR threshold shift across frequencies was not statistically different between SENS-401 or SENS-401 + prednisolone treatment groups (51.4±11.6 dB vs 58.4±927, p=0.163, two-tailed t-test). Neither was ABR threshold recovery across frequencies (15.8±10.8 dB vs 11.0±9.7, p=0.317, two-tailed t-test).
These results suggest that the efficacy of otoprotective treatment with the small molecule clinical candidate drug SENS-401 is not affected by concomitant administration of a standard-of-care corticosteroid following a clinical treatment regimen at human equivalent dose.

Disclosures: J. Dyhrfjeld-Johnsen: A. Employment/Salary (full or part-time):; Sensorion. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sensorion. **M. Petremann:** A. Employment/Salary (full or part-time):; Sensorion. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sensorion. **C. Romanet:** A. Employment/Salary (full or part-time):; Sensorion. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sensorion. **C. Tran Van Ba:** A. Employment/Salary (full or part-time):; Sensorion. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sensorion. **P. Liaudet:** A.

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Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

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Title: Age-related hearing loss - How a monoallelic single point mutation impairs auditory processing

Authors: *A. BURGHARD, D. L. OLIVER, N. MOREL
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Abstract: The *Ahl* mutation in the Cdh23 gene ($Cdh23^{753A>G}$) is known to lead to the age-related hearing loss phenotype observed in many inbred mouse strains. This phenotype involves an early onset of age-related high frequency hearing loss, which leads to moderate hearing deficits at only 6-months of age, and severely hearing impaired animals within one year. While previous studies on Cdh23 mutations have focused on the comparison of homozygous for the mutation vs homozygous wild-type, we investigated how the *Ahl* mutation on a single allele alters auditory capabilities of mice over age. To compare auditory phenotypes to the specific genotype, animals were genotyped via Saenger sequencing of genomic DNA. The hearing thresholds were established using click-evoked auditory brainstem response (ABR) and amplitude-modulation following response (AMFR) measurements. The latter was also used to assess the temporal processing abilities of the animals. For the audiogram, the AMFR stimuli had a 0.3 octave narrow-band noise carrier frequency and a 42.9 Hz modulation frequency shaped by a sine wave raised to the exponent 8. To test the temporal processing abilities, the frequency with the lowest threshold was stimulated at 30 dB above threshold and the modulation frequency was varied from 17-544 Hz. Mice homozygous for the $Cdh23^{753A/A}$ mutation showed a high frequency hearing loss beginning at 3 months of age which progressed until no high frequency hearing was detectable at one year. In contrast, the $Cdh23^{753G/A}$ mice did not show hearing loss and showed no differences in hearing thresholds across ages or compared to $Cdh23^{753G/G}$ mice. However, other aspects of hearing function of heterozygous mice were affected. We looked at sound intensity coding via amplitude (amplitude growth function) at the level of the auditory nerve

(ABR wave I). While it shows a steep growth for young animals, the curve flattens for the one-year old group in $Cdh23^{753A/A}$ and $Cdh23^{753A/G}$ mice, but not $Cdh23^{753G/G}$ mice. This indicates an intensity coding deficit in $Cdh23^{753A/A}$ and $Cdh23^{753A/G}$ mice. Moreover, when the temporal precision of the AMFR was tested, we found a decline in peak synchrony for high modulation frequencies in mice homozygous and heterozygous mice for the mutation. This also indicates a peripheral deficit. In conclusion, the *Ahl* ($Cdh23^{753A>G}$) mutation has effects on auditory abilities besides hearing thresholds. These deficits in temporal precision and intensity coding were also present in animals heterozygous for this mutation. Since Cdh23 mutations are seen in mouse and human, it is important to assess auditory processing and hearing in both heterozygous and homozygous individuals in more detail.

Disclosures: D.L. Oliver: None. **N. Morel:** None.

Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 482.17/EE4

Topic: D.06. Auditory & Vestibular Systems

Title: Age related changes in the populations of human spiral ganglion neurons expressing parvalbumin, gaba and nmdar 2b: stereological study

Authors: *C. KAUR[1], T. G. JACOB[2], T. C. NAG[2], A. THAKAR[3], D. BHARDWAJ[4], T. S. ROY[2]
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Abstract: The elderly need optimal hearing for their personal and social life that helps them maintain physical and mental well-being. Presbycusis is progressive deterioration of hearing associated with aging. It is multifactorial disorder. Animal studies suggest that imbalance of neurotransmitters and/or other environmental factors result in decreasing number of SGNs with aging. The calcium current produced during neuronal activity can be neurotoxic if it is not buffered by calcium-binding proteins (CBPs). We have already shown that Parvalbumin (PV) is the predominant CBP of the SGNs. But even with adequate CBPs an imbalance between the excitatory Glutamate and the inhibitory GABA, probably related to loud sounds may lead to neurotoxicity and decrease the total number of first order neurons of the auditory pathway. Therefore, the present study aims to provide estimates of total number of SGNs using Nissl-staining, and immunoreactivity to PV, GABA and NMDAR-2B (receptor for Glutamate) using unbiased stereology in 35 human temporal bones from cadavers of 11 to 80 years of age at the time of death. These were obtained from the mortuary with approval from Institute ethics committee. Cochleae were divided into two groups, group I (n=25) included cochleae from 11-60 years and group II (n=10) had cochleae ranging from 61-80 years. The cochleae containing

the SG were dissected, fixed, decalcified, cryoprotected and serially sectioned (30μm) in horizontal plane. Every 7th section was stained with Nissl or for PV, GABA and NMDAR-2B and used for counting the total number of SGNs with the Optical Fractionator. The mean number of SGNs stained by Nissl and PV in group I was 25,675 ± 3607 and 25,119 ± 3251 and in group II was 12,101 ± 1729 and 12,580 ± 480 respectively. Mean GABAergic and NMDAR-2B positive SGNs in group I was 25,242 ± 596 and 24,001 ± 633 and in group II was 12,211 ± 526 and 13,142 ± 519 respectively. No significant changes were observed in the estimates of Nissl, PV, GABA and NMDAR 2B positive SGNs from age 11-60 years, but after the age of 60 years SGNs population was halved ($p<0.001$). The present study demonstrated that there are age-related changes in the number of PV, GABA, and NMDA receptor-expressing SGNs that might contribute to neural degeneration as a function of age, the critical age being 60-years of age.

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Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 482.18/EE5

Topic: D.06. Auditory & Vestibular Systems

Support: Garnett Passe and Rodney Williams Memorial Foundation (GPRWMF)

Title: Age-related changes in cholinergic receptor expression and function in type II hair cells of the C57BL/6 mouse crista ampullaris

Authors: *L. A. POPPI[1], M. J. BIGLAND[1], H. TABATABAEE[1], H. R. DRURY[1], J. C. HOLT[2], R. LIM[1], A. M. BRICHTA[1], D. W. SMITH[1]
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Abstract: Introduction Cholinergic decline and sensory regression are commonly associated with the effects of ageing (1). The peripheral vestibular organs of the inner ear receive a significant cholinergic efferent innervation that can modify peripheral sensory activity before it reaches the CNS (2). A sensitive assay of peripheral vestibular function is the vestibular-ocular reflex (VOR), which is dependent on the normal activity of the vestibular organs. Interestingly, the basic VOR is not drastically affected by age (3), however, it has been shown recently that subtle features of the VOR such as *adaptation* and *compensation* are significantly impaired in aged mice (4). We therefore investigated the impact of ageing on the expression of cholinergic receptors and on the strength of cholinergic signalling as a potential source of impairment in peripheral vestibular function.
Methods All procedures were approved by and conducted in accordance with the University of

Newcastle Animal Care and Ethics Committee (ACEC). Changes to the cholinergic efferent vestibular system were examined in the cristae of male mice from three age groups; juvenile - 3 weeks, adult - 4-6 months, and aged - 24 months or more. Whole cristae were homogenized and mRNA expression of nicotinic ACh receptor (nAChR) subunits and Ca^{2+}-activated K^+ channels were compared using qPCR. Patch clamp recordings were obtained from type II vestibular hair cells, and whole-cell responses to exogenous ACh application were compared across the three age groups. Cholinergic efferent fibres and terminals were also qualitatively compared using immunofluorescence and confocal microscopy.
Results A significant reduction in the expression of alpha1, alpha9, and alpha10 nicotinic ACh receptor subunits, and the BK channel, was observed in the cristae of aged vs. adult C57BL/6 mice. In type II hair cell recordings, whole-cell responses to ACh were significantly reduced in aged vs. adult type II hair cells. We observed no qualitative differences in the morphology or distribution of cholinergic efferent terminals across the three age groups tested.
Conclusion Results show that there is a decline in postsynaptic cholinergic function in the cristae of aged C57BL/6 mice. This decline would reduce the impact of central control over vestibular sensory organs, and may contribute in part to age-related presbyastasis.
References 1. Schliebs *et al.* (2011). *Behav Brain Res*, 221:555-63. 2. Poppi *et al.* (2018). *J Neurophysiol*, 119(1):312-25. 3. McGarvie *et al.* (2015). *Front Neurol*, 6:154. 4. Khan *et al.* (2017). *Neurobiol Aging*, 51:122-31.

Disclosures: L.A. Poppi: None. **M.J. Bigland:** None. **H. Tabatabaee:** None. **H.R. Drury:** None. **J.C. Holt:** None. **R. Lim:** None. **A.M. Brichta:** None. **D.W. Smith:** None.

Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 482.19/EE6

Topic: D.06. Auditory & Vestibular Systems

Support: NASA NAG13AL99G

Title: Topographic distribution of efferent projections in murine vestibular epithelia

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Abstract: Sensory epithelia of the vestibular labyrinth receive projections from efferent vestibular neurons, which are thought to provide centrifugal feedback. Vestibular efferent neurons are well-characterized with respect to their principal mode of neurotransmission (i.e.

cholinergic), laterality (both ipsi- and bi-lateral projections have been identified), and effects on afferent discharge. While the predominant receptor types mediating cholinergic feedback to inner ear sensory epithelia are nicotinic, recent evidence indicates that muscarinic neurotransmission also makes important contributions to vestibular efferent modulation (Holt et al. 2016; Lee et al. 2017). These data support the notion that this feedback component alters the dynamic coding capabilities by attenuating the influence of Kv7.4 (aka KCNQ4) channels within the inner face of the dendritic calyces. These channels exhibit a unique topographic distribution within the vestibular epithelia, where calyces exhibiting heaviest expression are found in a region extending beyond the utricular striola and crista central zone (Spitzmaul et al. 2012). The present investigation tested the hypothesis that efferent terminals within vestibular epithelia exhibit a similarly heterogeneous distribution, supporting a consequential role of muscarinic-driven efferent modulation. Sensory epithelia from adult mouse labyrinths were harvested and immunohistochemically processed using methods previously described (Hoffman et al. 2018). Anti-vesicular choline transporter (VChT) was used to identify efferent terminals within whole mounts of utricular and crista epithelia. The specificity of VChT immunolabeling was verified through experiments examining colocalization with choline acetyltransferase (ChAT). Notably, anti-KCNQ4 immunolabeling elucidated epithelial regions exhibiting the heaviest expression in afferent calyces. Furthermore, we found that efferent terminal density was not homogeneous across utricular and crista topography; the region of highest density VChT-positive terminals expanded beyond the utricular striola or crista central zone. This finding indicates that the heterogeneous distribution of efferent terminals is not specifically confined by factors related to these specialized regions. However, the region of greatest efferent terminal density was coincident with the regions of epithelia that harbored calyces exhibiting high KCNQ4 expression. These data infer that centrifugal modulation by efferent neurons may result from muscarinic tuning of the dendritic generator potential by modifying the “m” current through KCNQ4.

Disclosures: J.J. Saldate: None. **S. Jobbins:** None. **F.E. Schweizer:** None. **L.F. Hoffman:** None.

Poster

482. Auditory and Vestibular Systems: Hair Cells and the Periphery

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 482.20/EE7

Topic: D.06. Auditory & Vestibular Systems

Support: FAG grant, Basel

Title: Somatostatin analog pasireotide promoted cochlear hair cells protection, survival and function after aminoglycoside treatment *in vivo*

Authors: *V. PETKOVIC[1], K. KUCHARAVA[1], M. SEKULIC-JABLANOVIC[1], L. HORVAT[2], D. BODMER[3]
[1]Dept. of Biomedicine, Inner Ear Reserch, Basel, Switzerland; [2]HNO-Klinik, Kantonsspital Baselland, Liestal, Switzerland; [3]Dept. of Biomedicine, Clin. for Otorhinolaryngology, Basel, Switzerland

Abstract: Hair cells of the mammalian auditory system do not regenerate. Loss of sensory hair cells of the inner ear due to aminoglycoside exposure is major cause of hearing loss. The neuropeptide somatostatin and its selective analogs have provided neuroprotection by activating five somatostatin receptor (SSTR) subtypes. We previously demonstrated that somatostatin receptors are expressed in the mammalian inner ear and somatostatin, octreotide and pasireotide can protect hair cells from gentamicin-induced hair cell death in vitro. The aim of the presented study was to investigate the neuroprotective properties of the most metabolically stable somatostatin analog pasireotide against gentamicin in the mice model in vivo. After 5 days pasireotide pre-treatment and 10 days subcutaneous administration of the pasireotide and gentamicin, the ototoxicity was inhibited as confirmed by auditory brainstem responses (ABR) measurement. We observed a significant threshold shift compared to the gentamicin group at 8, 16 and 24 kHz. Additionally, we found that the pasireotide protects auditory hair cells from gentamicin ototoxicity by activating Pi3k - Akt signaling transduction pathway proved on gene and protein level by using of SH6 specific Akt inhibitor. A drug as pasireotide with a proven safety record could provide an faster path to an approved new treatment.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 483.01/EE8

Topic: D.06. Auditory & Vestibular Systems

Title: Auditory learning and perception modulates neuronal activity in the auditory midbrain

Authors: *C. CHEN[1], L. DE HOZ GARCÍA-BELLIDO[2]
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Abstract: Neural networks are extremely dynamic, and neuronal activity can be modulated by many factors, such as the environment, hormone level and mental states. Changes in network states could further influence sensory stimulus perception. It has been shown that neural activity and representations can be modulated to affect sensory processing in the auditory cortex. As the first convergence station in the auditory pathway, the inferior colliculus (IC), a subcortical

region, might change its neuronal activity during behavior. However, whether and how auditory learning and perception modulate activity in the auditory midbrain has not been well studied. To address this issue, we compared IC neuronal activity in different behavioral contexts -- during a tone discrimination task (conditioned learning) and during passive listening. In the task, mice required to discriminate a 'safe' tone paired with reward and a 'conditioned' tone paired with punishment. We found that IC responses to the conditioned tone were suppressed during behavioral engagement, while those to the safe tone were enhanced. Spontaneous activity increased significantly during task engagement compared with passive listening. This increase was paralleled by a global increase in response gain and signal-to-noise ratio during passive hearing after conditioning.
Previous research from our group found that statistical learning (no rewards/punishment) changes the IC neuronal response patterns in anesthetized mice. We further tested whether statistical learning alters neural activity also in behaving animals. Mice were exposed to predictable sounds, initiated by the animal, and random sounds (unpredictable). We did not observe significant changes in spontaneous activity during sound exposure. Interestingly, we found that exposure to predictable, but not random sounds, decreased the baseline local field potential in the IC. This result suggests that expectation regulates the ongoing local field potential, thereby possibly influencing signal detection.
In summary, these findings suggest that the inferior colliculus activity is modulated transiently during behavioral training, and this modulation differs between conditioned and statistical learning. These changes may play a role in regulating sensory gating during auditory learning and perception.

Disclosures: C. Chen: None. **L. de Hoz García-Bellido:** None.

Poster

483. Auditory Processing: Perception, Cognition, and Action

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 483.02/EE9

Topic: D.06. Auditory & Vestibular Systems

Support: ERC-2014-CoG AUDADAPT

Title: Closed-loop stimulation reveals the brain state-dependence of auditory perceptual sensitivity

Authors: *L. WASCHKE, J. OBLESER
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Abstract: Instantaneous brain states, that is neural activity prior to stimulus onset, affect the processing of sensory information and subsequent conscious perception in a host of ways.

Particularly, the degree of pre-stimulus neural synchronization as captured by low-frequency power is thought to affect the encoding and perception of auditory stimuli in non-human animal models, with less synchronization resulting in more thorough encoding. We recently demonstrated a strikingly similar pattern in human subjects by using time-resolved entropy of the EEG signal to approximate pre-stimulus neural synchronization and relate it to ensuing perceptual decisions.
In an endeavour to confirm and extend those findings, we constructed a closed-loop experimental setup within which we recorded EEG and pupillometry data from human subjects (N = 18) and processed it using a near real-time algorithm: Time-varying entropy of EEG-signals from auditory cortical regions was calculated before a continuously adapting criterion was used to determine periods of relatively high (peaks) or low entropy (troughs). Tone stimuli were then presented into these high- and low-entropy brain states, respectively, and subjects performed a challenging pitch discrimination task upon these tones. We expected that peak-entropy states would not only be accompanied by reduced low oscillatory power, but also lead to enhanced tone-evoked responses and neural encoding, and ultimately greater perceptual sensitivity (as determined by the modelled psychometric curve).
Replicating our previous results, we found higher entropy to be associated with decreased low-frequency oscillatory power and an increase in phase coherence shortly after tone onset. Furthermore, inverted u-shaped relationships between pre-stimulus entropy and both phase coherence and ERP magnitude were found, with medium entropy resulting in the strongest evoked response. Importantly, this pattern of neural activity was mimicked by behaviour: response speed was higher for tones presented at peaks as compared to troughs but highest at medium levels of pre-stimulus entropy. Importantly, the same relationship was present for perceptual sensitivity. Thus, pre-stimulus entropy likely impacts perceptual sensitivity by altering evoked activity and the encoding of sensory information.
These results validate a promising conceptual approach to quantify states of neural synchronization in the EEG and additionally offer new insights into the brain state-dependence of human perception. We discuss our findings in the context of rapid fluctuations in arousal and associated neuromodulatory changes.

Disclosures: L. Waschke: None. **J. Obleser:** None.

Poster

483. Auditory Processing: Perception, Cognition, and Action

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 483.03/EE10

Topic: D.06. Auditory & Vestibular Systems

Support: Wellcome Trust WT091681MA
NIH DC000242

Title: O-15 Water PET study of speech-in-noise processing in cochlear implant patients

Authors: *P. E. GANDER[1], L. L. PONTO[2], I. CHOI[2], B. J. GANTZ[2], B. MCMURRAY[2], T. D. GRIFFITHS[3]
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Abstract: One of the most important issues in hearing impairment (HI) is difficulty with speech in noisy real-world environments. Recent research in normal hearing listeners indicates that auditory cortex is active while abstracting speech objects from noise and provides input to fronto-temporal networks for further perceptual, attentional, and semantic analysis. We sought to understand whether the neural mechanisms by which cochlear implant (CI) listeners detect speech in noisy environments are similar to individuals with normal hearing. We tested a group of hearing-preservation (hybrid) CI users with devices that combine residual low frequency acoustic hearing with high frequency electric hearing.
N = 9 CI users were compared to N = 10 age-matched normal-hearing (NH) control participants. Cerebral blood flow was measured using [15O]Water positron emission tomography while the participants listened to 2-min blocks of continuous sentences-in-noise or noise alone (matched on RMS sound level). On a given run for speech-in-noise (+7 dB), 30 unique sentence tokens (~2.5 sec length) were presented (1.5 sec inter stimulus interval). Twelve scans (6 each condition, random order) were acquired to allow for single-subject inference.
Robust activations were found in single subjects for the contrast speech-in-noise vs noise in the auditory cortex (lateral Heschl's gyrus, planum polare, and planum temporale) and inferior frontal cortex (frontal operculum and inferior frontal gyrus) bilaterally ($p<0.05$). The activity patterns were very similar across subjects.
The NH control participants were compared to the CI users for evaluation of the neural substrate of the network and overall activity level. No significant interaction was demonstrated between group and the speech-in-noise minus noise contrast in auditory and inferior frontal cortex. Six NH control participants were also scanned for a second session within six months of the previous scan to evaluate the reliability of activation patterns. Across 78 anatomically-defined regions-of-interest, regional activation levels normalized to global activity were compared between time 1 and time 2 for both noise and speech-in-noise conditions. All correlations between the sessions were above 0.9.
A frontal and temporal network of brain activity was demonstrated for speech-in-noise in hybrid CI users. These results were reliable at the single-subject level, which allows for a longitudinal investigation of CI users after device activation. The results support a similar system for speech-in-noise processing in hybrid CI patients and normal hearing listeners.

Disclosures: P.E. Gander: None. **L.L. Ponto:** None. **I. Choi:** None. **B.J. Gantz:** None. **B. McMurray:** None. **T.D. Griffiths:** None.

Poster

483. Auditory Processing: Perception, Cognition, and Action

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 483.04/EE11

Topic: D.06. Auditory & Vestibular Systems

Title: Neuronal activity of the primary- and the secondary auditory cortices during elicitation of mismatch negativity (MMN) in freely-moving rats

Authors: *E. JODO[1], S. EIFUKU[2]
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Abstract: The mismatch negativity is a change-specific event-related potential that is usually invoked by auditory stimuli deviating from established patterns of regularity. The reduction of MMN is a reliable biological property of patients with schizophrenia. The main electrical source of MMN is now considered to be located in the auditory cortex (AuC). However, it remains to be elucidated how the unit activity of AuC neurons is during elicitation of the MMN. In this study we recorded the MMN from the surface of the frontal cortex (FC) and unit activity of AuC neurons simultaneously during auditory stimulation in freely-moving rats. Recording was executed under two different conditions. In one condition two auditory stimuli with different frequency (3000, 6000Hz) and different probability of occurrence (10, 90%) were sequentially presented with stimulus onset asynchrony of 0.3s (odd-ball condition). In the other condition (many-standard condition) ten frequency-different auditory stimuli including former two stimuli (3000, 6000 Hz) were sequentially presented with the equal probability of occurrence (10%). The duration of each stimulus is 0.1s in both conditions. The human MMN-like potential with a peak latency of about 50 ms was recorded from the surface of FC near the midline. This MMN-like potential was notably larger to the deviant tone (10%) in the odd-ball condition than that both to the standard tone (90%), and to the non-deviant tone that was presented in the many-standard condition with the same probability of occurrence and pitch as the deviant tone. The waveform of local field potential (LFP) recorded in the primary AuC (pAuC) had notable bimodal peaks that temporally correspond to the rise and decay of the tone, and exhibited no significant change between deviant- and non-deviant tones. The LFP in the secondary AuC (sAuC) ventral to the pAuC exhibited a MMN-like waveform, and its amplitude depended on whether the stimulus was deviant or non-deviant. The unit activity of sAuC neurons differentially responded between deviant- and non-deviant tones, while pAuC neurons did not exhibit such change-specific differential responses. However, most of sAuC neurons exhibited not excitatory responses, but inhibitory responses during elicitation of the MMN.

Disclosures: E. Jodo: None. **S. Eifuku:** None.

Poster

483. Auditory Processing: Perception, Cognition, and Action

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 483.05/EE12

Topic: D.06. Auditory & Vestibular Systems

Title: Auditory sensory gating effect study using EEG source localization techniques

Authors: *D. GUPTA[1], F.-S. CHOA[1], E. HONG[2]
[1]Computer Sci. and Electrical Engin., Univ. of Maryland Baltimore County, Baltimore, MD;
[2]Maryland Psychiatric Res. Ctr., Baltimore, MD

Abstract: Auditory paired click paradigm is a simple non-invasive model where two audio clicks, denoted as S1 and S2 that are 500ms apart, are administered to a subject. S2 is the second redundant click and hence, gated out in the neurological processing. This is characterized by the fact that amplitude of the P50 wave has lower amplitude post S2 than post S1. However, people suffering with schizophrenia cannot suppress or filter the redundant and unnecessary stimuli and therefore, their neurological response to S2 is not suppressed. Studies show that their P50 wave in response to S2 is reduced by 10-20% only as compared with 80-90% in controls (Wan, Li, et al. International Journal of Psychophysiology, 2008). Although the result has demonstrated the sensory gating effect difference of normal controls and patients, however, the mechanism remains to be elucidated. In our study, we use EEG sLORETA techniques to analyze auditory processing from 18 subjects, 9 controls and 9 schizophrenia patients. By using auditory paired click paradigm as the stimuli, we investigate alpha wave propagation along the brain pathways for all subjects post both S1 and S2. We focused on the alpha wave activity because studies suggested that alpha wave is associated with inhibition given that our study focuses on sensory gating (Klimesch et al Brain research reviews, 2007). Overall, we see that less Region Of Interest (ROI) are active during S2 in controls than that post S1 whereas patients show overall more active brain regions during S2 than S1 as summarized in the table below. As a part of the auditory cortical network, frontal lobe plays a major role in processing sound after cochlea, temporal lobe and auditory thalamus. Within the frontal lobe, post the auditory clicks, we observed that higher number of regions activated in less time for controls and lesser number of regions activated in patients with the alpha activity (p-value=0.0473<0.05) thereby indicating speeded processing. These conclusions contribute towards a better understanding of our auditory processing.
Table: Summary of active common ROIs across 9 controls and 9 patients post first and second auditory click (S1 and S2 respectively) during paired auditory click paradigm

Summary of active common ROIs across 9 controls and 9 patients post first and second auditory click

Region of Interest (ROI)	Patient S1	Patient S2	Control S1	Control S2
Inferior Frontal Gyrus, Middle Frontal Gyrus, Middle Temporal Gyrus, Postcentral Gyrus	active	active	active	active
Precentral Gyrus	active	active	active	-
Superior Frontal Gyrus	active	-	active	-
Middle Occipital Gyrus	active	active	-	active
Inferior Parietal Lobule	-	active	active	active
Inferior Temporal Gyrus	-	active	-	-
Superior Temporal Gyrus	-	active	active	active
Cuneus	-	-	active	-
Total active:	4	6	6	4

Disclosures: D. Gupta: None. **F. Choa:** None. **E. Hong:** None.

Poster

483. Auditory Processing: Perception, Cognition, and Action

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Program #/Poster #: 483.06/EE13

Topic: D.06. Auditory & Vestibular Systems

Support: NSF GRFP 2017216247
NIH Grant R56DC016408

Title: Learned context dependent categorical perception in songbirds

Authors: *T. SAINBURG[1], M. THIELK[2], T. GENTNER[1]
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Abstract: Songbirds and humans rely on categorical perception of smoothly varying acoustic spaces to discretize (and discriminate) the elements in their vocal communication signals. In humans, the boundaries between perceptual categories (phonemes) are often not fixed, but can shift based upon long-term language exposure and short-term contextual cues, such as preceding phonemes within a word or multisensory cues as in the McGurk effect. Recent work with Europeans starlings, a species of songbird, has revealed a shared perceptual space for song syllable categories that, like speech, is shaped directly by the learning environment (Thielk et al., 2016). Whether or not syllable category boundaries can be shifted by short-term contextual cues

remains an open question. To investigate this, we trained European starlings (n=6) to categorically label smoothly varying natural song syllables, generated from the latent-space of a convolutional neural network, using a two-alternative-choice operant conditioning procedure. Once the birds learned this basic syllable categorization, we introduced a second set of song syllables that acted as contextual cues on each trial. Thus, on each trial the bird heard two syllables, a cue followed by a target, where the cue carried information about the likelihood that the target syllable was in one category or the other. We show that the contextual information provided by these cues differentially alters the birds' perception of categorical syllable boundaries, producing predictable shifts in their psychometric functions. To explore the neurophysiological basis of this short-term contextual modulation, we recorded extracellular spiking responses to playback of syllables in the learned categories and cues using multichannel arrays in the secondary auditory cortical regions CM and NCM (caudal mesopallium and caudo-medial nidopallium) of trained birds. Initial analyses reveal many neurons that respond categorically, with more similar responses to acoustic variability within a category compared to variability that spans the learned categorical boundary. Additional analyses investigate the degree to which NCM and/or CM neuromorphic functions are directly altered by the presence or absence of the contextual cue.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

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Title: Understanding speech in background noise relies on similar processes to figure-ground segregation

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Abstract: Speech-in-noise (SIN) perception is a critical everyday task that varies widely across individuals and cannot be explained by the pure-tone audiogram, which measures thresholds for detecting sounds in quiet. This finding is unsurprising, because speech is usually heard at suprathreshold levels. Instead, the difficulty likely arises because listeners must separate speech from simultaneously-occurring background sounds. We predicted that the neural processes that

underlie successful SIN might partially overlap with those that underlie successful auditory figure-ground segregation. As a first step, we examined how much common variance links speech-in-noise perception to auditory figure-ground perception, and how this relationship depends on the properties of the figure to be detected.
We presented sentences from the Oldenburg matrix corpus (e.g., "Alan has two old sofas") simultaneously with multi-talker babble noise. We adapted the target-to-masker ratio to determine the participant's threshold for reporting 50% of sentences correctly. Our figure-ground stimuli included one based on Teki et al. (2013; PMID 23898398) in which each 50 ms time window contains random frequency elements; subjects were required to detect certain elements (the figure) that remained fixed from one time window to the next. We also tested figures that changed in frequency over time, mimicking the formants of speech, and participants had to discriminate gaps that occurred in the “figure” and “background” components.
Performance for the fixed-frequency figure explained ~7% of the variance in SIN perception in previous work, and our preliminary results (N=15) replicate this relationship. Preliminary results suggest that performance for the speech-like figures explain a greater proportion of the variance. These results in normally-hearing listeners support a source of variance in speech-in noise perception related to figure-ground analysis that is unrelated to audiometric thresholds, consistent with previous work demonstrating cortical contributions to both speech-in-noise and figure-ground perception. Furthermore, our results imply that different types of figure-ground stimuli index different cognitive processes, which contribute differently to speech-in-noise perception.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

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Program #/Poster #: 483.08/FF1

Topic: D.06. Auditory & Vestibular Systems

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Title: Similarities and differences in cortical dynamics during sensation and short-term memory in mice performing auditory and somatosensory discrimination

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Abstract: Sensory information may immediately lead to a behavioral response or it may be temporally stored in short-term memory. These processes involve many and distant neocortical areas. It is currently unknown how sensory inputs of different modalities are processed and transformed into actions and where information is held during short-term memory. To answer these questions, we used wide-field calcium imaging in head-restrained mice expressing GCaMP6f in layer 2/3 excitatory neurons. Animals were trained in a 'go/no-go' auditory discrimination task (4 kHz versus 8 kHz) or in an analogous whisker tactile task (rough texture, P100 grit size, versus smooth texture, P1200). Both task types required a delayed response after a few seconds. Some animals were trained in both tasks. For both tasks we found that sensory stimuli evoked a larger response for 'go' compared to 'no-go' trials in the respective sensory areas (auditory and barrel cortex). During the subsequent short-term memory phase the cortical activation pattern depended on the animal's behavioral strategy during sensation, with animals either being active (motor-engaged) or passive. For active animals and in both task types, neuronal activation during the delay consistently occurred in a medial frontal premotor area (M2). In contrast, a region posterolateral to primary visual cortex was prominently engaged during the delay in passive animals. Our results suggest that reward-predicting stimuli ('go') of different sensory modalities are first integrated in the respective sensory areas and then may converge along common pathways to either M2 or P, depending on behavioral strategy, for maintaining information in short-term memory.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

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Topic: D.06. Auditory & Vestibular Systems

Support: GACR 16-17823S

Title: Mice lacking GABAB receptor auxiliary subunit KCTD12 exhibit hearing impairments and susceptibility to tinnitus

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Abstract: $GABA_B$ receptors ($GABA_BRs$) are the G protein-coupled receptors for γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the central nervous system. Native $GABA_BRs$ assemble from principal $GABA_{B1}$ and $GABA_{B2}$ subunits and auxiliary KCTD

subunits that increase $GABA_BR$ surface expression and accelerate kinetics of the receptor response. Recent studies suggested the KCTD12 isoform as a risk modifier in chronic tinnitus, phantom perception of sound in the absence of external stimuli. In this study we used KCTD12 null mutant (KCTD12-/-) mice to test the role of KCTD12 in an animal model of tinnitus. Compared to C57BL (wild type, WT) mice, KCTD12-/- mice showed significantly elevated hearing thresholds estimated by recording of auditory brainstem responses (ABR) and the middle latency responses (MLR). Tinnitus was induced by exposure of mice to narrow band noise (116 dB SPL centered at 10 kHz, 1h) and its presence was monitored by measuring the gap prepulse-induced inhibition of the acoustic startle reflex (GPIAS) before and 2 weeks after the noise exposure. We observed that KCTD12-/- mice had lower basal GPIAS than WT mice (35.5 ± 14.6% vs. 52.5 ± 9.2%, $p < 0.001$). As a reduction of GPIAS could be due to masking the gap by phantom sounds, the results suggest that KCTD12-/- mice might have a chronic tinnitus. Exposure to noise strongly impaired the ability to detect gap in sound in both animal groups. Two weeks after the exposure, GPIAS dropped to insignificant levels in 60% of WT mice and in 100% of KCTD12-/- mice. Thus, the results indicate a higher sensitivity of KCTD12-/- mice to tinnitus induction. Our experiments also showed reduced amplitudes of click-evoked ABR but not MLR in control KCTD12-/- or noise-exposed WT mice. This together with our previous observation of high expression levels of KCTD12 in the auditory brainstem supported the link between tinnitus incidence and impaired GABAergic transmission in the dorsal cochlear nucleus (DCN). Indeed, our further experiments showed a significant reduction of both $GABA_B$ receptor surface expression and baclofen-evoked membrane currents in the fusiform but not cartwheel or stellate cells in DCN slices from control KCTD12-/- or noise-exposed WT mice. This indicated the importance of KCTD12 for subcellular distribution of $GABA_B$ receptors in DCN neurons and suggested that tinnitus might be a symptom of decreased $GABA_B$ function in the auditory brainstem.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

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Program #/Poster #: 483.10/FF3

Topic: D.06. Auditory & Vestibular Systems

Support: ERC Consolidator Grant EUAUDADAPT

Title: Attentional modulation of neural speech tracking and alpha power independently support speech comprehension in middle-aged adults

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Abstract: Speech comprehension in noisy, multi-talker situations is facilitated by the engagement of auditory selective attention and by the generation of context-based semantic predictions. Here, we investigated how healthy aging and its associated gradual decline in sensory acuity and cognitive functioning affect the relative balance of these cognitive strategies. Specifically, we asked whether age changes at the performance level would be mediated by concomitant changes at the neural level.
In an EEG study focused on healthy middle-aged human adults (*N*=73; 39–70y), participants listened to two competing, dichotically presented sentences. They were probed on the last word in one of the two sentences. Critically, two visual cues preceded auditory presentation. First, a spatial-attention cue either indicated the to-be-probed side, thus invoking selective attention, or did not provide any information about the to-be-probed side, thus invoking divided attention. The second cue specified a general or a specific semantic category for the final word of both sentences, thus allowing to utilize a semantic prediction.
At the behavioral level, we observed a general performance benefit for informative compared to uninformative cues. Following a specific semantic cue, participants responded faster but not more accurately. Selective-attention cues lead to more accurate and faster responses. In addition, this relative, cue-related benefit in performance increased with age.
The analysis of EEG data revealed a similar modulation of neural dynamics by the two cues. Selective attention trials yielded a pronounced lateralization of 8–12 Hz alpha power during sentence presentation. Moreover, in selective attention trials the to-be-attended sentence envelopes were neurally tracked more closely, as indexed by better reconstruction accuracies in a linear decoding model. However, reconstruction accuracy was co-modulated by the semantic cue: under divided but not selective attention, reconstruction was more accurate for the specific compared to the general cue. Notably, both the degree of alpha lateralization and neural speech tracking predicted task performance but they did so independently of one another and independent of age.
In sum, our results provide evidence for the joint influence of attentional control and semantic predictions on listening success. They point towards a segregation of age-related changes at the neural and performance level in middle-aged adults. Moreover, our results indicate an independent attentional modulation of low-frequency auditory tracking and the lateralization of alpha power.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

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Program #/Poster #: 483.11/FF4

Topic: D.06. Auditory & Vestibular Systems

Support: ONR

Title: Top-down and bottom-up predictions in auditory decision-making

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Abstract: Auditory perceptual decision-making is mediated by both bottom-up (i.e., incoming sensory stimuli) and top-down (e.g., different cognitive and task-relevant pieces of information) processes. For example, changes in stimulus salience, such as regularity violation, can bias perceptual decision-making through bottom-up attention. Likewise, prior knowledge can also modulate decisions by prioritizing specific features of stimuli (top-down processing). However, the effects of top-down and bottom-up processing on auditory decision-making are not well understood. We investigated how both bottom-up regularity violations and top-down instructed expectations affect auditory decisions.
Human subjects listened, via headphones, to sequences of high-frequency (2000 Hz) or low-frequency (500 Hz) tone bursts (duration: 300 ms with a 10-ms $\cos^2$ ramp; inter-burst interval: 100 ms) that were embedded in a background of broadband noise. The subjects reported whether the last tone in each sequence (the "test tone") was "low frequency" or "high frequency" by pressing the left or right button, respectively, on a gamepad. We titrated difficulty by varying the sound level of the test tone relative to the noisy background. Bottom-up processing was manipulated by varying the sequence of tone bursts presented just before the test tone ("pre-tones") in terms of (1) the ratio of high- and low-frequency pre-tones (5:1 and 1:5), and (2) the number of pre-tones, which were selected from an approximately exponential distribution (range: 0-14) to minimize the ability of the subject to predict the onset of the test tone. Top-down processing was manipulated by presenting, before sequence onset, a visual cue that indicated the prior probability that the test tone could be high or low frequency within a given block of trials (corresponding to ratios of low- versus high-frequency test tones of 5:1, 1:1, 1:5).
Preliminary results indicate that both the top-down and bottom-up manipulations caused choices biases. These biases were largest when stimulus discriminability was lowest, consistent with principles of signal detection theory. For the top-down manipulation, increasing the prior probability for one alternative biased choices and simultaneously decreased response times for that alternative. For the bottom-up manipulation, choices were biased toward the frequency value of the preceding tones, whereas choices toward the opposite frequency showed reduced reaction times. Further analyses and modeling of choices and response times in a drift-diffusion framework will help identify the computations used to incorporate these two sources of information into perceptual decisions.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

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Support: ERC ADAM
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ANR-10-IDEX-0001-02 PSL*

Title: Tracking stimulus statistics from sensory cortices to frontal cortex

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Abstract: Complex, cluttered acoustic environments, such as a busy street, are characterised by their ever-changing dynamics. Despites their complexity, listeners can readily detect changes in continuous acoustic streams. However, the neural basis of the extraction of relevant information in complex continuous streams for goal-directed behavior is currently not well understood. As a model for change detection in complex auditory environments, we designed spectrotemporally broad tone clouds whose statistics change at a random time. Ferrets were trained to detect these changes. Hence, they are faced with the dual-task of estimating the baseline statistics and detecting a potential change in those statistics at any moment, mimicking real-life challenges. To characterize the extraction and encoding of relevant sensory information along the cortical hierarchy, we performed electrophysiological recordings in the primary auditory cortex (A1), secondary auditory cortex (PEG) and frontal cortex (FC) of the behaving ferret. A1 neurons exhibited strong onset responses and change-related discharges specific to neuronal tuning. PEG population showed reduced onset-related responses, but more categorical change-related modulations. Finally, a subset of FC neurons (dlPFC/premotor) presented a generalized response to all change-related events only during behavior. We show using a GLM that the same subpopulation in FC encodes for the sensory and decision signal.
In addition, PEG and FC population dynamics showed a time-dependent evolution within trials and before the change occurred, possibly reflecting an online estimation of the ongoing baseline statistics, a necessary process in this dual-estimation task. All together, these area-specific responses suggests a behavior-dependent mechanism of sensory extraction and generalization of task-relevant event.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

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Topic: D.06. Auditory & Vestibular Systems

Support: NIH F32 DC015966

Title: Speaker-normalized vowel representations in human auditory cortex

Authors: M. J. SJERPS[1,2], *N. P. FOX[3], K. JOHNSON[4], E. F. CHANG[3,5,6]
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Abstract: Speech perception is a computationally challenging task, in part because the acoustic dimensions critical for distinguishing among speech sounds are the same as those that distinguish among different speakers. For example, while a given speaker's /u/ has a lower first formant (F1) than his or her /o/, vowels produced by tall speakers (with long vocal tracts) have lower F1 formants than those of short speakers (with short vocal tracts). Consequently, a tall man's /o/ and a short man's /u/ might be acoustically identical. Behavioral research has shown that listeners overcome such ambiguity by relying on context: an ambiguous vowel between /u/ and /o/ is perceived as /o/ after a sentence spoken by a tall man (low F1), but as /u/ after a sentence spoken by a short man (high F1). To investigate the neurobiological basis of speaker-dependent "normalization," we recorded neural activity directly from parabelt auditory cortex via subdurally-implanted high-density electrocorticography (ECoG) grids while human participants listened to and identified vowels from a synthesized /u/-/o/ continuum after context sentences with high or low F1 ranges. Behavioral data replicated past normalization results. Analysis of the ECoG recordings revealed direct evidence that context-dependent (i.e., normalized) vowel representations emerged rapidly within parabelt auditory cortex. Distinct cortical sites that were sensitive to vowel F1 also responded differentially to the same acoustic token depending on whether it was preceded by a low or high F1 speaker. These normalized vowel representations were preceded by a brief window (~80ms) during which acoustically veridical (context-independent) encoding of target sound acoustics dominated, suggesting that normalization first emerges in cortical processing. Normalization may partly emerge as a result of local sensitivity to the contrast between spectral properties of the context and the incoming speech. These results highlight the key role auditory cortex plays in the integration of incoming sounds with their

preceding acoustic context, leading to the emergence of talker-normalized encoding of speech sounds which is critical to resolving the lack of invariance in speech perception.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

Location: SDCC Halls B-H

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Topic: D.06. Auditory & Vestibular Systems

Title: Intermodal audiovisual attention differentially modulates Spontaneous Otoacoustic Emissions (SOAEs) at low frequencies

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Abstract: The auditory system is marked by rich efferent connectivity with fibers reaching even into the periphery to modulate activity at the hearing nerve either directly (lateral olivocochlear pathway) or indirectly (medial olivocochlear pathway; MOC). While mainly protective functions have been emphasized in the past, this unique neural architecture could in principle enable the modulation of cochlear activity by top-down processes such as attention. Indeed, direct efferent pathways exist from the auditory cortex to the Superior Olivary Complex, from which relevant fibers originate that innervate parts of the cochlea. Attentional modulations of cochlear activity have been repeatedly shown for the MOC via the assessment of sound-evoked optoacoustic emissions. Early works were unable to demonstrate attentional modulations of SOAEs and works in this domain have been scarce from thereon. In the current study (N=22) we focus on this issue by implementing a Posner-style cued attention task, in which a visual cue at the beginning of the trial indicated whether to attend to the visual or auditory modality of an upcoming bimodal stimulus. The task was to perform a simple discrimination task in the cued modality, while ignoring the input in the task-irrelevant modality. Recording otoacoustic emissions, the focus of our analysis was on the silent cue-target interval (2 seconds). We implemented a novel analysis approach in which band-restricted power fluctuations were derived by shifting band-pass filters from 500-2500 Hz and calculating instantaneous power via Hilbert transformation. A Fourier transformation was then performed on these otoacoustic emission time-series and the spectra were compared between attend auditory and attend visual trials. This analysis revealed significant differences, which were noticeably strongest in the relevant sound frequency range of the discrimination task (~1000-2000 Hz) and dominant at low frequency modulations (<10 Hz). This study is the first to clearly show an attentional modulation of SOAEs and underline that the MOC can be engaged by top-down processes in absence of any sound stimulation. In current

works we are investigating simultaneously recorded MEG signals to disclose the cortical networks that putatively drive the MOC during silent periods.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

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Topic: D.06. Auditory & Vestibular Systems

Support: NSF of China 61473169

Title: Interactions between intra- and inter-areal connections of human insula in processing emotional sounds

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Abstract: Previous studies have demonstrated that the human insula are involved in two complementary sub-networks (Zhang et al., 2018 and Cauda et al., 2011), in which the posterior insula (PI) is connected to the sensory cortex and shows selective responses to sensory stimuli including auditory stimuli, where the anterior insula (AI) is connected to the limbic system and shows selective responses to emotional stimuli. To dissect the contributions of PI-to-Heschl's gyrus (HG) and AI-to-Amygdala sub-networks during emotional and non-emotional sounds processing in passive and active attention conditions, we applied conditional Granger causality analysis to assess the directional influences among the neural signals (iEEG) simultaneously recorded from HG, PI, AI and Amygdala of epilepsy patients. Our results showed that connections of the PI-HG sub-network were significantly stronger for emotional stimuli than non-emotional stimuli, but attention level showed no influence. While the connections of the AI-Amygdala sub-network were significantly influenced by both stimuli types and attention level. Furthermore, we found the connections of the PI-HG sub-network were highly dependent on the feedback signals from the AI-Amygdala sub-network during emotional stimuli condition, where the PI-HG sub-network had no influence on the connections of the AI-Amygdala sub-network. In addition, we found the connections between sub-networks are influenced by lateral interactions within the sub-network. Our findings suggest that feedback signals from higher order sub-network and lateral connections within the sub-network closely interact to mediate emotion perception from auditory stimuli.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

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Topic: D.06. Auditory & Vestibular Systems

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Title: Human superior temporal gyrus tracks spectral entropy during speech perception

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Abstract: Speech is a highly dynamic signal, composed of complex spectral and temporal modulations, which map onto linguistic units like phonetic features and words. Previous work has shown that the superior temporal gyrus (STG) encodes fine-scale acoustic-phonetic representations of speech, and has identified two functional-anatomical zones, one that responds primarily to onsets and fast temporal modulations (posterior STG), and another that responds to post-onset input and a wide range of spectral modulations (middle-anterior STG). It remains unclear precisely what features of acoustic speech input these sub-regions encode. To understand how speech-evoked activity in these regions relates to the actual spectrotemporal information content of the acoustic input, we applied an information-theoretic approach that describes speech in terms of spectral entropy. Specifically, we investigated the encoding of spectral multiscale entropy (MSE), a measure that describes the degree of structure in the acoustic power spectrum. We found that MSE successfully characterizes the structure of the acoustic signal for natural speech, such that speech sounds with more spectral structure (e.g., vowels containing formants) have lower entropy than speech sounds with less spectral structure (e.g., fricatives, characterized by high-frequency broadband noise). To understand whether MSE correlates with brain activity, we recorded direct neural population activity using electrocorticography (ECoG) in neurosurgical patients while they listened to ~400 naturally-spoken sentences. We correlated activity in the high-gamma (HG; 70-150Hz) range with MSE calculated on the power spectrum using non-overlapping 15ms windows. We found that activity in the two functional-anatomical zones on STG was correlated with MSE differently: posterior STG neural populations showed relatively weak positive correlations (stronger HG responses for higher entropy sounds), while middle STG neural populations showed strong negative correlations (stronger HG responses for lower entropy sounds). Together, these results demonstrate that speech-evoked neural activity in

human secondary auditory cortex tracks the spectral complexity and information of the acoustic input, as well as its spectrotemporal and phonetic properties.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

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Title: Behavioral modulation of sound processing in mouse auditory cortex during a virtual foraging task

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Abstract: The brain is tasked with processing and providing meaning to sensory inputs in a variety of contexts. For example, while hunting, the snap of a twig may signal the approach of a prey animal, but in another context it may simply mean the presence of a friendly conspecific. The valence of sensory stimuli changes between contexts, and such contextual changes are known to modulate neural responses in sensory cortex. Because these early sensory areas occupy a nexus between the ascending sensory pathway and top-down inputs from areas involved in coordinating action, contextually-modulated responses are believed to be directly related to behavioral outcomes. To test how task engagement modulates sound processing in auditory cortex, we have developed a virtual foraging task in which head-fixed mice run on a floating trackball and receive rewards for licking during a ‘go’ sound stimulus and time-out punishments for licking during a ‘no-go’ stimulus. Here we present results from a set of experiments in which rewarded stimuli were either upward or downward frequency-modulated sweeps. After achieving proficiency on this task, acute extracellular physiological recordings in auditory cortex were performed using multichannel translaminar probes over a period of multiple days and behavioral sessions. During these recordings, we presented the same stimulus set in a passive context for comparison with task-engaged neural responses. Consistent with previous studies, we find many

instances of neural response suppression during task engagement relative to the passive condition. However, we also find that responses in task-engaged auditory cortex are sometimes enhanced, and that such enhancement appears to be related to the cortical depth of the recording site. We also find that neural response onset latencies shift during task, but that the degree and sign of these shifts is heterogeneous. By varying the sound level of both 'go' and 'no-go' stimuli during task-engaged and passive physiological recordings, we also show that the degree of neural response modulation is related to task difficulty. We interpret these results in the context of a circuit model in which sound processing in the auditory cortex is modulated by behavioral context.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

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Title: Enhancing categorical sound perception with envelope timing cues

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Abstract: Our ability to classify temporally dynamic sounds such as speech and non-speech vocalizations is highly robust to variations in tonal frequency composition due to the ability to perceive timing cues in the sound envelope (Shannon et al., 1995). Vocalization sequences are acoustically distinguished by timing cues including the acoustical edges created by abrupt onsets and characteristic vocalization durations (Khatami et al., 2018). Humans and other mammals can use these timing cues to discriminate stationary sound bursts (Friedrich and Heil, 2017; Heil et al., 2003, Kelly et al., 2006). However, it remains an open question as to whether we perceive onset and duration timing cues independently and whether this translates well to sound burst sequences. Since auditory cortices are specialized to respond to onset or sustained duration of transient sounds (Osman et al., 2018, Hamilton et al., 2017), we wondered if having both timing cues provides a perceptual advantage. Here, we hypothesize that the combination of onset and duration timing cues enhances categorical perception of synthetic vocalization sequences that lack tonal cues but have onset and duration timing cues. First, we examined categorical two-alternative forced choice discrimination of a set of sound burst sequences that varied in plateau

duration of the sound burst from short (100ms) to long (200ms) where the sounds lack fixed tonal cues (unfrozen white noise), onset cues (jittered onset) and amplitude (roved amplitude) cues. Furthermore, we were able to independently vary the slope of the sound envelope surrounding each sound burst in order to examine the combined sensitivity to onset slope and duration timing cues. Subjects performed a binomial (two) choice paradigm where they were to choose the right and left sides for short and long sounds, respectively. The Palamedes MatLab toolbox was used to fit a cumulative normal four-parameter sigmoid psychometric function to percent correct data points across a behavioral test session. We found that humans and rodents readily discriminate short versus long duration sound bursts in sequences and that training improves this categorical discrimination. In humans, the temporal resolution for plateau duration discrimination was enhanced with the addition of slow onset slope cues (e.g., reduced from 38 ms to 8 ms). These results support our hypothesis that combining onset and duration timing cues enhances categorical perception of extended and variable sound sequences.

Disclosures: H.L. Read: None. **P.J. Satonick:** None. **C.R. Cody:** None. **T.P. Nolan:** None.

Poster

483. Auditory Processing: Perception, Cognition, and Action

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 483.19/FF12

Topic: D.06. Auditory & Vestibular Systems

Support: MEXT KAKENHI (Grant Number: 17H01769)
JSPC Research Fellowship for Young Scientists (Grant Number: 18J21644)

Title: Auditory prosthesis with an infrared laser: Replication of acoustic intensity information

Authors: *Y. TAMAI, Y. ITO, K. HORINOUCHI, K. MATSUMOTO, S. HIRYU, K. I. KOBAYASI, T. FURUYAMA
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Abstract: Cochlear implants bypass damaged hair cells in a cochlea and stimulate cochlear nerves electrically. One of the greatest drawbacks of the cochlear implant is that the devices require surgical intervention. Infrared laser stimulation is a novel method for neural stimulation. It stems from optical absorption of water. The laser causes instantiable temperature rise and opening of heat-sensitive ion channel. In contrast to electric stimulation, infrared laser stimulate nerves without contacting the tissue. Our goal is to develop a novel auditory prosthesis by applying infrared laser stimulation to a hearing aid. The auditory prosthesis with the infrared laser does not need invasive surgery because the laser can generate neural responses without contacting tissues. The purpose of this study was to investigate whether the infrared laser could stimulate cochlear nerves from an ear canal through a tympanic membrane, and the stimulation

could replicate ‘acoustic intensity information’ by changing radiant exposure. Mongolian gerbils (*Meriones unguiculatus*) were used as subjects. An optic fiber was inserted into their ear canals and irradiated cochlear nerves through their tympanic membranes with the infrared laser. A pulsed infrared laser (0.5 - 20.5 µJ/pulse) and a clicking sound (30 - 90 dB pe SPL) were presented. As results, cochlear microphonic and compound action potentials (CAPs) were recorded when a clicking sound was presented, while infrared laser stimulation only induced CAPs. As radiant exposure increased, the CAP amplitude increased from 0 to 317 µV, and the CAP latency decreased from 2.2 ms to 1.6 ms; similar tendency was observed for clicking sounds (CAP amplitude: 0 - 332 µV, CAP latency: 2.8 - 1.7 ms). In subsequent experiments, flavoprotein fluorescence imaging of auditory cortex was performed to reveal whether the intensity coding of infrared laser stimuli was observed in auditory cortex. Results show that auditory cortex was activated by infrared laser irradiation, and the greater response was recorded as radiant exposure increased. These results suggest that infrared laser stimulation could bypass the need for hair cell depolarization and directly create cochlear nerves responses, and that the laser stimulation could replicate ‘acoustic intensity information’ in auditory pathways.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

Location: SDCC Halls B-H

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Program #/Poster #: 483.20/FF13

Topic: D.06. Auditory & Vestibular Systems

Support: Greater Milwaukee Foundation Grant 20162470 (A.S.G.)
US-Israel Binational Science Foundation Grant 2013400 (A.S.G.)
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Title: Auditory scene analysis and object perception rely upon shared neural mechanisms

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Abstract: The transduction of acoustic input into perception requires auditory scene analysis (ASA) and the subsequent grouping of stimuli into one or more “auditory objects”. Music, an emergent property of sound, can be thought of as an auditory object resulting from the grouping of disparate sounds into a unified percept. Thus, auditory cognition depends on the relationship between low-level properties of auditory stimuli and resultant musical gestalts. Our previous behavioral research has shown that manipulations of low-level properties (i.e., amplitude,

timbre) can modulate the perceived musicality of auditory sequences (Randall & Greenberg, 2016), however, the neural instantiation of these processes remains unexplored. We presented participants with auditory stimuli comprised of randomly generated pure tone sequences for which they provided perceived musicality ratings. We replicated the findings of Randall & Greenberg (2016) by demonstrating that the manipulation of ASA cues had an attenuating effect on musicality judgements. We then used fMRI to measure neural activation elicited by the most and least musical sequences (musicality manipulation), along with those same sequences altered in either amplitude or timbre (ASA manipulation). To explore the functional architecture underlying ASA and auditory object analysis, we uncovered 2 partially distinct networks: (1) a music processing network (via a separate music localizer), and (2) an ASA network (via a contrast of base sequences vs. ASA manipulated sequences). Mean BOLD response time-courses from regions of interest (ROIs) within each network produced functional profiles that appeared to be modulated by musicality manipulations, ASA manipulations, or both. Thus, based on their patterns of functional activation, we identified sub-networks of ROIs that seem to perform common computations. Some regions seem to be involved in discriminating music from non-music while others track low-level features that comprise an auditory perceptual object. Finally, we examined the correlations between behavior (musicality ratings) and BOLD activation for each ROI. Overlapping regions of both the musicality and ASA networks appeared to show stronger correlations between behavior and neural activity. The existence of shared neural mechanisms that correlate with behavioral ratings and underlie both ASA and music perception suggests that low-level features of auditory stimuli play a direct role in auditory object perception.

Disclosures: G. Gurariy: None. **R. Randall:** None. **A.S. Greenberg:** None.

Poster

483. Auditory Processing: Perception, Cognition, and Action

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 483.21/FF14

Topic: D.06. Auditory & Vestibular Systems

Title: Spectrotemporal processing of consonant clusters in theta and high gamma in native-English and native-Polish bilingual adults

Authors: *M. WAGNER[1], S. ORTIZ-MANTILLA[2], V. L. SHAFER[3], A. BENASICH[2]
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Abstract: Studies examining cortical responses to speech sound sequences using ECoG have revealed maximal neural activity in high gamma between 70 to 150 Hz. Few studies, however, have examined native-language phonological processing in this range. In the current study, we

used dense array EEG to examine left auditory cortical responses to native and nonnative consonant clusters, comparing measures of high gamma and theta oscillatory activity. As short-duration phonemic segments are sampled within high gamma, we predicted native-language processing of the phonological segments within consonant clusters to be reflected in measures of high gamma, but not theta. EEG was recorded as 24 native-English and 24 native-Polish bilingual adults listened to same and different nonsense word pairs. Nonsense words contained the onset clusters /st/ and /pt/. Whereas the /st/ cluster occurs in both the Polish and English languages, the /pt/ cluster is never heard in word onset in the English language. A three-dipole source model was fit at the time intervals for N1 (94-124 ms) and P2 (176-206 ms), which explained 90% of the data within the time frame reflecting sensory processing (24 to 388 ms). Using time-frequency analysis, we examined induced temporal spectral evolution (TSE) oscillatory activity between -100 to 900 ms in high gamma (62-90 Hz) and theta (2-8 Hz) bands in source space. Statistical analysis was conducted using data clustering in combination with permutation testing. Results revealed language group differences to the /pt/ cluster in high gamma, but not theta. Reduced high gamma was found in English listeners relative to Polish listeners to the /pt/ cluster during early stage sensory processing and increased activity was found between 400 and 900 ms, which may reflect re-analysis of the unfamiliar cluster. In response to the /st/ cluster, no language group differences were found in high gamma, but greater activation was found in the theta band for the Polish listeners relative to the English listeners. Interestingly, within group comparisons examining responses to the clusters in both theta and high gamma found the English listeners to have increased activation to the /pt/ relative to the /st/ cluster, whereas, the Polish listeners showed a reversed pattern, with increased activation to the /st/ relative to the /pt/ cluster. These results suggest that native-language processing is reflected at early stages within left auditory cortex in high gamma. As /pt/ is never heard in word onset in English and /st/ is less common in the Polish language, increased activation in both theta and high gamma bands may indicate increased processing for the less familiar speech sound sequences.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

Location: SDCC Halls B-H

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European Research Council (ERC CoG, MECHIDENT)

Title: Directed effective connectivity in the human and monkey brain: Auditory cortex impact on inferior frontal gyrus, hippocampus and anterior cingulate cortex

Authors: *F. ROCCHI[1,2], H. OYA*[4], F. BALEZEAU[3,2], Z. KOCSIS[3,2,4], J. GREENLEE[4], T. D. GRIFFITHS[3], M. HOWARD III[4], C. I. PETKOV[3,2]
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Abstract: The correspondences or differences between human and nonhuman primates in connectivity between auditory cortex and other brain regions remain open questions: What is the evidence for evolutionary conservation or specialization in effective connectivity between auditory cortex and brain regions that in humans are implicated in language, memory or learned vocal production? Here we had the opportunity to directly compare electrical microstimulation of site specific contacts available in human epilepsy patients being monitored for surgical resection. We also conducted comparative auditory cortex microstimulation in two rhesus macaques. Microstimulation was combined with functional Magnetic Resonance Imaging (fMRI) to assess the directed effective connectivity induced by electrically stimulating auditory cortical sites. Stimulation of primary auditory cortex (field A1) in the macaques resulted in significant fMRI responses in several brain regions ($p < 0.05$, cluster corrected), including the inferior frontal cortex (areas 44 and 45), regions of the hippocampus and the anterior cingulate cortex. In the monkeys, we also compared the stimulation of primary field A1 to sites in the caudal belt adjoining the non-primary fields CL and CM. In human patients with clinically implanted depth electrodes in Heschl's gyrus (HG), we microstimulated contacts located in the medial HG (a primary like region of auditory cortex; $n = 17$; 2 excluded from a total of 19 because of poor MRI registration). Stimulation of the medial HG resulted in significant fMRI responses in inferior frontal cortex, parts of the hippocampus and anterior cingulate cortex. These observations suggest a considerable amount of correspondence between humans and monkeys in effective connectivity between auditory cortex and other brain regions, which in humans have been implicated in various language functions, cognition or learned vocal production.

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Poster

483. Auditory Processing: Perception, Cognition, and Action

Location: SDCC Halls B-H

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Title: Predictive sequence learning modulates inter-regional oscillatory coupling in human intracranial recordings

Authors: *Y. KIKUCHI[1], C. K. KOVACH[2], R. CALMUS[1], P. E. GANDER[2], A. E. RHONE[2], K. V. NOURSKI[2], H. KAWASAKI[2], T. D. GRIFFITHS[1,2,3], M. A. HOWARD, III[2], C. I. PETKOV[1]
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Abstract: Dynamic environments generate sequences of sensory events that affect brain oscillations at different frequencies. Moreover, feed-forward and feed-back interactions are evident in oscillatory phase and frequency interactions, yet little is known about how learning-related plasticity changes oscillatory dynamics in neural networks. Using intracranial recordings from both human and monkey auditory cortex, we previously reported phase-amplitude coupling between low-frequency phase and gamma amplitude in auditory cortex after the learning of temporal relationships in sequences of speech sounds drawn from an Artificial Grammar (AG; Kikuchi et al., PLoS Biology, 2017, 15(4):e200219). In the monkeys as an animal model, the prior results pointed to oscillatory influences on auditory cortex neurons emanating from other brain regions. Here, we sought to identify the sources of these influences using the extensive coverage with depth and grid recording electrodes offered by human intracranial recordings in epilepsy patients being monitored for surgery. We used the same AG learning paradigm as in the prior study, where participants were first exposed to representative rule-based sequences of nonsense words. In the subsequent testing phase, we presented the participants with sequences that were either consistent with the AG or contained specific violations of learned ordering relationships. Inter-regional phase interactions were measured by phase angle differences between recording sites weighted by the evolution of the transitional probabilities over all previously encountered sequences. Sequencing-related modulation of oscillatory phase coupling

was observed between auditory cortex (Heschl's gyrus, HG) and a number of sites, including the hippocampus, lateral superior temporal gyrus, anterior temporal lobe and inferior frontal gyrus (IFG). Further analyses showed that frequency-specific phase coupling tracked the changes in transitional probabilities within three oscillatory bands (theta: 3-8 Hz, beta: 15-29 Hz, gamma: 40-100 Hz). Moreover, during initial learning, HG interacted with the hippocampus and IFG most prominently in the theta band. A more extensive network was involved after the learning phase, with cortical network modulation in response to violations of the learned sequencing relationships involving a broader set of regions. Oscillatory phase-based coupling in human intracranial recordings provides insight into inter-regional neural interactions at different stages of predictive sequence learning, which may refine hypotheses for further testing using monkeys as a model system.

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Poster

484. Visual Cortex: Circuits and Populations II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 484.01/FF17

Topic: D.07. Vision

Title: Contour feature representation in monkey V4

Authors: *R. JIANG, S. TANG
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Abstract: We recorded responses of macaque V4 layer 2/3 neurons to 5000 nature visual stimuli by two-photon calcium imaging. We found that the orientation pinwheel derived by orientation components within nature images is almost identical to that derived by bar stimuli. We also found that neurons favoring nature images containing curvatures are spatially separated form those preferring images with polygonal lines, which we confirmed by examining with contour feature stimuli containing curvatures and polygonal lines directly. Many of the curvature preferring neurons are located in the center of one of the pinwheels. In addition, we found some neurons that are sensitive to the orientation of the symmetry axis of the contour feature rather than the orientation of the contours. Our results reveal the spatial organization of contour feature representation in V4.

Disclosures: R. Jiang: None. **S. Tang:** None.

Poster

484. Visual Cortex: Circuits and Populations II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 484.02/GG1

Topic: D.07. Vision

Support: NIH Grant EY022122-05

Title: Patterned optogenetic stimulation of ferret V1 to examine cortical mechanisms of cross-orientation suppression

Authors: *S. WANG[1], K. D. MILLER[2], S. D. VAN HOOSER[1]
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Abstract: The study of how neural circuits integrate sensory information and generate functional behaviors has long been a pursuit of the neuroscience field. To understand the principles that underlie the neural computations is critical to understand the intelligence in general. A recently proposed theory, *stabilized supralinear network (SSN)*, has shed light on how canonical computations can be implemented in neural circuits. It uses simple constructions based on biologically plausible parameters, yet it is able to explain many widely studied sensory responses. In particular, it predicts that cortical responses to multiple inputs sum sublinearly when the inputs are not very weak, providing a circuit basis for the phenomenological "normalization" model.
Guided by this theory, we are interested in testing the neural mechanisms of a phenomenon observed in the visual cortex, *cross-orientation suppression*, in order to understand the operating principles of cortical circuits. Cross-orientation suppression refers to fact that visual responses are strongly suppressed when two orthogonally overlapped grating stimuli are presented simultaneously compared to the sum of the responses to the single grating stimuli presented alone. Though previous work suggests the origin of the suppression comes from thalamocortical connections, cortex itself may still contribute to the suppression, which is indeed indicated by the SSN model about the role of local cortical circuits in cross-orientation suppression. We adopted optical and optogenetic tools to directly activate the orientation columns of ferret visual cortex, in a way akin to the visual stimulation using gratings with various orientations, to test whether suppression could be generated directly from the cortical circuits.
A novel optical system, "ProjectorScope 2", is developed in the lab that allows us to perform brain surface imaging to identify orientation columns, and subsequently activate these local areas that have channelrhodopsin-2 expression. Preliminary results showed that simultaneous optogenetic stimulation of both preferred and orthogonal orientation columns produced suppressed responses compared to a linear summation of the responses to the optogenetic stimulation of preferred orientation columns alone and orthogonal columns alone. The responses

of visual stimulation of the preferred orientation and optogenetic stimulation of the orthogonal orientation columns also elicited sublinear responses. These results suggest that the cortex may operate in the SSN regime, but further experiments are needed to test this hypothesis.

Disclosures: S. Wang: None. **K.D. Miller:** None. **S.D. Van Hooser:** None.

Poster

484. Visual Cortex: Circuits and Populations II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 484.03/GG2

Topic: D.07. Vision

Support: KAKENHI 16K01965
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Budget of Kyoto Sangyo University

Title: Local organization of spatial frequency tuning dynamics in the cat primary visual cortex

Authors: *H. TANAKA[1], I. OHZAWA[2]
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Abstract: Spatial frequency (SF) is a prominent visual feature to which most neurons in the primary visual cortex (V1) exhibit tuning selectivity. To fully understand the role of V1 in processing of SF, details should be explored by which the population of V1 neurons cooperatively works to transmit and process SF information. At the level of individual neurons, it is known that V1 neurons often show SF tuning dynamics, typically shifting toward high values, but exhibiting a variety of time courses. However, on the population level, it remains unknown how neurons with a variety of SF tuning dynamics are locally clustered, and how these clusters systematically mediate the wide range of SF signals transmitted in V1 that could change dynamically during response time. To explore these issues, we vertically penetrated cat V1 with a multi-electrode array and recorded the activities of a large number of V1 neurons covering the dominant SF range in V1. The time courses of SF tuning of these neurons were measured by a subspace reverse correlation technique using a random sequence of flashed sinusoidal gratings. We found that the range of SFs transmitted by the whole population rapidly increased in the early response phase, and that a wide range of SFs were continuously signaled for most of the V1 response period. Locally, nearby neurons exhibited various tuning dynamics. Typically, they were first tuned to relatively similar SFs, whereas later their tunings became more diverse. The mean values of optimal SFs of local clusters of neurons increased uniformly and slightly over time, as is consistent with the theory of coarse-to-fine processing. Therefore, our results indicate that local SF tuning clusters increase their SF coding range with time, and as a whole systematically share the wide and increasing range of SFs coded in V1, keeping SF signal

transmission stable during response time, as well as allowing functional diversity within a cluster.

Disclosures: H. Tanaka: None. **I. Ohzawa:** None.

Poster

484. Visual Cortex: Circuits and Populations II

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Program #/Poster #: 484.04/GG3

Topic: D.07. Vision

Support: NHMRC APP1066588
NHMRC APP1120667
ARC CE140100007

Title: Network structure within and between marmoset V1 and MT facilitates natural image coding

Authors: *E. ZAVITZ, M. A. HAGAN, B. H. OAKLEY, Y. T. WONG, N. S. C. PRICE
Monash Univ., Clayton, Australia

Abstract: The middle temporal area (MT) computes motion direction based on the inputs it receives from direction-selective neurons in primary visual cortex (V1). Existing models of the hierarchical computations between these areas are among the best defined of any model of cortical processing, yet the stimulus space of visual inputs on which they have been tested remains poorly explored. While most studies characterise neural responses using only gratings or dots, the natural visual world contains information at a range of spatial scales, and this information is often phase aligned. There is evidence that this structure shapes the nervous system so that natural images are encoded efficiently by single neurons. In this work, we examined how the structure of visual information impacts the way it is represented by both single neurons and populations, across two levels of the visual hierarchy. To reveal how visual information is successively represented by V1 and MT, we made extracellular electrophysiological recordings in five anaesthetised marmoset monkeys (Callithrix jacchus). We used separate multielectrode arrays in each area to record simultaneously from dozens of neurons in each of V1 and MT with overlapping receptive fields. We implanted a Utah array in V1, and a linear array in MT; the linear array was implanted perpendicular to the brain's surface to characterise neurons within the same cortical column. We recorded activity in these populations while we presented motion stimuli with a range of spatial structures: dots, sine waves, square waves, and phase-randomised square waves. These patterns evoke strong direction-tuned responses in MT, but recruit distinct V1 populations, which allows us to examine the representation produced in MT as a function of the representation in V1. We assessed whether

the functional network we engaged was changing by measuring the variability of single neuron responses (Fano factor), and the shared variability between neurons (spike count correlations). We found that both response variability and shared variability were lowest during broadband, phase-aligned stimulation within and between areas V1 and MT. This suggests that the network architecture in both areas is optimised to represent broadband, phase aligned contours.

Disclosures: E. Zavitz: None. **M.A. Hagan:** None. **B.H. Oakley:** None. **Y.T. Wong:** None. **N.S.C. Price:** None.

Poster

484. Visual Cortex: Circuits and Populations II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 484.05/GG4

Topic: D.07. Vision

Title: Inhibition stabilization is a widespread feature of mouse cortical networks

Authors: *B. C.-Y. AKITAKE[1], A. SANZENI[1], C. E. LEEDY[1], N. BRUNEL[2], M. H. HISTED[1]
[1]NIH/NIMH, Bethesda, MD; [2]Neurobio., Duke Univ., Durham, NC

Abstract: Strong recurrent synaptic coupling in networks like the cortex can provide several advantages for computation, allowing networks to track fast feedforward inputs, amplify weak signals, and perform noise-robust classification.
A signature of strongly coupled networks is that excitatory neurons are unstable and activity is stabilized by recurrent inhibition, which tracks and balances excitation. However, modeling studies have suggested that inhibition stabilization, and thus a significant amount of recurrent input, may arise only in the presence of external or sensory activity (Ahmadian, 2013).
Here we show that several cortical networks in the mouse -- visual, auditory, and somatosensory cortex -- are stabilized by inhibition even at rest, i.e. when sensory stimuli are not being delivered. Further, we found inhibitory stabilization even when network activity was reduced by light anesthesia, suggesting that inhibition stabilization is a widespread phenomenon in cortical areas across a range of activity levels and network states.
We expressed a depolarizing opsin in all inhibitory cells using VGAT-ChR2 mice (n=6). Inhibitory stabilized networks show paradoxical suppression of inhibitory neurons when inhibitory cells are directly excited (Tsodyks, 1997), so to assess inhibition stabilization, we recorded neurons extracellularly while stimulating inhibitory cells optogenetically. We classified inhibitory cells (N=70 well-isolated single units, over 10 experiments) as those that responded to optogenetic stimulation when most recurrent network activity was pharmacologically blocked (CNQX, APV, and bicuculline). Consistent with previous measurements, waveform widths had a bimodal distribution and inhibitory neurons had narrower spikes compared to excitatory cells.

Identified inhibitory cells showed clear paradoxical suppression when animals were awake (49% ± 8 (sem) reduction in inhibitory firing with optogenetic stimulation) and after light (0.25% isoflurane) anesthesia (65% ± 10 (sem)).
These results suggest that strong coupling and inhibition stabilization are fundamental principles of cortical circuits.

Disclosures: B.C. Akitake: None. **A. Sanzeni:** None. **C.E. Leedy:** None. **N. Brunel:** None. **M.H. Histed:** None.

Poster

484. Visual Cortex: Circuits and Populations II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 484.06/GG5

Topic: D.07. Vision

Title: Mice improve their ability to detect novel, "off-manifold" stimuli after learning

Authors: *L. N. RYAN, S. P. DUFFY, P. K. LAFOSSE, M. H. HISTED
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Abstract: Sensory stimuli evoke patterns of activity that are constrained by brain functional and structural properties, such as the pattern of synaptic inputs in a brain region. Other -- non-natural -- patterns of activity can be elicited by external stimulation. Such “off-manifold” patterns may be difficult to process for brain circuits as they do not lie on the space or manifold that encompasses the set of sensory-evoked patterns. While neurons can be trained to generate novel patterns of activity within the intrinsic manifold (Golub et al. 2018), it is unknown if and how cortical circuitry must change to support an animal’s ability to recognize novel off-manifold patterns of activity. Here, we train mice to report off-manifold optogenetic stimuli delivered to excitatory cells (Emx1-Cre; Chrimson) and find that animals improve their detection performance for such stimuli over the course of days, showing learning that encompasses both gradual improvement in response speed and response sensitivity. Animals are first trained to detect visual stimuli, and when performance is stable, an optogenetic stimulus is added to the near-threshold visual stimulation. Animals take an average of 4.25 days (∓3.3 s.d., n=4; 1450.25 trials ∓934.97 s.d., n=4) to begin to report the optogenetic stimulus. After first acquisition of the optogenetic task, we track learning in two steps. First, mice shorten their reaction times for constant stimulus intensity (mean reaction time decrease over 6 days = 80.39 ms ± 14.04 ms s.d., n=4). Second, we lower stimulus intensity and animals’ detection threshold decreases as they become more sensitive to the stimulus (mean final max power = 11% ± 7.28% of starting power, s.d., n=2). It will be important to understand the underlying circuit changes associated with our observed behavioral effects.

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Poster

484. Visual Cortex: Circuits and Populations II

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Program #/Poster #: 484.07/GG6

Topic: D.07. Vision

Title: Cortical circuits implement optimal context integration

Authors: *R. IYER[1], S. MIHALAS[2]
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Abstract: Neuronal responses in early visual cortex are primarily driven by inputs to the classical receptive field and are influenced by stimuli in the surround. This type of response modulation is thought to arise due to the statistical structure present in natural scenes, with the surround providing context for the information in the classical receptive field. Lateral connections between neurons in the same cortical area are thought to be responsible for transmitting information in the near surround. Recent experimental studies have demonstrated like-to-like connectivity between excitatory neurons coding for the same feature (e.g. orientation) and specific rules for connectivity of inhibitory neuron types. On the other hand, normative models of lateral interactions, relying on sparsity and saliency in the optimal representation of natural images, predict functional inhibition between excitatory neurons. Assuming that an excitatory neuron represents the probability of a feature being present in the sensory stimulus, we hypothesize that lateral connections serve to optimally (in a Bayesian sense) integrate evidence from the surround. We show that such optimal integration of contextual information can be implemented by a neuronal network. Using natural scene statistics obtained from the Berkeley Segmentation DataSet and in-vivo electrophysiological data from awake mouse V1 neurons, we compute the synaptic weights resulting from optimal integration of contextual information.
We show that this network has like-to-like connectivity between excitatory neurons, in agreement with experimental observations. The distance dependence of connections is similar to those observed experimentally and these results generalize to other classes of receptive fields. The network also needs multiple types of inhibition - local normalization, surround inhibition and gating of inhibition from the surround - which we map to the parvalbumin (PV), somatostatin (SST) and vasoactive intestinal peptide (VIP) expressing interneuron cell classes respectively.
We explore the capacity to include higher order correlations in our network via multiple applications of the surround influence. We are also exploring the relation between normative models of classical receptive fields and the optimal context integration model which is used to

generate extra classical receptive fields.
We hypothesize that optimal integration of context is a general computation of cortical circuits.

Disclosures: R. Iyer: None. **S. Mihalas:** None.

Poster

484. Visual Cortex: Circuits and Populations II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 484.08/GG7

Topic: D.07. Vision

Title: Convolutional neuronal networks with optimal lateral connections are more robust to noise and predict signal and noise correlations in mouse visual cortex

Authors: B. H. HU, *S. MIHALAS
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Abstract: Convolutional neuronal networks have had great success in many applications as well as in describing neural responses in the ventral stream of primates. In contrast to what is known from biology, these networks focus on feedforward visual processing, largely ignoring the influence of recurrent connections. They also focus on supervised rather than unsupervised learning. Visual processing in the brain makes use of lateral connections and information from extra-classical receptive fields. The brain is also able to learn structured representations in a largely unsupervised manner with little to no labeled data. We leverage recent work demonstrating how Bayes-optimal lateral connections can be learned through an unsupervised method, a modified version of Hebbian learning rule. We combine this optimal context integration with deep learning to not only learn different features within a convolutional neuronal network, but also the optimal lateral connections between the neurons encoding these features. These connections can be implemented using a collection of cell types and lateral connections which match well biological observations in cortical circuits. We then demonstrate the influence of lateral connections by testing our model on two standard image datasets: MNIST and CIFAR-10. In additional to the original images, we also generate noisy versions of the images by adding additive white gaussian noise and salt-and-pepper noise in increasing levels. Importantly, we only train our model on the original images. As expected, increasing levels of noise degrades model performance for both the MNIST and CIFAR-10 datasets; however, models with optimal lateral connections are more robust to this noise and are able to achieve higher classification accuracies on both datasets, especially at higher noise levels. We also use these noisy images to test for signal and noise correlations among pairs of neurons in the model. We find positive correlations between noise and signal correlations in our model, which is consistent with two-photon recordings from neurons in the Allen Brain Observatory. This finding is in contrast to sparse coding hypotheses, which predict a negative correlation between noise and signal

correlations. Furthermore, we find that these positive correlations increase in deeper layers of the model. Our findings have implications for how correlations may limit information transmission within convolutional neuronal networks. Our results also suggest that the integration of lateral connections into convolutional neuronal networks is an exciting avenue of future research.

Disclosures: B.H. Hu: None. **S. Mihalas:** None.

Poster

484. Visual Cortex: Circuits and Populations II

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FEDER

Title: Spiking avalanches properties across different levels of cortical spiking variability

Authors: *A. FONTENELE[1], N. A. P. VASCONCELOS[2,3], C. SOARES-CUNHA[3], B. COIMBRA[3], A.-J. RODRIGUES[3], N. SOUSA[3], P. CARELLI[1], M. COPELLI[1]
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Abstract: Cortical circuits work on different levels of fluctuations, with behavioral relevance even in very local neuronal populations. This diversity of states has been observed during both evoked and spontaneous activity. A recent framework used to deal with complexity underlying the diversity of states is the critical brain hypothesis. It proposes that the brain operates near a critical state, at the border between qualitatively different types of cortical dynamics. Power-law distributions of avalanche sizes and durations have been employed as a key signature of such a critical state in neuronal activity. We investigated the changes of the properties of spiking avalanches throughout the different levels of fluctuations in spiking activity from large neuronal populations in primary sensory cortical areas of urethane-anesthetized rats. We found a striking difference in spiking avalanche properties across different levels of spiking variability, especially in which spiking avalanche distribution are best fitted by power laws (under the AIC criterion), with statistical self-affinity similar to 1/f noise. Based on this information, we propose that there is an intermediate level of variability in which the corresponding neuronal population activity in primary sensory cortices best approach its critical point.

Disclosures: A. Fontenele: None. **N.A.P. Vasconcelos:** None. **C. Soares-Cunha:** None. **B. Coimbra:** None. **A. Rodrigues:** None. **N. Sousa:** None. **P. Carelli:** None. **M. Copelli:** None.

Poster

484. Visual Cortex: Circuits and Populations II

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Topic: D.07. Vision

Support: EMBO
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Title: Inter-areal coordination and dendritic integration in visual cortex

Authors: *M. FISEK, D. HERRMANN, A. EGEA-WEISS, T. LEE, M. HAUSSER
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Abstract: A striking feature of the mammalian neocortex is its laminar structure. Cortical layers are specialized both morphologically and physiologically, but the ultimate functional roles different layers subserve has remained elusive. One of the most prominent differences between layers is the apical dendrites of their constituent neurons. Neurons in superficial layers, in comparison to deeper neurons, have shorter apical dendrites - suggesting that inputs to their apical dendrites, which tend to come from other cortical areas, might have more influence on the soma. In order to provide a link between dendritic activation patterns, inter-areal coordination, and laminar specialization, we performed in vivo two-photon calcium imaging experiments simultaneously in two visual cortical areas, primary visual cortex (V1) and the higher visual area LM. We presented a diversity of visual stimuli, and allowed head-fixed animals to run freely on running wheels without reward. We imaged spontaneous, sensory-evoked and locomotion-related activity in layer 2/3 or layer 5A using a combination of driver-Cre lines, and transgenic or viral reporter expression. By examining pairwise correlations across the two cortical areas, we show laminar specialization in terms of inter-areal coordination. In a separate set of experiments under similar conditions, we co-expressed the green glutamate indicator iGluSnFR and the red calcium indicator jRGECO1a and performed dual-color volume imaging of activity in apical and basal dendritic domains. We imaged activity in V1 or area LM separately, and examined sensory stimulus-evoked as well as locomotion-evoked changes in input (glutamate) and output (calcium) signals recorded across large fields of view, representing bulk signals in the tissue. Our results show that the correlation between apical dendritic glutamate signals and somatic calcium signals depends on stimulus and locomotor state. We find similar dependences in both V1 and LM. We are currently extending these experiments to monitor glutamate and calcium signals in

V1 and LM simultaneously. Together, these experiments will improve our understanding of the dendritic and synaptic mechanisms underpinning inter-areal coordination during visual processing.

Disclosures: M. Fisek: None. **D. Herrmann:** None. **A. Egea-Weiss:** None. **T. Lee:** None. **M. Hausser:** None.

Poster

484. Visual Cortex: Circuits and Populations II

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Title: *In vivo* quantification of single-cell targeted optogenetic stimulation with a digital micro-mirror device

Authors: *R. AOKI, A. BENUCCI
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Abstract: Circuit optogenetics with spatial-temporal patterned illumination at single-cell resolution is gaining much attention as a tool to dissect the neuronal functional connectivity within and across brain regions. Current methodologies are often cost ineffective, require high, possibly tissue-damaging laser power, and are note easily integrated with optical systems targeting deep brain regions (Yang and Yuste, 2018, Curr. Opin. Neurobiol.). Here, we present an approach based on a digital micro-mirror device (DMD) for a cost-effective, low laser power manipulation of neural activity with single-cell precision, millisecond temporal resolution, and easy integration with optical systems for patterned optogenetic stimulations in deep brain regions. First, using cortical slices of different thicknesses, we quantified the XYZ volumetric power density profile associated to a small excitation disk. At the focal plane, 120 um deep from the surface, a 25 um diameter disk (640 nm wavelength, via a 16x objective) was confined to a very small region (sigma = 11.6 +- 0.6 um, mean +- sem, Gaussian fit, peak 0.956 +- 0.126 mW/mm^2, n=5 measurements). With depth, the disk diameter increased, as measured by a calibrated CCD camera focused on the bottom side of the sample and the light power rapidly and significantly decreased (sigma = 14.8 +- 0.8 um, peak 0.494 +- 0.040 mW/mm^2, n=5 at z=170 um, sigma = 21.2 +- 0.8 um, peak 0.131 +- 0.010 mW/mm^2, n=5 at z=220 um). Above the focal

plane, we estimated the power increase from standard measures of light absorption and scattering in brain tissue (Helmchen and Denk, 2005, Nat. Methods). We then used the measured volumetric intensity profile, to estimate in-vivo the XYZ probability of single-cell excitation in neurons expressing ChrimsonR and GCaMP8 in mouse V1. At the focal plane, we reproduced z-slices of the volumetric intensity profile for a 25 um disk by corresponding adjustments of the excitation disk diameter and the light intensity. We then measured the probability of eliciting a response in a targeted cell by displacing the center of illumination at various lateral distances from the cell's center. This measure provides an upper-bound estimate since responses can be induced not only by direct illumination but also indirectly by excitation of en-passant neurites. In conclusion, our data supports the notion that single-cell excitation can be achieved *in vivo* with DMD technology. We are currently planning to test this methodology with gradient-index (GRIN) lens implantation for patterned optogenetic stimulation in deep brain regions.

Disclosures: R. Aoki: None. **A. Benucci:** None.

Poster

484. Visual Cortex: Circuits and Populations II

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Eli Lilly
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Title: Tauopathy in primary visual cortex causes feature-specific changes in visual function

Authors: *C. WU[1], A. BLOCKEEL[2], S. G. SOLOMON[1], K. D. HARRIS[1], K. G. PHILLIPS[2], A. B. SALEEM[1]
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Abstract: The overexpression and aggregation of tau is observed in a class of neurodegenerative diseases termed tauopathies. Individuals with tauopathy, and animal models of the disease, show a loss of behavioural and cognitive function - the mechanisms of which are yet unknown. We asked how tauopathy changes information processing capabilities of neural populations. Specifically, we investigated how information processing is altered in the Tg4510 model of tauopathy in primary visual cortex (V1); an area where the relationship between stimulus features, single unit responses, and the circuits and mechanisms underlying them, is relatively well characterised.
For this study, we took advantage of the fact that the expression of Tau in Tg4510 mice can be

suppressed by doxycycline. Thus, at 2.5 months old, mice were assigned to tau positive (Tau+) and tau suppressed (Tau-) groups. Tau- animals were administered doxycycline through drinking water (experimenters were blinded to the group identity). We conducted chronic awake head-fixed recordings in V1 of 5-6.5 month old mice, presenting a variety of visual stimuli, including drifting grating stimuli that varied across feature dimensions such as orientation, contrast, or size. Recording sessions were repeated over the course of several weeks, allowing us to obtain multiple recordings from each mouse.
Tau+ and Tau- mice showed clear differences in the oscillatory local field potentials in V1, with Tau+ mice showing a suppression of narrow-band gamma (55-65 Hz) power. Single unit responses (2201 cells for Tau+, 2230 for Tau-) to a sparse noise stimulus were less selective and less reliable in the Tau+ group. To characterise information processing, we fit response models to single unit responses to drifting grating stimuli which varied along specific feature dimensions. Responses to other stimulus features, such as spatial frequency, were unchanged between the two groups. Surprisingly, Tau+ mice showed enhanced orientation selectivity, measured by both model fit quality and the orientation selectivity index. They also showed a larger suppression of response after being adapted to a specific orientation.
In conclusion, tauopathy shows clear effects on information processing in the visual cortex. This was not through a non-selective decrease in responsiveness, but instead enhanced some types of processing, such as orientation selectivity, while disrupting others such as responses to sparse noise. These selective effects on neural function may reflect selective patterns of tauopathy within visual areas.

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Poster

484. Visual Cortex: Circuits and Populations II

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Topic: D.07. Vision

Support: the Alfred P. Sloan Foundation

Title: Role of higher visual areas in detecting orientation and contrast changes

Authors: *M. JIN, L. L. GLICKFELD
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Abstract: Mouse visual cortices are highly interconnected, but form orderly processing streams that refine visual information to accurately guide behavior. While neurons in mouse primary visual cortex (V1) are functional heterogeneous, neurons in higher visual areas (HVAs) are

specialized for processing distinct features of visual stimuli. This indicates that HVAs might have distinct perceptual roles and if so, specialized sensory information must be routed via distinct pathways to guide different behaviors. Therefore, we first aim to test the requirement of HVAs (AL, LM and PM) in visually guided behaviors such as detecting orientation or contrast changes. We train water-restricted mice to report visual changes by manipulating a lever and optogenetically silence each HVA via exciting inhibitory interneurons to determine if this can impair animal's perceptual ability. We found that silencing area V1 (n=6), LM (n=4) and AL (n=7) caused significant reductions in both hit and false alarm rate in an orientation change detection task, resulting in an increase in orientation detection threshold and a decrease in sensitivity (d-prime). However, silencing PM (n=3) did not affect any of the perceptual measurements, despite the efficacy of neuronal recruitment by task stimuli and silencing by optogenetic activation having been validated electrophysiologically. Since contrast detection might be more broadly encoded by visual circuits, we tested if PM is required for contrast detection instead. However, while silencing areas V1 (n=4), LM (n=5) and AL (n=3) consistently increased contrast detection thresholds, silencing area PM (n=6) had no effect on contrast detection. Overall, our data shows that area V1, AL and LM, but not PM are required for orientation and contrast change detection. This suggests that 1) information necessary for visual perception is routed through V1, LM and AL; and 2) similar circuits/computations may be used to detect orientation and contrast changes. Ongoing experiments are aimed at dissociating the function of areas LM and AL in visual processing, and determining whether area PM is specialized in detecting changes in other features such as speed.

Disclosures: M. Jin: None. **L.L. Glickfeld:** None.

Poster

484. Visual Cortex: Circuits and Populations II

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Topic: D.07. Vision

Support: Cognitive Sciences & Tegnologies Council, Tehran, Iran.
Neuroscience Research Center, Shadid Beheshti University, M.C., Tehran, Iran.

Title: The electrical stimulation of the dorsal raphe nucleus (DRN) changes visual responses of neurons in primary visual cortex

Authors: *S. ROSTAMI, P. GHADERI, L. DARGAHI, M.-S. SAFARI
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Abstract: Introduction: Serotonergic system is involved in many basic functions including motor control, sleep, learning and memory, pain and sensory processing. Serotonin (5-HT)

transmission forms a major modulatory network within sensory systems. This network influences various information-processing mechanisms. Serotonin has been shown to be involved in visual processing, specifically orientation processing, at the cortical and retinal level. We investigated subthreshold and supra threshold responses of excitatory and inhibitory neurons using in vivo patch-clamp recording in layer II/III of primary visual cortex(V1).
Method: Naive mice of either sex (postnatal days 40-70) are used. Animals were anesthetized and craniotomy was done on the region of interest in V1. For electrical stimulating of the DRN serotonergic system, a bipolar tungsten electrode was inserted into the DRN. Whole-cell recordings from putative inhibitory and excitatory neurons in layer II/III of V1 was performed. In order to data acquisition and visual stimulation, square-wave grating (0.04 cycle/deg) at 100% contrast moved on an LCD in 12 directions at 30 degree steps (0-360 degrees) and 5 contrast patterns. Membrane potentials (subthreshold and supra threshold) were recorded at current-clamp mode. Data were analyzed by matlab software. For statistical analysis, values without and with DRN stimulation from the same cells were compared with T-test.
Results: Electrical stimulation of the serotonergic system seems to be decrease spontaneous and evoked potentials (subthreshold and supra threshold responses) of putative excitatory and inhibitory neurons in V1 during orientation selectivity and contrast response function. By Calculating of mean neuronal firing rate in different orientations and contrasts, then fitting a cousinous function, the shape of the response curve has changed, as well as the reduction of the response amplitude was observed with the stimulation of DRN. In such cases, serotonin seems to have a gain control function. The response curve become wider at preferred orientation and neuron more sensitive to direction of visual stimulus. Moreover, tendency to respond in higher contrast in this series of neurons was observed.
Conclusion: We are interested to find how serotonergic system change tuning curve of neurons in v1. Temporal and spatial dynamic of serotonin neuromodulation are another goals of our study. We suppose that the serotonergic system plays an important role in neural network dynamics in visual cortex sensory processing, which is essentially different cell-type and layer specific.
Keywords: serotonergic system; visual response; primary visual cortex

Disclosures: S. Rostami: None. **P. Ghaderi:** None. **L. Dargahi:** None. **M. Safari:** None.

Poster

484. Visual Cortex: Circuits and Populations II

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Topic: D.07. Vision

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Title: Neurotransmitter receptor bases for spatial summation in visual cortex by in-vivo single-unit recording and juxtacellular injection

Authors: *X. SONG[1], T. AN[2], C. ZHENG[2]
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Abstract: In primary visual cortex, modulation of neuronal response by stimuli in the extraclassical receptive field play important roles in visual information processing. Based on the presence or absence of surround suppression, we subdivided the neurons into two categories: surround-suppressive (SS) cells, and surround-non-suppressive (SN) cells. It is unknown whether these two types of spatial summation properties are related to neurotransmitter receptor distributions on these cells. Using in vivo single-unit recording and juxtacellular injection of tracer, combined with receptor immunocytochemistry, we have studied the immunocytochemical features of the SS and SN neurons. Significant differences were found in density of excitatory and inhibitory neurotransmitter receptors between the two types of neurons. SN neurons have densely distributed Glu2/3 receptors and relatively small amount of $GABA_A$ receptors on the surface of proximal dendrites and cell body. We found the reverse is true for SS neurons. As Glu2/3 receptors are the main targets of excitatory synaptic input and $GABA_A$ receptors are the main targets of inhibitory synaptic input, the differences in receptor characteristics between the SS and SN neurons may underlie the distinct surround modulation effects of these two types of neurons.
Key words: primary visual cortex; surround-suppressive neurons (SS); surround-non-suppressive neurons (SN); $GABA_A$ receptor; Glu2/3 receptor

Disclosures: X. Song: None. **T. An:** None. **C. Zheng:** None.

Poster

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Brown Institute for Brain Sciences
Brown Initiative for Computation in Brain and Mind

Title: Large-scale system identification of mouse primary visual cortex

Authors: *D. LINSLEY, T. SERRE
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Abstract: The presence of significant nonlinearities in visual cortex neuron responses has impeded their characterization. Recent progress in representational learning, a branch of machine learning concerned with the discovery of optimal representations to predict data, combined with the availability of large-scale neural recordings and computational resources offer a unique opportunity to tackle this challenge. Here, we leveraged machine learning methods to model calcium imaging data from the Allen Brain Observatory. We fitted computational neuroscience models to predict neural activity from nearly 4,000 cells in layers 2/3 and 4 of the mouse primary visual cortex (VISp). We found that end-to-end trainable convolutional neural networks (CNNs) which learn filters from data offer a better fit compared to the fully-connected difference-of-gaussian (DoG) filters of previous work (Antolik et al. 2016). This is consistent with prior work on smaller datasets (Klindt et al., 2017) and suggests that feature learning and weight-sharing across the visual field supports system identification. How do these models relate to classical receptive field mapping methods? We explored this by comparing model fits to the estimated spatial profile of first-order receptive fields derived from the same neurons using sparse correlation methods. CNN fits were significantly more correlated with these receptive field profiles in layer 4 than in layers 2/3, suggesting that CNN models account for nonlinearities in the neural response not captured by linear methods. In contrast, DoG models were correlated consistently with receptive field properties across cortical layers. Together, these results emphasize the need to develop new computational- and data-based solutions for modeling the nonlinearities in neural response profiles. We expect that better neural characterizations will emerge from computational architectures which combine feedforward mechanisms with recurrent connections that implement nonlinear neural computations.

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Poster

485. Visual Cortex: Circuits and Populations III

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Vision for Tomorrow

Title: Aberrant population receptive fields in albinism reveal new types of retino-cortical miswiring

Authors: *E. J. DUWELL[1], J. MATHIS[2], J. CARROLL[3], E. A. DEYOE[2]
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Abstract: In albinism, the temporal retinal afferents decussate pathologically at the optic chiasm, resulting in partially superimposed right and left hemi-field representations in visual cortex. Previous fMRI studies in albinism have suggested that single voxels in these regions of hemi-field overlap respond to two mirror image locations across the vertical meridian (Hoffmann et al., 2003). However, population receptive fields (pRFs) in regions of hemifield overlap in albinism have not yet been quantitatively modeled. To address this, we used conventional ring and wedge stimuli with fMRI at 3T to map cortical retinotopy and model single voxel pRFs throughout the visual hierarchy in 5 subjects with albinism. We hypothesized that voxel time courses in regions of hemi-field overlap would be best modeled by a dual rather than a single gaussian pRF model, and that these dual gaussian profiles would be positioned at approximate mirror image locations across the vertical meridian. To test these hypotheses, all voxels in visual areas V1, V2 and V3 were fit with both single and dual gaussian pRF models. We then compared the model fits by using the residual sum squared error and number of model parameters to compute Akaike's information criterion. To assess the degree to which dual pRFs were precisely mirrored across the vertical meridian, we calculated the angle formed by the line transecting the two pRF centers and the horizontal meridian. RESULTS: On average, 44.3% of all voxels in V1-V3 occurred in hemi-field overlap zones with 55.7% in non-overlap zones as determined by monocular right and left hemi-field expanding ring activation maps thresholded at a correlation coefficient of 0.3. As predicted, we found that overlap regions had a significantly higher percentage of dual pRF voxels than non-overlap regions (14.1% vs. 9.5% respectively, $p = 0.03$) and the incidence of dual pRFs was similar across all three visual areas. However, we also found that a large percentage (48.5%) of dual pRF voxels fell outside the regions of hemi-field overlap. Additionally, of the nearly 1500 dual pRF voxels which met thresholding criteria in V1-V3, 38.4% were oriented at greater than a 45-degree angle with respect to the horizontal meridian. Of this group, 38.4% were straddling the horizontal meridian rather than the vertical meridian and some dual pRFs were aligned parallel to the vertical meridian. These data reveal that the pattern of right-left hemi-field overlap in albinism is more complicated than previously appreciated and suggest that a second type of misrouting may also occur in albinism: the miswiring of the upper and lower hemi-fields to the proper side of the calcarine sulcus in V1.

Disclosures: E.J. Duwell: None. **J. Mathis:** None. **J. Carroll:** None. **E.A. DeYoe:** None.

Poster

485. Visual Cortex: Circuits and Populations III

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Title: Circuit mechanisms of correlated neural variability

Authors: *L. NURMINEN[1], A. M. CLARK[2], A. ANGELUCCI[3]
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Abstract: Neural responses to repeated presentation of the same stimulus vary stochastically from trial-to-trial and this variability is correlated across neurons. While experimental studies have produced a detailed picture of the parameters affecting the magnitude of correlated variability, a mechanistic understanding of this phenomenon has mainly come from theoretical studies.
To uncover how feedback circuits contribute to correlated variability in primate V1, we recorded single and multi-unit responses (24-channel V-probe) through a V1 column while optogenetically inactivating feedback connections from V2. The neural silencer ArchT was expressed in V2 neurons by injecting 1:1 mixture of Cre-expressing AAV9 (AAV9.CaMKII.Cre) and Cre-dependent AAV9 carrying the genes for ArchT and GFP (AAV9.Flex.CAG.ArchT-GFP) into V2. Three 360 nl injections were made parallel to the V1-V2 border (identified using optical imaging). The axon terminals of feedback neurons projecting from V2 to V1 were selectively inactivated by targeting 565 nm light to V1 while V2 was shielded from light.
The relationship between stimulus size and correlated variability was investigated by varying the diameter of a grating centered on the receptive fields of the recorded neural population. As stimulus size was increased, correlations first increased to a peak and then began to decrease until a plateau was reached. Qualitatively, the correlation vs. size functions resembled stereotypical size tuning functions of V1 neurons. Quantitatively, however, these functions systematically peaked at a smaller stimulus diameter than the simultaneously measured size tuning functions. Thus, the relationship between firing-rate and correlation was non-monotonic. The magnitude of the correlations at the function peak was on average 0.4 vs 0.2 at the largest diameter. In some neuron pairs, positive correlation at small stimulus size turned to negative correlation when the stimulus was large. The effect of inactivating V2-to-V1 feedback depended on stimulus size. When the stimulus was small, inactivating feedback reduced correlations whereas the correlations were increased when the stimulus was of intermediate size.
Here, we provide causal evidence that feedback from extra-striate cortical areas contributes to correlated variability in primate V1. Our results suggest that evaluating the impact of correlated variability on visual information processing using a feedforward framework may prove inadequate.

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Poster

485. Visual Cortex: Circuits and Populations III

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Program #/Poster #: 485.04/HH1

Topic: D.07. Vision

Title: Neural response variability and divisive normalization

Authors: *R. COEN-CAGLI
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Abstract: Variability is a widespread feature of neuronal activity in sensory cortex: repeated measurements of neuronal spike counts in response to the same sensory input are variable. Much work has been devoted to understanding how this neuronal variability might limit the reliability of perception, and what processes are in place to control it. Variability may also be a genuine coding dimension of neuronal activity, beyond average firing rate, as it is modulated by stimulus onset, stimulus dimensions (e.g. contrast, orientation), and non-sensory signals (e.g. attention, locomotion). For this reason, it is important to develop models of cortical activity that capture how changes in the stimulus affect both firing rate and variability. Linear-Nonlinear-Poisson models rely on restrictive assumptions of static nonlinearity and Poisson variability. Several extensions exist that go beyond Poisson, but they typically oversimplify, or ignore altogether, the nonlinear stimulus dependence. This nonlinear behavior is often accurately described by divisive normalization (DN), a canonical computation evident across multiple brain areas: the firing rate of a neuron is the ratio between the stimulus drive to its receptive field, and the stimulus drive to an ensemble of other neurons (termed normalization signal). However, DN models typically ignore response variability. Recent work suggests DN may also modulate variability, beyond firing rate, but this work relies entirely on simulations. To address these issues, here we derive new mathematical results linking DN and the across-trial spike count distribution. We treat the numerator and the normalization signal in DN as random variables, and derive an estimator of the mean and variance of their ratio, which provides an excellent approximation. Under plausible assumptions, this model displays Poisson-like behavior and rate-dependent Fano factors consistent with cortical data. While it is not possible to measure the normalization signal experimentally, we demonstrate how to infer its latent state using our model. We then show analytically and in simulation, that increasing the strength of the normalization signal always decreases the Fano factor. This leads us to the general prediction that experimental manipulations that engage DN should stabilize cortical activity regardless of the specific brain area and experimental manipulation. This prediction is supported by our analysis of macaque V1 data for contrast (N=3 animals) and size (N=8) tuning, and we are currently testing it in areas V2 and MT.

Disclosures: R. Coen-Cagli: None.

Poster

485. Visual Cortex: Circuits and Populations III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 485.05/HH2

Topic: D.07. Vision

Support: NIH U01 NS 094368-03

Title: Neighboring cortex diversely shapes stimulus responses in V1, as revealed by optogenetic suppression

Authors: *A. R. ANDREI[1], S. R. DEBES[1], R. JANZ[1], J. L. SPUDICH[2], V. DRAGOI[1]
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Abstract: Understanding how the local network context changes the responses of cortical neurons is a fundamental problem in systems neuroscience. Visual cortical neurons are embedded into local circuits consisting of excitatory and inhibitory interactions. Although local circuits are generally assumed to be homogeneous in structure, mounting evidence suggests that the variability and strength of local inputs vary significantly across the cortex. Here we examined the role that neighboring, lateral networks play in shaping stimulus responses in the V1 of awake macaque. It has been proposed that nonlinear neural responses, such as contrast response normalization, are mediated by local networks. However, this relationship has never been causally tested. To address this, we inhibited the activity of glutamatergic neurons using Gt-ACR2, a chloride-conducting channelrhodopsin, and recorded the activity of neurons several hundred microns away, while monkeys performed a contrast detection task. In the absence of a visual stimulus, the optogenetic suppression had little-to-no effect on the firing rate of the neighboring neurons. However, in the presence of a visual stimulus, we observed a striking range of contrast-dependent changes in firing rate in the neighboring cells. We report here that the neighboring network shapes stimulus responses according to 4 general motifs - weak suppression/facilitation across contrast levels, facilitation/suppression at low/high contrasts, and facilitation/suppression at high/low contrasts - present in specific proportions throughout the cortical column and within cortical layers. These response patterns are well captured by the standard normalization model, which presumes that local network provides both an additive and a divisive component to individual neurons. Our study provides the first causal evidence that the circuitry capable of mediating normalization effects is located within the local lateral network. Further, we propose that these 4 motifs are indicative of distinct classes of connection patterns between cortical columns.

Disclosures: A.R. Andrei: None. **S.R. Debes:** None. **R. Janz:** None. **J.L. Spudich:** None. **V. Dragoi:** None.

Poster

485. Visual Cortex: Circuits and Populations III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 485.06/HH3

Topic: D.07. Vision

Support: NSF IIS-1254123
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NSF IOS-1556388

Title: Corticalee column as an information-preserving decoder of neural inputs

Authors: *T. O. SHARPEE[1], J. BERKOWITZ[2]
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Abstract: Cortical tissue has a circuit motif termed the cortical column, which is thought to represent its basic computational unit but whose function remains unclear. Here we propose, and show quantitative evidence, that the cortical column performs computations necessary to decode incoming neural activity with minimal information loss. The cortical decoder achieves higher accuracy compared to simpler decoders found in invertebrate and subcortical circuits by incorporating specific recurrent network dynamics. These recurrent dynamics also makes it possible to choose between alternative stimulus categories. The structure of cortical decoder predicts quadratic dependence of cortex size relative to subcortical parts of the brain. We quantitatively verify this relationship using anatomical data across eighteen mammalian species, including rodents, insectivores, and primates. The analysis identified two factors that control brain expansion within and across mammalian orders. The first factor that controls brain expansion within orders, e.g. within primates, is the average dimensionality of inputs processed by each column. Among primates, humans have the largest value. The estimated input dimensionality for the mouse matches experimental reports on the number of layer 5 projection neurons in the mouse motor cortex. The second factor, which controls brain expansion across orders, is the number of neuronal types per input dimension. It is 10 times larger in primates compared to rodents. The results account for recent observations for the small number of excitatory cell types in rodents. The also explain co-variation between the number of projection and intratelecephalic neurons in layer 5 mouse motor cortex. Overall, the results reveal a new constraint on the evolution of brain circuits and offer a new perspective on the computational function of cortical columns.

Disclosures: T.O. Sharpee: None. **J. Berkowitz:** None.

Poster

485. Visual Cortex: Circuits and Populations III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 485.07/HH4

Topic: D.07. Vision

Support: HHMI

Title: Neural straightening of natural videos in macaque primary visual cortex

Authors: *Y. BAI[1], O. J. HÉNAFF[2], J. CHARLTON[1], I. M. NAUHAUS[1], E. P. SIMONCELLI[2], R. L. GORIS[1]
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Abstract: Many behaviors rely on predictions about the future state of the environment derived from recent observations. Prediction is most robust along a straight, or linear trajectory. Yet, under natural circumstances, the stream of visual input typically evolves according to highly non-linear dynamics. It thus stands to reason that computations within the visual system work to linearize the temporal dynamics of visual representations, thereby enabling more robust predictions of future states of the environment. Recent psychophysical work has provided strong evidence for this hypothesis by showing that the human visual system selectively straightens the temporal trajectories of natural image sequences, thus facilitating their extrapolation (Hénaff, Goris, Simoncelli, 2018).
How does straightening emerge from the cascade of transformations performed by the visual system? We hypothesize that the successive stages of processing incrementally linearize the dynamics of visual representations. Here, we investigated the straightness (conversely, curvature) of representations of natural image sequences in the primary visual cortex (V1). We recorded neural population activity in area V1 of anesthetized macaque monkeys using multi-electrode laminar arrays while briefly presenting individual video frames taken from natural videos. As a control, we also presented stimuli taken from “unnatural” synthetic videos to determine whether neural straightening is specific to behaviorally relevant sequences. We developed a new computational analysis technique to quantify the “straightness” of a population vector’s trajectory.
Preliminary results from five V1 populations (ranging in size from 26–61 units) reveal that neural representations of natural videos exhibit trajectories that are on average straighter than the trajectories described by the stream of incoming light intensities. Moreover, neural straightening is limited to natural videos. For our synthetic, unnatural videos, we found an increase in the curvature of the neural representation relative to the intensity domain. Together, these results

suggest that computations in the early visual system contribute to realizing a major behavioral goal: making the visual environment predictable in time.

Disclosures: Y. Bai: None. **O.J. Hénaff:** None. **J. Charlton:** None. **I.M. Nauhaus:** None. **E.P. Simoncelli:** None. **R.L. Goris:** None.

Poster

486. Visual Cognition: Decision Making I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 486.01/HH5

Topic: D.07. Vision

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Simons Collaboration on the Global Brain
Pew Charitable Trusts
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Cold Spring Harbor Laboratory

Title: Rat posterior striatum and frontal orienting fields are part of a modality-independent circuit for decision-making

Authors: *L. CHARTARIFSKY, S. PISUPATI, A. K. CHURCHLAND
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Abstract: Decision-making often relies on information from diverse sources. Existing work has begun to uncover individual areas supporting this process, but structures are usually probed using sensory signals from only one modality. Therefore, little is known about whether common circuits support decisions about multiple modalities, e.g., auditory vs. visual signals. Furthermore, a major emphasis of current work is the cortex; the contribution of subcortical structures remains largely mysterious. Here, we aimed to determine whether there are brain areas causal to decisions about different sensory modalities, focusing on the frontal orienting fields (FOF) and posterior striatum (pStr). FOF, and more recently, pStr have been implicated in auditory decision-making, but little is known about their role in visual decisions. To test this, we trained freely moving rats to report whether the underlying rate of a visual, auditory or multisensory stimulus was higher or lower than an abstract category boundary. Using precise models to characterize specific perceptual parameters, we were able to describe psychophysical data and understand the involvement of pStr and FOF in multisensory decision-making. In keeping with previous findings, unilateral muscimol inactivation of FOF (n=5 rats, 0.1-0.4 ug) and pStr (n=5 rats, 0.075-0.125 ug) drove an ipsilateral bias on auditory trials. Interestingly,

decisions on visual trials showed similar bias. Our model suggested that the bias did not arise from changes in how evidence was accumulated, but instead from an increased tendency to make "guesses" in the ipsilateral direction. To determine whether changes in decision-making simply reflected an increased tendency to favor the ipsilateral side, we compared behavior on a "sure bet" task in which the rat was explicitly instructed (via a salient LED) which side would be rewarded. Performance was preserved on the sure-bet task, suggesting that behavioral effects were restricted to situations in which there was uncertainty about the correct outcome. Moreover, changes in movement time to the left vs. right reward port were small and idiosyncratic across animals and sites, suggesting that effects on decision-outcome were not due to a muscimol-induced motor impairment. Taken together, these results argue that FOF and pStr are part of a circuit common to decisions about multiple sensory modalities that is engaged during uncertain situations. Our model suggests that these areas may confer value to choices and that inactivation leads to devaluation of the contralateral choice.

Disclosures: L. Chartarifsky: None. **S. Pisupati:** None. **A.K. Churchland:** None.

Poster

486. Visual Cognition: Decision Making I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 486.02/HH6

Topic: D.07. Vision

Title: Dynamic representations of multiple stages of sensory-motor transformation in the lateral intraparietal cortex during decision making

Authors: *Z.-Q. LIN, Z. ZHANG, C. YIN, T. YANG
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Abstract: During decision making, one often has to accumulate multiple pieces of evidence. Previous studies have shown that neurons in the lateral intraparietal area (LIP) encode accumulated evidence for eye movement decisions. However, it is hotly debated whether accumulation occurs in the LIP or somewhere else. Here, we approach this problem with a task in which each piece of evidence has first to be assembled from different stimulus dimensions before it is accumulated. We reason that one would be more likely to observe the representations of each information processing step in the LIP if it is where the accumulation occurs.
In this two-alternative forced-choice task, the monkey viewed 6 shapes sequentially in each trial and made an eye movement choice afterwards between a red and a green target. The shapes were selected randomly with replacement from a pool of 6. Each shape could be either red or green, and was associated with a weight. The sum weight from the shapes with the same color indicated the log ratio between the likelihoods of the target with this color yielding a reward and not. Therefore, the decision of eye movements had to be accumulated from each single piece of

evidence that combined the shape's weight, color, and the target configuration.
After the monkey learned the task, we recorded LIP neurons' activities when it performed this task. We selected neurons with delay-period activity and spatial selectivity in a memory saccade task. During recordings, either the red or the green target could appear in the receptive field of the recorded neuron (T_{in}), and the other target was placed in the opposite hemifield. Consistent with the previous studies, we found that the LIP neurons encoded accumulated evidence during decision making. Furthermore, we observed that the neurons also encoded each shape's weight independently from either color or target configuration, and whether the shape's color was consistent with the T_{in} color. The representations of the weight and the color consistency were only in a transient window after each shape's onset, while the representation of the accumulated evidence for eye movements was maintained and updated when new shapes were presented throughout a trial. We, however, did not observe the representation of single piece of evidence for eye movements in the LIP. These observations suggested the LIP was likely where the sensory-motor transformation occurred during decision making.

Disclosures: Z. Lin: None. **Z. Zhang:** None. **C. Yin:** None. **T. Yang:** None.

Poster

486. Visual Cognition: Decision Making I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 486.03/HH7

Topic: D.07. Vision

Support: TUBITAK Grant 217K163

Title: A recursive bayesian updating scheme to model the effect of prediction on individuation

Authors: *B. M. URGEN, H. BOYACI
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Abstract: Predictive computation has become a prominent alternative to model the brain function. Consistent with such computational models, previous studies showed that prior information speeds up perceptual decisions for the detection of the location of a stimulus. In this study we present a recursive Bayesian updating scheme, in which posterior of an iteration is used as the prior of the next, to model empirical results of an individuation (detection of spatial location) task within the framework of predictive computation. In the behavioral experiment centrally presented task irrelevant cues, face or house, provided information about the prior probability of the upcoming image category. Next, an intact (target) image was shown on either left or right periphery. On the opposite side a scrambled version of the same image was presented. This was followed by presentation of masks, which were different scrambled versions of the target image. Participants' task was to indicate the spatial location of the intact target

image while maintaining their fixation on the fixation dot during the trial. The validity of the category cue was set at 100%, 75%, 50%, 25% in different experimental sessions, and participants were informed about the probability of cue-validity prior to the experiments. In each trial, the duration of the target presentation was determined using an adaptive staircase procedure in a 2-AFC paradigm. Duration thresholds were computed in congruent and incongruent trials separately (in terms of cue-target category associations). Two-sample paired t-tests were conducted to investigate whether task irrelevant predictive cues (as priors) have an effect on duration thresholds in congruent and incongruent trials. The results showed that thresholds were higher in incongruent trials than in congruent trials only in 75%-validity condition, suggesting that prediction has an effect on individuation only when the prediction's validity is relatively high ($t(6)=-2.8919$, $p<0.0276$). Our Bayesian scheme was able to successfully capture the pattern observed in human observers, suggesting that schemes with iterative priors may lead to better models of human behavior than approaches using static priors.

Disclosures: B.M. Urgen: None. **H. Boyaci:** None.

Poster

486. Visual Cognition: Decision Making I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 486.04/HH8

Topic: D.07. Vision

Title: Prior information guides perceptual decision making in a remarkably flexible manner

Authors: *J. CHARLTON, Y. BAI, R. L. GORIS
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Abstract: Perceptual systems operate in the presence of uncertainty. When the sensory input is ambiguous, prior experience guides our interpretation of the environment, suggesting perception obeys the laws of probabilistic inference. While some characteristics of the sensory environment are stable, others vary with context. Here, we seek to determine the limits of our ability to integrate context-specific priors with incoming sensory information when the context changes over short timescales. We measured perceptual judgments of stimulus orientation under three different task contexts, each associated with a different distribution of stimulus orientation. Stimuli were drifting sinusoidal gratings (diameter: 1.25 deg. of visual angle), presented for 500 ms in the near-periphery (eccentricity: 3.2 deg.). Prior to stimulus onset, task-context was communicated to the observer via the color of the fixation mark. Crucially, after an initial training phase, task-context could switch from trial to trial. We estimated observers' reliance on prior information by fitting their behavioral reports with an observer model in which stimuli are represented by 1-D Gaussian distributions and perceptual decisions arise from comparing the internal representation to a fixed decision-criterion. We found that different task contexts were

associated with different decision-criteria, consistent with the optimal inference strategy. Moreover, reducing stimulus contrast yielded a stronger dependency of criterion on task context, and hence a stronger reliance on prior information. Interestingly, criterion placement did not depend on the level of context stability across trials. Thus, even immediately upon switching task context, context-specific information is readily accessible to be integrated with sensory signals. Together, these findings demonstrate that the visual system flexibly deploys optimal inference strategies when performing perceptual tasks, and hence is well adapted to operate in rapidly changing environments.

Disclosures: J. Charlton: None. **Y. Bai:** None. **R.L. Goris:** None.

Poster

486. Visual Cognition: Decision Making I

Location: SDCC Halls B-H

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Topic: D.07. Vision

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McKnight Scholars Award

Title: Sensory and decision-making processes underlying perceptual adaptation

Authors: *L. SHA[1], N. WITTHOFT[2], J. WINAWER[3], R. KIANI[4]
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Abstract: Perceptual systems adapt to their inputs. As a result, prolonged exposure to particular stimuli alters judgments about subsequent stimuli. This phenomenon is commonly assumed to be sensory in origin. Changes in the decision-making process, however, may also be a component of adaptation. Here, we quantify sensory and decision-making contributions to adaptation in a facial expression paradigm. As expected, exposure to happy or sad expressions shifts the psychometric function toward the adaptor. More surprisingly, response times show both an overall decline and an asymmetry, with faster responses opposite the adapting category, implicating a substantial change in decision-making process. Specifically, we infer that sensory changes from adaptation are accompanied by changes in how much sensory information is accumulated for the two choices. We speculate that adaptation influences implicit expectations

about the stimuli one will encounter, causing modifications in the decision-making process as part of a normative response to a change in context.

Disclosures: L. Sha: None. **N. Witthoft:** None. **J. Winawer:** None. **R. Kiani:** None.

Poster

486. Visual Cognition: Decision Making I

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Title: Representation of the dynamics of decision-making process in the lateral intraparietal cortex during face discrimination

Authors: *G. OKAZAWA, R. KIANI
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Abstract: Past studies have shown that a frontoparietal network, including lateral intraparietal cortex (LIP), represents the dynamics of integration of evidence for sensory decisions based on simple stimuli such as stochastic moving dots or geometric shapes in probabilistic classification tasks. Our perceptual decisions, however, often involve more complex visual stimuli such as objects and faces, which are composed of multiple features. Decisions based on these stimuli are likely to rely on integration of evidence over space as well as time. Do similar decision-making processes underlie discrimination of simple and more complex stimuli? We studied population responses of LIP neurons, while monkeys performed a fine face discrimination task by reporting facial identity or expression with a saccadic eye movement. Three key features of our task made it possible to infer the computations that furnished the monkey's choice: 1) a custom-made morph continuum between two prototype faces in which different facial features could vary independently enabled us to quantify spatial integration of facial features; 2) a special masking paradigm enabled us to introduce subliminal fluctuations in the features and quantify temporal integration of evidence; 3) variable stimulus viewing duration on different trials enabled us to probe termination criterion for the decision. Similar to humans (Okazawa et al, SfN 2016), monkeys performed the task by integrating sensory evidence over space and time and varied the weighting of facial features depending on task characteristics (facial identity or expression). Compatible with previous studies, LIP neurons modulated their responses to reflect

spatiotemporal integration of sensory evidence. However, many neurons showed only small response modulations during the stimulus viewing and large modulations that reflected the choice after stimulus offset, while the monkey waited for a Go cue to initiate its saccade. Further, although response modulations during stimulus viewing represented stimulus strength, the ordering of the responses of many neurons deviated from expectations based on past studies: stimuli closest to the category boundary evoked the strongest responses for both choices. The results point at subtle but significant differences in LIP neural responses during face discrimination and direction discrimination, indicating that the same set of computations may differentially engage parietal cortex in the two tasks.

Disclosures: G. Okazawa: None. **R. Kiani:** None.

Poster

486. Visual Cognition: Decision Making I

Location: SDCC Halls B-H

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Topic: D.07. Vision

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International Research Scholar from the Howard Hughes Medical Institute to R. M. B.

Title: Representation of choice bias in the activity of prearcuate gyrus during perceptual decision making

Authors: *G. MOCHOL[1], R. KIANI[2], R. MORENO BOTE[1]
[1]Ctr. for Brain and Cognition, Pompeu Fabra Univ., Barcelona, Spain; [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Optimal decision making often depends on integration of current sensory information with prior history of choices, rewards and stimuli. Such biases may be beneficial especially when sensory information is weak or ambiguous, and prior history carries relevant information about upcoming stimuli or rewarding actions. However, little is known about the neuronal correlates of such biases and how they influence the decision-making process. Here, we report the existence of history-dependent biases in the behavior of highly-trained monkeys performing a motion direction discrimination task and demonstrate a neuronal representation of the bias in the activity of prearcuate gyrus (PAG) neurons. In our task, stimulus direction and strength varied randomly

from trial to trial, making previous history uninformative for future choices. Nonetheless, monkeys showed small but significant biases that fluctuated at two distinct time scales: slow (tens to hundreds of trials) and fast (previous trial). On each trial, fast bias reflected previous choice and outcome, while slow bias reflected the monkey's choice preference within tens of neighboring trials. Knowing these biases significantly improved our ability to predict monkeys' upcoming choice on individual trials. Importantly, the highest increase in the prediction accuracy was observed for trials with weaker motion strengths, suggesting a stronger role of prior history in shaping the choice when sensory information was limited (accuracy increase >2.5% for difficult stimulus with p(correct)<0.75, compared to a reference model with the stimulus strength as the only predictor). The pre-stimulus population activity of PAG neurons represented the fast and slow biases, indicating a correlate for both types of bias in the prefrontal cortex. The same activity was also informative about the monkey's upcoming choice with higher prediction accuracy for sessions with stronger representation of bias in PAG activity. Further analyses of a descriptive model suggested that this predictive power was a consequence of representing bias signals. Since the same PAG neurons also represented past choices and feedback that shaped the subjective bias, they could offer a compact circuit for the computation of prior history signals and leveraging those signals to guide behavior.

Disclosures: G. Mochol: None. **R. Kiani:** None. **R. Moreno Bote:** None.

Poster

486. Visual Cognition: Decision Making I

Location: SDCC Halls B-H

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Topic: D.07. Vision

Support: R01MH109180
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Simons Collaboration on the Global Brain
T32 EY007136

Title: Confidence about choices informs changes of strategy based on feedback

Authors: *M. ESTEKI[1], B. PURCELL[2], R. KIANI[2]
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Abstract: Natural environments are dynamic and their changes can render known reward associations and previously successful decision strategies ineffective. When environment changes are not explicitly cued, we can learn about them and adjust our decision strategy only

based on the outcome of ongoing and past decisions. An essential computation for such learning is to determine whether negative feedbacks can be attributed to changes of the environment. We had previously shown that a Bayesian decision maker would depend on the expected accuracy of past choices to solve this attribution problem (Purcell & Kiani, 2016). Here, we test whether humans rely on their subjective confidence about choices that led to negative feedback in order to detect environment changes and update their decision strategy. Six participants performed a variant of the direction discrimination task (Britten et al, 1992). On each trial, subjects observed a patch of random dots surrounded by four targets. Each target was an elongated bar. The net motion direction was either rightward or leftward, and the targets were arranged into two pairs of right-left above and below the dots. We refer to the pairs as the upper and lower environments. Only one environment was active on each trial. The active environment stayed fixed for a random number of trials and then switched without an explicit cue. Subjects made a single saccade to one of the targets to simultaneously report their direction choice (right or left), environment choice (upper or lower), and confidence about motion direction (saccade landing point along the target). Feedback was not dependent on confidence and positive feedback was given only if the chosen target represented both the correct motion direction and the active environment. Consequently, subjects could receive negative feedback because of their mistakes about motion direction or because of changes in the environment. We show that human subjects were much more likely to switch environment following negative feedback on trials in which they were more confident about motion direction. Further, subjects were more likely to switch after a sequence of negative feedbacks, especially when they were associated with higher confidence. Finally, the influence of confidence on environment switches could not be explained by objective difficulty, as negative feedback on trials with similar motion strengths could lead to staying in the old environment or switching, depending on confidence. The results indicate that humans integrate their confidence across past choices to guide future decision strategy, mimicking a Bayesian decision maker.

Disclosures: M. Esteki: None. **B. Purcell:** None. **R. Kiani:** None.

Poster

486. Visual Cognition: Decision Making I

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Program #/Poster #: 486.09/HH13

Topic: D.07. Vision

Support: F32-EY019851
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E. Bronson Ingram Chair in Neuroscience

Title: Visual search strategies: Performance monitoring by macaque supplementary eye field during speed-accuracy tradeoff

Authors: *T. R. REPPERT, R. P. HEITZ, J. D. SCHALL
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Abstract: Continuing our investigation of the neural mechanisms of speed-accuracy tradeoff (SAT), we report new observations about strategic adjustments of performance and associated neural activity in the supplementary eye field (SEF). Two macaque monkeys were trained to emphasize speed or accuracy of responding cued by the color of a central fixation stimulus. Response time (RT) was adjusted with associated changes in error rate. Monkeys had difficulty with-holding responses on trials that cued accuracy. The probability of a mis-timed response was higher in the Accurate relative to the Fast condition, particularly on trials immediately following a cue switch from Fast to Accurate responding. Thus, monkeys produced two types of errors: (1) mis-directed responses, and (2) mis-timed responses. We recorded from 72 neurons in SEF. Visually responsive neurons did not signal the location of the search target as observed (Purcell, Weigand, Schall 2012). Baseline activity and response magnitude of visually responsive neurons was higher on Fast relative to Accurate trials. Neurons signaled both mis-directed and mis-timed errors. Mis-directed errors were signaled immediately post-saccade, but mis-timed errors were signaled only after the absence of expected fluid reward. These results complement our previous findings in frontal eye field and superior colliculus (Heitz & Schall 2012; Reppert, Servant, Heitz, Schall 2018), generalize to visual search our previous findings during saccade countermanding (Stuphorn, Taylor, Schall 2000), and extend our understanding of modulation of cortical neural activity during speed-accuracy tradeoff.

Disclosures: R.P. Heitz: None. **J.D. Schall:** None.

Poster

486. Visual Cognition: Decision Making I

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Robin and Richard Patton through the E. Bronson Ingram Chair in Neuroscience

Title: Visual search strategies: Priming of pop-out in macaques

Authors: *J. A. WESTERBERG, A. V. MAIER, J. D. SCHALL
Dept. of Psychology, Vanderbilt Univ., Nashville, TN

Abstract: Repetition in task performance is known to induce changes in behavioral measures. The priming of pop-out variant of visual search is one such example. In sequences of the same pop-out task (e.g. repeated trials of a red target among green distractors) response times become faster and accuracy improves with repetition. Previous work has demonstrated that concurrent with these behavioral changes are modulations in neural responses in the Frontal Eye Fields, namely enhancement of visual activity when the target appears in the receptive field of the neuron, and suppression when the receptive field contains a distractor (Bichot & Schall 2002). While priming of pop-out modulates activity in this attentional-control structure, the influence of earlier visual areas, such as V4 is unclear. Behavioral and physiological data was collected from monkeys performing a color pop-out visual search task. Target and distractor combinations were presented for ten trial blocks before a switch occurred. Each switch entailed the target color becoming the distractor and the distractor color becoming the target. The observed behavior replicated previous human and macaque work in the form of faster response times and greater accuracy with repetition across a block of trials. Further analysis of response time distributions revealed that repetition did not simply speed up response times. Specifically, rather than an overall shift in the long-tailed distribution of response times with repetition in a block, the distribution evolved to be bimodal with repetition. This finding suggests that a fast target selection process is facilitated with repetition and during task performance, both fast and slow processes can be observed.

Disclosures: J.A. Westerberg: None. **A.V. Maier:** None. **J.D. Schall:** None.

Poster

486. Visual Cognition: Decision Making I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 486.11/HH15

Topic: D.07. Vision

Support: R01-EY08890
P30-EY008126
Robin and Richard Patton through the E. Bronson Ingram Chair in Neuroscience

Title: Visual search strategies: Induction of shape selectivity in macaque frontal eye field

Authors: *K. A. LOWE[1], T. REPPERT[2], J. D. SCHALL[1]
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Abstract: Visual search task performance is influenced by rules, demands, and reward contingency. In difficult tasks, sub-optimal shortcuts may be discovered that offer a satisfying rate of reward. Sato and Schall (2003) introduced a visual search task to assess functionally distinct processing stages through the logic of separate modifiability. Monkeys attended to an elongated color singleton among distractors to encode the orientation, cuing either a pro- (vertical) or anti- (horizontal) saccade. We introduced elongated distractors, in which case the singleton cues either congruent or incongruent responses. Errors revealed three patterns: (1) errant anti-saccades avoided the singleton; (2) errant anti-saccades were concentrated on stimuli closer to the correct endpoint than to the singleton; and (3) errant saccades were directed to vertical distractors. We recorded from 141 neurons in the frontal eye field (FEF). In early sessions, where performance was markedly impaired on anti-saccade trials, Type II visual neurons, which only select saccade endpoint, were common, but Type I visual neurons, which select first the color singleton and then the saccade endpoint, were not. Unexpectedly, ~30% of the sample showed shape selectivity, even when responses were restricted to stimuli that were neither looked at nor task-relevant. This selectivity was exhibited in two ways: (1) responses to vertical stimuli were categorically distinct from responses to horizontal or square stimuli, which in turn showed identical responses; or (2) responses were graded along an aspect-ratio continuum. This finding replicates a previous discovery that feature selectivity can be induced in FEF depending on performance strategy (Bichot, Schall, Thompson 1996). These results indicate that a monkey discovered that sufficient reward could be earned just by shifting gaze to any stimulus cuing pro-saccade and demonstrate the influence of strategic factors in visual search performance.

Disclosures: T. Reppert: None. **J.D. Schall:** None.

Poster

486. Visual Cognition: Decision Making I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 486.12/HH16

Topic: D.07. Vision

Support: NIH F31EY029155
NIH R01MH115555

Title: What goes where: Using stimulus representations from both visual streams to guide behavior

Authors: *W. J. JOHNSTON, K. MOHAN, D. J. FREEDMAN
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Abstract: The primate visual system is divided into two anatomically segregated visual processing streams: The ventral “what” stream is specialized for object recognition and shape processing, culminating in the inferotemporal cortex (ITC), and the dorsal “where” stream is specialized for spatial processing and the production of visually guided behaviors, culminating in posterior parietal cortex (e.g., the lateral intraparietal area (LIP)). Here, we ask how image representations and familiarity encoding in the ventral stream region ITC can be leveraged by dorsal stream regions, such as LIP, to inform visually guided behavior.
We trained two monkeys on a preferential looking task (PLT) in which the animal freely views two natural images, each one of which the animal has seen either 0 - 10 times (novel) or >1000 times (familiar). On average, the animals viewed novel images 380 ms longer than familiar images in the first second of the free viewing period -- and made 66% of their initial saccades to the novel image. How does image familiarity influence saccade choice? Here, in each animal, we recorded from one of two brain regions believed to be involved in this task: ITC and LIP. Neurons in both regions were modulated by image familiarity during the task (50/70 units in ITC, $p < .05$, permutation test; 40/71 units in LIP, $p < .05$, bootstrapped AUC). Both regions also encoded familiarity prior to the first saccade: 75 - 100 ms prior for the ITC population (population average, $p < .05$, permutation test) and 39 - 89 ms prior for the LIP population (17/40 units, $p < .05$, Mann-Whitney U-test) -- indicating that both regions may be involved in guiding saccadic choices. In a second behavioral task in which making saccades based on image familiarity would cause the animal to make errors, we show that 37/40 LIP units reduce the strength of their familiarity modulation ($p < .05$, Mann-Whitney U-test).
We hypothesize that (1) ITC computes image familiarity and (2) LIP integrates the familiarity representation from ITC only when familiarity is relevant to the animal’s behavior (as in the PLT, but not in the second task). How is this integration performed given the differences between ITC and LIP representations? We show that two interacting populations of recurrently connected units -- one analogous to the dorsal stream, the other to the ventral stream -- can perform the integration so long as both populations encode one common, stimulus-unique feature. We argue that this commonly encoded feature is likely to be stimulus position in retinotopic space, and show how integration is altered by differences in the accuracy and resolution of ventral stream position representations.

Disclosures: W.J. Johnston: None. **K. Mohan:** None. **D.J. Freedman:** None.

Poster

486. Visual Cognition: Decision Making I

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Topic: D.07. Vision

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McKnight Scholar award

Title: Stable encoding of visual categories during task switching in the parietal cortex

Authors: *K. MOHAN, O. ZHU, S. K. SWAMINATHAN, D. J. FREEDMAN
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Abstract: Primates exhibit exceptional flexibility in their behavior. Indeed, we can use the same visual input to guide a variety of decisions and actions. To understand the neural basis of flexibility, we trained monkeys to categorize the same random-dot motion stimuli under two different task paradigms - with an eye-movement versus a hand movement depending on a colored cue shown at the start of the trial. In both motion categorization tasks, monkeys grouped 360° of motion directions into two categories according to the same category boundary. In the first task (a one-interval categorization task (OIC)), a single sample stimulus was presented and the monkeys rapidly reported its category membership by making a saccade to either a red or green target to report "category 1" or "category 2" respectively. In the second task (a delayed match-to-category task (DMC)), a single sample stimulus was followed by a second test stimulus after a 1 second delay and the monkeys reported whether they belonged to the same category by releasing a manual lever to report "category match". We recorded from 102 lateral intraparietal (LIP) neurons in two monkeys during flexible switching between the OIC and DMC tasks. LIP neurons exhibited a diversity of complex response profiles with mixed tuning and dynamics to various task-relevant variables. While single neurons represented complex mixtures of task-relevant variables in both tasks, the neural population showed robust category selectivity that was remarkably similar across the two tasks. Employing SVM classifiers to quantify direction and category selectivity, we find that stimulus direction and category can be reliably decoded (75% direction decoding, 90% category decoding) during the sample period in both tasks. Critically, we show that a category decoder trained on one task can accurately generalize and decode category on the untrained task, suggesting that shared representations mediate categorical decisions in both tasks. While category-dependent responses were conserved in both tasks, other task-relevant variables such as motion direction and choice were influenced by cognitive demands unique to the OIC and DMC tasks. First, neuronal populations encoded more direction information in the OIC task than in the DMC task as evidenced by single neuron ROC measures and population decoding. Second, choice signals were independently encoded in both tasks since choice decoders trained on one task did not generalize and predicted choice accuracies at chance. Our findings demonstrate that parietal neural circuits can mediate flexible task-switching by differentially formatting relevant information in a task-dependent manner.

Disclosures: K. Mohan: None. **O. Zhu:** None. **S.K. Swaminathan:** None. **D.J. Freedman:** None.

Poster

487. Visual Sensory-Motor Processing I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 487.01/II1

Topic: D.08. Visual Sensory-motor Processing

Support: NRF-2017R1A2B3008270
NRF-2017M3C7A1030798

Title: Roles of cingulate cortex in controlling sensory-guided motor actions

Authors: *J.-H. KIM, S.-H. LEE
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Abstract: Sensory information guides animals to carry out well-controlled motor actions by updating reinforcements associated with it. Rewards facilitate 'go' actions to the stimuli, whereas less reward or punishment make animals adequately take 'no-go' actions. During the perceptual behaviors, robust activities are recruited at many cortical regions, from the sensory cortex to the frontal motor areas. The cingulate cortex (Cg) has been identified as a key structure that mediates top-down modulation of visual responses in the primary visual cortex (V1) of mice. However, contribution of Cg activity in making proper motor actions to the sensory cues remains to be determined. Here, we investigated functional roles of Cg in performing the visual detection task in head-fixed mice. Pharmacological inactivation of Cg impaired both go (licking after stimuli) and no-go (no-licking without stimuli) actions with increasing impulsive licking actions. By recording single unit activities in Cg and V1, we found that Cg neurons show stronger visually-evoked responses in hit trials than miss trials. Moreover, subset of Cg neurons that are not driven by the stimuli show clear reduction in their activity during the impulsive licking in no-go trials. These action-related activities were not observed in V1 neurons, indicating that Cg neurons receiving visual inputs play crucial roles in transforming sensory information into proper motor actions. Collectively, our data demonstrate that Cg neurons encode both sensory-evoked signals that are transformed to go actions and motor inhibition signals that prevent impulsive actions to execute goal-directed behaviors in mice.
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Disclosures: J. Kim: None. **S. Lee:** None.

Poster

487. Visual Sensory-Motor Processing I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 487.02/II2

Topic: D.08. Visual Sensory-motor Processing

Support: NIH Grant 1U19NS104653

Title: Modeling three-dimensional prey capture in larval zebrafish

Authors: *A. D. BOLTON[1], M. HAESEMEYER[1], J. JORDI[1], V. MANSINGHKA[3], F. ENGERT[2]
[2]MCB, [1]Harvard Univ., Cambridge, MA; [3]MIT, Cambridge, MA

Abstract: Predatory animals rely on accurate sensory perception, predictive models of prey motion, and precise striking movements to catch moving prey. Larval zebrafish robustly intercept moving paramecia during feeding, providing a tractable model system for the study of sensorimotor integration, trajectory prediction, and spatial attention. No studies, however, have ever examined the movement patterns of hunting zebrafish in their natural 3D setting, neglecting clear vertical movements during hunting sequences. Moreover, the precise movements of paramecia have never been recorded, preventing analysis of spatial attention and trajectory prediction by the fish. To address these issues, we have constructed a 3D-imaging setup to simultaneously record the movements of fish and paramecia during prey capture. We analyze this data using BayesDB, a probabilistic programming tool used to estimate the full joint distribution of zebrafish bout statistics and paramecia movement variables. Regression models, BayesDB generated models, and ideal models generated from machine learning are compared, pointing to possible strategies fish use to capture their tortuously moving prey.

Disclosures: A.D. Bolton: None. **M. Haesemeyer:** None. **J. Jordi:** None. **V. Mansinghka:** None. **F. Engert:** None.

Poster

487. Visual Sensory-Motor Processing I

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Program #/Poster #: 487.03/II3

Topic: D.08. Visual Sensory-motor Processing

Support: NSERC DG 402677

Title: Development of optogenetic tools in the optic flow circuits of birds

Authors: *M. S. ARMSTRONG[1], D. R. WYLIE[2], D. L. ALTSHULER[1]
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Abstract: As an animal moves through its environment, visual motion occurs across the entire retina. This large-field visual motion, known as optic flow, provides the primary sensory input for a diverse set of visual guidance strategies used by animals with image-forming eyes, and is used for controlling posture, locomotion and navigation. Information derived from optic flow is conveyed to the cerebellum by two specialized pathways through the midbrain, identified here by their distinct destinations in the cerebellum; the vestibulocerebellum (VbC) and the oculomotor cerebellum (OCb). Anatomical and electrophysiological studies of these circuits in birds generated the hypothesis that the midbrain-oculomotor cerebellar pathway integrates local motion with optic flow for movements involved in obstacle avoidance or flight through cluttered environments, while the midbrain-vestibulocerebellar pathway controls velocity, centering and odometry. To test this hypothesis, we have developed optogenetic protocols in these midbrain-cerebellar pathways in zebra finches (*Taeniopygia guttata*) to manipulate optic flow circuits during free flight. We have imaged successful expression of channelrhodopsin-2 (ChR2) and archaerhodopsin (Arch T) in visual nuclei in the tectofugal and visuocerebellar pathways, and we have confirmed that these regions respond to light stimulus with multi-unit optrode recordings. We chronically implanted ChR2 expressing birds with fiber optics and flew them in a tunnel with visual stimulus while tethered to a 473nm laser. Once birds acclimated to flight with the tether, we stimulated them mid-flight and tracked changes in flight behavior. To target each pathway separately, we have simultaneously begun development of terminal field stimulation and retrograde expression of opsins in the VbC and OCb. These techniques will allow us to determine whether these parallel midbrain-cerebellar pathways are responsible for different responses to visual information depending on environmental conditions like obstacle avoidance vs. centering and odometry.

Disclosures: M.S. Armstrong: None. **D.R. Wylie:** None. **D.L. Altshuler:** None.

Poster

487. Visual Sensory-Motor Processing I

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Program #/Poster #: 487.04/II4

Topic: D.08. Visual Sensory-motor Processing

Support: UCL IMPACT studentship

Sir Henry Dale Fellowship 101195/Z/13/Z

Title: Modulation of visuomotor behaviour by a cholinergic midbrain circuit

Authors: *P. M. HENRIQUES, I. H. BIANCO
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Abstract: A long-standing question in ethology is how animals are able to sustain behavioural routines that allow multiple elementary behaviours to be combined to achieve an overall goal. One example is the hunting behaviour of zebrafish larvae, which is characterized by a set of discrete visuomotor events that begin with prey detection, followed by goal-directed turns and swims and ultimately end with prey capture. The optic tectum (OT), the largest retinorecipient structure in the teleost brain, is critically required for hunting: OT neurons are tuned to prey-like visual features, tectal activity immediately precedes hunting initiation and OT ablation abolishes hunting. However, the tectum is interconnected with numerous other brain regions and little is known about how OT activity might be modulated and how activity is coordinated during behavioural routines tracking a single prey. Here we show that the nucleus isthmus (NI; homologous to the parabigeminal nucleus of mammals), a conserved midbrain cholinergic nucleus, is required for sustaining hunting routines in zebrafish larvae. We identified two types of NI neurons characterised by distinct axonal projection patterns: The first cell type targets both ipsilateral anterior OT as well as AF7, a retinorecipient pretectal region thought to be involved in hunting. The second type of NI cell projects bilaterally to the deep OT layers. Laser ablation of the NI, with subsequent analysis of naturalistic hunting behaviour, revealed that while hunting initiation rates and motor kinematics were unaltered, ablated animals showed an elevated probability of aborting their hunting routines midway through prey tracking. Other features of hunting and other visuomotor behaviours remained unaltered. Moreover, 2-photon Ca^{2+} imaging of tethered larvae under closed-loop virtual reality conditions showed that NI neurons are active during hunting behaviour. These results suggest that the NI modulates pretectal and tectal activity to allow the animal to sustain a target-directed hunting response and ultimately capture its prey. In line with a role for the NI in a midbrain attentional network in other vertebrates, this may fit within a conserved role in controlling attention to salient, ethologically relevant stimuli, thereby allowing for the maintenance of behavioural routines in the presence of competing distractors.

Disclosures: P.M. Henriques: None. **I.H. Bianco:** None.

Poster

487. Visual Sensory-Motor Processing I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 487.05/II5

Topic: D.08. Visual Sensory-motor Processing

Support: HFSP LT000626/2016-L

Title: Neuronal mechanisms of minute-long evidence accumulation in the larval zebrafish brain

Authors: *A. BAHL[1], F. ENGERT[2]
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Abstract: Signals in the natural world are often weak, noisy, or even conflicting. Hence, animals need to integrate information in both the spatial and temporal domain to decide on the next favorable behavioral action. It might take a significant amount of time until a reliable decision can be made. This poses a computational challenge for neuronal networks consisting of neurons operating on millisecond timescales. Electrophysiological recordings in primates during decision-making tasks have found brain regions with accumulating neuronal activity (area LIP). So far, due to technical difficulties in primates, comprehensive descriptions of the underlying neural mechanisms were only possible for local circuits.
Here we present a novel assay to study sensory integration and decision-making, using the larval zebrafish as a model. When presented with stimuli consisting of hundreds of moving dots, freely-moving as well as head-embedded larval zebrafish follow the overall motion coherence and improve performance over the time of stimulus presentation. We find that with increasing motion coherence, responses become more correct and occur earlier. Modeling reveals that the behavior is quantitatively explained by a classical leaky diffusion-to-bound model.
We performed brain-wide two-photon functional calcium imaging experiments and found that neurons in the anterior hindbrain have very slow dynamics, and that network as well as single neuron activity can ramp for up to a minute. More specifically we find a cluster of excitatory neurons with dynamics closely following our expectations from a slow leaky integrator. We also find an adjacent cluster of inhibitory neurons which reflect a state of stimulus uncertainty. Measuring behavioral decisions while simultaneously imaging these clusters reveals that the decision threshold for a directional swim is reached whenever the excitatory integrator population activity exceeds the uncertainty inhibitory population.

Disclosures: A. Bahl: None. **F. Engert:** None.

Poster

487. Visual Sensory-Motor Processing I

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Topic: D.08. Visual Sensory-motor Processing

Support: Max Planck Institute
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Title: Constructing behaviorally-relevant central brain representations from naturalistic motion computation in the retina

Authors: *B. T. YILDIZOGLU[1], C. RIEGLER[2], J. E. FITZGERALD[3], R. PORTUGUES[4]
[1]Max Planck Inst. for Neurobio., Muenchen, Germany; [2]Dept. of Mol. and Cell. Biol., Harvard Univ., Cambridge, MA; [3]Howard Hughes Med. Inst., Ashburn, VA; [4]Max Planck Inst. of Neurobio., Martinsried, Germany

Abstract: Sighted animals use visual information to compute environmental motion signals that guide behavior. Prior studies have shown that visual processing in multiple species is tuned for computational cues that accurately predict motion under naturalistic stimulation conditions. However, the circuits implementing naturalistic motion-guided behavior in vertebrate nervous systems remain unclear. Here we show that neurons in the larval zebrafish pretectum integrate retinal signals tuned for naturalistic motion cues to represent visual motion stimuli according to their relevance for optomotor behaviors. We focus on behavioral responses to glider stimuli, a set of complex stimuli that have previously been linked to naturalistic motion processing. We observed that zebrafish exhibit strikingly similar behavioral responses to those found in flies. We then imaged fluorescence calcium responses of neurons in the pretectum, which is implicated in several motion-guided behaviors. Interestingly, we found that we could accurately model the responses of pretectal neurons as a threshold-linear combination of stimulus response patterns corresponding to several elements of optomotor behavior, and neurons were spatially-clustered according to their behavioral correlates. Finally, we imaged functional signals from RGC axon terminals, using transgenic larvae that expressed presynaptically localized SypGCaMP6s under control of the RGC-specific promoter Islet2b, to find retinal ROIS with response patterns sufficient to construct the pretectal representation. Thus, the zebrafish retina extracts diverse higher-order motion cues necessary for naturalistic behavior. The principles, algorithms, and circuits of visual motion processing seem remarkably conserved across the animal kingdom, so our results likely pertain to motion-guided behaviors in diverse vertebrate nervous systems.
All experiments were performed on larval zebrafish (6-7 dpf) in four experimental cohorts. Behavioral responses in freely swimming zebrafish were measured for 140 fish. Fluorescent calcium responses in the zebrafish pretectum were imaged in 35 head-embedded fish. We simultaneously measured pretectal and behavioral responses in 8 tail-free but head-embedded fish. Finally, fluorescent calcium responses from retinal ganglion cell arborization field in the central brain were measured in 42 fish.

Disclosures: B.T. Yildizoglu: None. **C. Riegler:** None. **J.E. Fitzgerald:** None. **R. Portugues:** None.

Poster

487. Visual Sensory-Motor Processing I

Location: SDCC Halls B-H

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Topic: D.08. Visual Sensory-motor Processing

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Title: Brainwide organization of neuronal activity and convergent sensory-motor transformations in larval zebrafish

Authors: *Y. MU[1], X. CHEN[2], Y. HU[3], A. KUAN[4], M. NIKITCHENKO[3], O. RANDLETT[3], H. I. SOMPOLINSKY[5], F. ENGERT[2], M. AHRENS[1]
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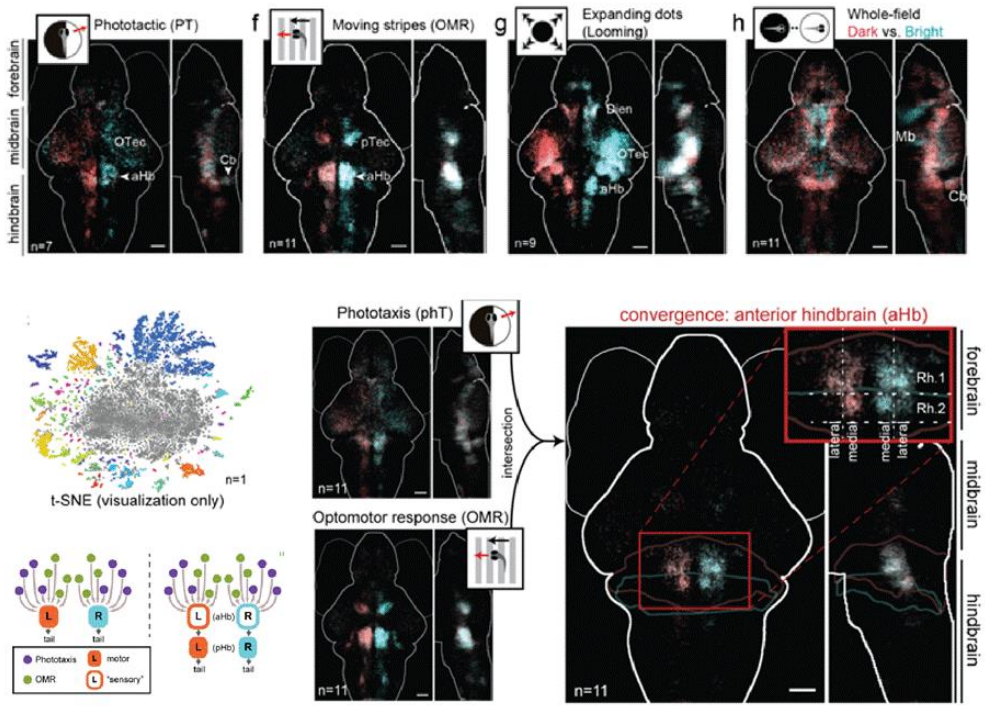
Abstract: Simultaneous recordings of large populations of neurons in behaving animals allow detailed observation of high-dimensional, complex brain activity. However, experimental design and analysis approaches have not sufficiently evolved to fully realize the potential of these methods. We recorded whole-brain neuronal activity for larval zebrafish presented with a battery of visual stimuli while recording fictive motor output. These data were used to develop analysis methods including regression techniques that leverage trial-to-trial variations and unsupervised clustering techniques that organize neurons into functional groups. We used these methods to obtain brain-wide maps of concerted activity, which revealed both known and heretofore uncharacterized brain nuclei. We also identified neurons tuned to each stimulus type and motor outputs, and revealed nuclei in the anterior hindbrain that respond to multiple stimuli that elicit the same behavior. However, these convergent sensorimotor representations were not tuned to instantaneous motor behavior, suggesting that they inform, but do not directly generate, behavioral output. These findings motivate a novel model of sensorimotor transformation spanning distinct behavior contexts, within which these hindbrain convergence neurons likely constitute a key step. We make these data and analysis resource publicly available to facilitate reuse of our methods and enable further community efforts for mining these datasets.



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Poster

487. Visual Sensory-Motor Processing I

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Topic: D.08. Visual Sensory-motor Processing

Support: Simons Foundation, Simons Collaboration on the Global Brain
Howard Hughes Medical Institute

Title: Experience-driven changes in behavior and brain states through brainwide neuromodulation in zebrafish

Authors: D. V. BENNETT[1], Y. MU[3], M. RUBINOV[4], S. NARAYAN[5], C. TSUNG-YANG[6], C. WANG[2], P. J. KELLER[2], T. KAWASHIMA[7], L. L. LOOGER[2], *M. B. AHRENS[8]
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Hutchinson Cancer Res. Ctr., Seattle, WA; [7]HHMI Janelia Res. Campus, Ashburn, VA; [8]Janelia Res. Campus / HHMI, Ashburn, VA

Abstract: Neuromodulatory systems can introduce flexibility in the way neural circuits process information and generate behavior, allowing animals to adapt to changing environments and behavioral demands. Modulations in swim vigor of larval zebrafish can be induced by cells in the serotonergic system, as their neural responses track the outcomes of actions and adjust behavior when these outcomes are of an unexpected magnitude. Here we extend the investigation of brainwide experience-dependent neuromodulation to other neuromodulatory systems by combining whole-brain light-sheet imaging in virtual environments with anatomically-specific delineation of neuronal populations and with brainwide activity perturbations. We imaged the entire brain at single cell resolution across multiple behavioral paradigms, and systematically searched the brain for signals that preceded, coincided, and followed behavioral switches. We implemented an automated cell-detection algorithm, factorized the resulting spatiotemporal data into groups of cells with similar activity, and standardized these brain areas across fish. By searching for neuromodulatory systems activated during behavioral switches, we found that the noradrenergic system modulates behavior and tracks the outcomes of swim actions in a complementary way to the serotonergic system. We identified downstream populations of cells that modulate neural dynamics in premotor circuits, and describe the computational properties of the neuromodulatory systems to delineate which experiences trigger their neuromodulatory output. Together these neuromodulatory systems enable experience-dependent modulation of brain state and behavior across different behavioral regimes.

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Poster

487. Visual Sensory-Motor Processing I

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Topic: D.08. Visual Sensory-motor Processing

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ARO W911NF-12-1-0594
NIH 5R01NS076467
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NIH R01027036
NIH EY007138-16

Title: Synaptic scale reconstruction of oculomotor circuitry in the larval zebrafish

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Abstract: Vertebrate eye movements are implemented largely in the brainstem by distinct nuclei where multiple sensory afferent axons converge very close to motor nuclei that control eye muscles.This includes inputs from the vestibular and saccadic neurons and outputs to abducens and oculomotor motor neurons. Many aspects of how unique sensory signals from these distinct neurons converge and transform to result in coordinated eye movement is not well understood. To understand the mechanisms by which this signal transformation occurs, we aim to anatomically reconstruct neurons involved in this circuit at synaptic resolution using serial-section electron microscopy (ssEM). To do this we combined two-photon functional calcium imaging followed by ssEM in the larval zebrafish. By registering functional calcium images to ssEM images we located neurons that carried eye-position sensitive signals, within the EM volume. This includes neurons that perform a velocity-to-position integration or neural integrators. Next, using machine learning and a crowd-sourced platform, we reconstructed ~3000 neurons that were synaptically connected to neurons that carried eye-position sensitive signals. We reconstructed neurons from areas involved in saccade production, neurons near vestibular nuclei, neurons involved in velocity-to-position integration and neurons in the abducens motor complex. This encompasses the flow of eye-position related signals, from sensory to motor neurons. From these reconstructions, we observed that the integrator neurons were comprised of at least three distinct groups of neurons, two of which are putative excitatory and one which is putative inhibitory. We further observed direct synaptic contacts between integrator neurons, consistent with our understanding of how integration can be performed by means of positive feedback. Similarly, we observed direct synaptic contact between the putative saccadic and vestibular neurons onto the abducens motor neurons. Finally, we classified the reconstructed neurons based on their features and constructed the connectivity matrix of all reconstructed neurons to reveal the organization of neurons that carry eye-position signals.

Disclosures: A. Vishwanathan: None. **J. Wu:** None. **N.L. Turner:** None. **D. Ih:** None. **K. Lee:** None. **N. Kemnitz:** None. **K. Daie:** None. **A. Ramirez:** None. **E. Aksay:** None. **H.S. Seung:** None.

Poster

487. Visual Sensory-Motor Processing I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 487.10/II10

Topic: D.08. Visual Sensory-motor Processing

Support: HHMI
Simons Foundation, SCGB

Title: Motor readiness through rebound in an identified sensory integrator

Authors: *E. YANG[1], M. ZWART[1], Z. WEI[1], M. RUBINOV[1], N. VLADIMIROV[1], S. NARAYAN[1], Y. MU[1], E. SCHREITER[1], T. KAWASHIMA[1], A. ABDELFATTAH[1], M. KOYAMA[1], L. LAVIS[1], J. FITZGERALD[1], J. GRIMM[1], S. DRUCKMANN[2], S.-I. HIGASHIJIMA[3], M. B. AHRENS[1]
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Abstract: While some actions are triggered directly by instantaneous incoming sensory information, most take into account internal information streams that represent information accumulated over longer time periods. Despite decades of study, much is still unknown at the level of neural circuits about how the brain integrates sensory information in between actions, stores this information, and transmits it to inform future actions. We made use of modern whole-brain microscopy methods and the advantages of genetically modified zebrafish to search the entire brain, cell-by-cell, during behavior, for neural integrators involved in motor preparation. Larval zebrafish respond to visual motion, but swim in discrete swim bouts. Accordingly, visual motion must be integrated in between swim bouts to influence future motor output. Our whole-brain activity screen identified a single brain region in the hindbrain that responds to visual flow, integrates and stores it in ongoing activity, and modulates future behavior. These neurons respond to stimuli that encourage the fish to swim, and integrate them so that temporally separated stimuli have an additive effect. Moreover, their activity levels are positively correlated with preceding levels of motor output. However, surprisingly, stimulating the neurons suppressed instantaneous swimming, yet advanced the onset time of future swims. Network models based on these results suggests a brainstem integrator network that, in between actions, stores visual information while actively suppressing motor output, and during actions transmits the stored information to premotor circuits through post-inhibitory rebound. Voltage imaging using novel voltage indicators revealed precise temporal dynamics of this population of neurons in relation to behavior consistent with this model. These findings suggest inhibitory integrators as a complementary alternative to integrate-to-bound models for sensory integration and motor decisions.

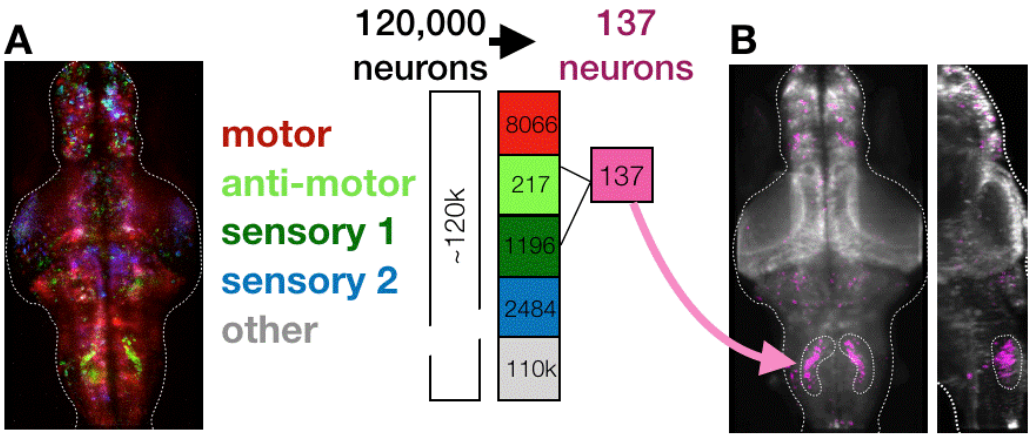

Fig.1. From whole brain activity to ~137 sensory integrator neurons through intersectional analysis.

Disclosures: E. Yang: None. **M. Zwart:** None. **Z. Wei:** None. **M. Rubinov:** None. **N. Vladimirov:** None. **S. Narayan:** None. **Y. Mu:** None. **E. Schreiter:** None. **T. Kawashima:** None. **A. Abdelfattah:** None. **M. Koyama:** None. **L. Lavis:** None. **J. Fitzgerald:** None. **J. Grimm:** None. **S. Druckmann:** None. **S. Higashijima:** None. **M.B. Ahrens:** None.

Poster

487. Visual Sensory-Motor Processing I

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Topic: D.08. Visual Sensory-motor Processing

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Karolinska Institutet's Research Funds

Title: Sensory organization in the primordial lamprey cortex

Authors: *S. MYSORE SURYANARAYANA, J. PÉREZ FERNÁNDEZ, P. WALLÉN, B. ROBERTSON, S. GRILLNER
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Abstract: The lamprey lateral pallium, is conserved in relation to the mammalian cortex with the same efferent connectivity, having projections to the basal ganglia and the different brainstem nuclei (Ocaña et al., 2015). Furthermore, it has a three-layered microcircuit *bauplan* that includes many features of the three-layered reptilian cortex, the mammalian piriform cortex and the neocortex and can be regarded as a primordial vertebrate cortex (Suryanarayana et al., 2017). We examine here, the organization of different sensory inputs to the lateral pallium. The lamprey pallium had been regarded as being entirely olfactory. However, we show that visual input is relayed to pallium via thalamus, along with processed visual information from pretectum/tectum. Extracellular multi-unit recordings showed that neurons in the dorsomedial pallium are activated in a retinotopic fashion by extracellular stimulation of the retina - the "visual" cortex. This visual region is distinct from motor regions. Stimulations of specific retinal quadrants elicited responses in separate visual pallial areas. Local injections of gabazine in the visual pallium resulted in the loss of this retinotopic organization indicating that GABAergic neurons may be responsible for maintaining specificity. Optic nerve stimulations during whole-cell recordings of pallial neurons elicited EPSP's and recruited inhibition. In ongoing experiments, we are investigating responses in visual pallium for visual stimuli delivered on a computer screen placed in front of the contralateral eye. Furthermore, local injections of gabazine in thalamus also resulted in the loss of retinotopy in pallium. We are investigating whether there is also a retinotopic organization maintained in thalamus, by whole cell recordings of prelabelled thalamo-pallial neurons and quadrant-specific extracellular stimulation. Somatosensory information is also relayed via thalamus, which receives inputs from the dorsal column nuclei, activated by sensory input. Extracellular stimulation of the dorsal column in the spinal cord, elicited responses in the ventromedial parts of the lateral pallium, distinct from the visual areas - a "somatosensory" cortex. Stimulation of the trigeminal nerve also elicited responses in rostrolateral areas, distinct from the visual area. Taken together, these findings represent the first report of the remarkable organization of sensory input in the cortex of the phylogenetically oldest vertebrate.

Disclosures: S. Mysore Suryanarayana: None. **J. Pérez Fernández:** None. **P. Wallén:** None. **B. Robertson:** None. **S. Grillner:** None.

Poster

487. Visual Sensory-Motor Processing I

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Topic: D.08. Visual Sensory-motor Processing

Support: NIH Grant NS078127
The Sloan Foundation
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Title: Humans use their prior knowledge to compensate for noisy mental transformations

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Abstract: Many skills rely on performing noisy computations on noisy sensory measurements. Bayesian models suggest that humans compensate for measurement noise and reduce behavioral variability by biasing perception toward prior sensory expectations. Whether the same holds for noise in mental transformations that observers apply to sensory measurement is not known. To determine whether humans rely on their prior knowledge to compensate for additional noise during mental transformations, we tested human subjects on four tasks, including 1) a time interval measurement and production task, 2) a length measurement and production task, 3) a center-out reaching task, and 4) a multiple-choice length discrimination task. In each task, we compared performance across two contexts. In one context, which we termed the “identity context”, responses had to match the stimulus veridically. This was compared to a "remapped context" in which subjects had to apply a non-unity transformation to the sensory measurements to produce accurate responses.
In all tasks, we observed an increased regression to the mean in the remapped context compared with the identity context. This behavior was consistent with a Bayesian model which mitigates the effects of mental transformation noise associated with mental transformations. These results suggest that humans not only optimize behavior to minimize the effect of measurement noise, but also adjust their behavioral responses to account for the additional noise associated with mental transformations.

Disclosures: E.D. Remington: None. **T.V. Parks:** None. **M. Jazayeri:** None.

Poster

488. Visual Sensory-Motor Processing II

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Uehara Foundation Research Fellowship

Title: Neural mechanisms for memory-dependent flexible decision making in mice

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Abstract: A hallmark of decision-making is the ability to flexibly combine a new sensory stimulus and past experiences, such as those stored in working memory, to generate an action for positive outcomes. In flexible decision-making, the same sensory information can lead to different decisions or actions depending on the content of working memory. We have developed approaches to study flexible decision-making in the mouse. Specifically, we have used optogenetic and calcium imaging tools to evaluate and compare the importance of neural activity in different cortical areas. We designed a novel delayed match-to-sample task for mice based on navigation in a virtual reality T-maze. In the task, at the start of the maze, a sample cue is presented, and its identity must be stored in the mouse's working memory during a delay segment. At the T-intersection, a mouse is presented with a test cue that the mouse must combine with working memory of the sample cue in order to make a turn in the appropriate direction. To identify cortical regions that are necessary for performance of the task, we bilaterally inhibited different cortical areas in a grid-wise manner across all of dorsal cortex with optogenetics. We evaluated the necessity of regions during distinct epochs of the task. Inactivation of posterior parietal cortex, primary visual area, and secondary visual areas reduced behavioral choice accuracy. The effect was most prominent when the inhibition was applied during the test cue presentation, suggesting a causal involvement of these regions in the integration of sensory and memory information to make a decision. We have also collected two-photon calcium imaging datasets from a wide range of cortical regions during the task. We are analyzing these data to understand population codes for various components of the task, including visual perception, working memory, and sensorimotor transformation. Also, we are using new information theory approaches to identify neural activity patterns that carry stimulus information that is used to inform the choice, and thus might be important for key sensorimotor transformations. By comparing many cortical regions in the same task, we aim to understand the flow of decision-related information across cortex during flexible decision-making.

Disclosures: S. Kira: None. **G. Pica:** None. **S. Panzeri:** None. **C.D. Harvey:** None.

Poster

488. Visual Sensory-Motor Processing II

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Program #/Poster #: 488.02/II14

Topic: D.08. Visual Sensory-motor Processing

Support: ZIAMH002920

Title: Brain networks, dimensionality, and global signal averaging in resting-state fMRI: Hierarchical network structure results in low-dimensional spatiotemporal dynamics

Authors: *S. J. GOTTS[1], A. W. GILMORE[1], A. MARTIN[2]
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Abstract: One of the most controversial practices in resting-state fMRI functional connectivity studies is whether or not to regress out the global average brain signal (GS) during artifact removal. Some groups have argued that it is absolutely essential to regress out the GS in order to fully remove head motion, respiration, and other global imaging artifacts. Others have argued that removing the GS distorts the resulting correlation matrices, qualitatively alters the results of group comparisons, and impairs relationships to behavior. At the core of this argument is the assessment of dimensionality in terms of the number of brain networks with uncorrelated time series. If the dimensionality is high, then the distortions due to GS removal could be effectively negligible. In the current study, we examine the dimensionality of resting-state fMRI data using principal component analyses (PCA) and network clustering analyses. In two independent datasets (Set 1: N=62, Set 2: N=32), scree plots of the eigenvalues level off at or prior to 10 principal components, with prominent elbows at 3 and 7 components. While network clustering analyses have previously demonstrated that numerous networks can be distinguished with high thresholding of the voxel-wise correlation matrices, lower thresholding reveals a lower-dimensional hierarchical structure, with the first prominent branch at 2 networks (corresponding to the previously described "task-positive"/"task-negative" distinction) and further stable subdivisions at 4, 7 and 17. Since inter-correlated time series within these larger branches do not cancel to zero when averaged, the hierarchical nature of the correlation structure results in low effective dimensionality. Consistent with this, partial correlation analyses revealed that network-specific variance remains present in the GS at each level of the hierarchy, accounting for at least 18-20% of the overall GS variance in each dataset. These results demonstrate that GS regression is expected to remove substantial portions of network-specific brain signals along with artifacts, not simply whole-brain signals corresponding to arousal levels. We highlight alternative means of controlling for residual global artifacts when not removing the GS.

Disclosures: S.J. Gotts: None. **A.W. Gilmore:** None. **A. Martin:** None.

Poster

488. Visual Sensory-Motor Processing II

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Program #/Poster #: 488.03/II15

Topic: D.08. Visual Sensory-motor Processing

Support: NIH Intramural Research Program

Title: Do task-negative responses reflect cortico-cortical competition from task-positive brain regions?

Authors: *K. D. CSUMITTA[1], A. OSSOWSKI[2], A. W. GILMORE[1], S. J. GOTTS[1], A. MARTIN[1]
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Abstract: Previous work has identified functional brain networks showing task-induced increases in activity and networks showing task-induced decreases in activity, known respectively as "task-positive" and "task-negative", or "Default Mode" (Raichle et al., 2001), networks. These systems are proposed to be intrinsically competitive, such that activity in one suppresses activity in the other (e.g., Fox et al., 2005; 2009). In the current study, we examine the relationship between task-positive and task-negative networks in the brain using a slow-event related fMRI task design in which 40 participants were asked to name pictures of common objects aloud. If these functional networks are intrinsically competitive, then: 1) trial-level BOLD responses across task-positive and task-negative voxels should be anti-correlated, and 2) the correlation between the BOLD response and behavior (Response Time, RT) in task-positive and task-negative regions should have opposite valence. To test these predictions, we extracted the peak BOLD response and naming RT for 100 naming trials. As expected, task-positive responses were found in occipitotemporal and lateral frontal brain regions and task-negative responses were observed in regions of the Default Mode Network (posterior cingulate, inferior parietal, ventromedial prefrontal, superior frontal gyrus, anterior STS, frontal pole, right middle frontal gyrus). Greater connectivity was also observed within- than across-networks. These results were thresholded to obtain 8 task-negative regions of interest (ROIs), and ROI trial-level BOLD responses for each participant were correlated with responses in the rest of the brain. In contrast to the competitive dynamics proposal, we found predominantly positive correlations between task-negative ROIs and the rest of the brain. This positive coupling was not obviously due to residual artifacts, and was supported by complementary analyses of run-level beta weights. Although a few areas showed RT-BOLD slope reversals between task-positive and task-negative regions, the portion of variance related to behavior was small and did not detract much from the overall positive coupling. Taken together, these results argue against the simple proposal that cortico-cortical competition explains the presence of task-negative responses. We conclude by highlighting alternate possible mechanisms, such as centralized gating through the thalamus.

Disclosures: K.D. Csumitta: None. **A. Ossowski:** None. **A.W. Gilmore:** None. **S.J. Gotts:** None. **A. Martin:** None.

Poster

488. Visual Sensory-Motor Processing II

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Program #/Poster #: 488.04/II16

Topic: E.04. Voluntary Movements

Support: Wellcome Trust
European Research Council
Paris Institute of Advanced Studies

Title: Perception-action patterns revealed by event-related potentials

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Abstract: The way we interact with our environment is often guided by the perception of salient events happening in it. Reconceptualising an example given by Pylyshyn (1986), a pedestrian who approaches a crossing will alter his action, i.e. will stop, instead of continuing his route, when the traffic light suddenly becomes red. What defines the relationship between such everyday actions and common sensory stimuli? In a series of nine experiments, we used (i) an isometric force paradigm and (ii) a voluntary movement task entailing complex visuomotor transformations, to examine whether the presence of an evoked response (ERP) affects motor output. In the isometric force experiments (n=4), we used a highly sensitive transducer to record fine-scale variations of isometric force exerted by the fingers, and measured EEG and EMG activity, while sudden and temporally unexpected stimuli of different sensory modalities were delivered. In the visuomotor task experiments (n=5), the same stimuli were delivered concomitantly to the beginning of the movement, which participants had to perform as fast and accurate as possible. EEG activity was recorded, and the temporal and spatial features of the voluntary movement were quantified using the movement parameters Movement Onset Time, Total Time Movement, Path, Accuracy and Speed. We obtained the following main results. First, salient sensory stimuli modulated motor output regardless of the sensory modality of the eliciting stimulus. Second, this modulation had distinct patterns depending on the specific task: (i) in the visuomotor task, the presence of sensory stimuli resulted in a reduction of Movement Onset Time and an increase in Accuracy, while (ii) force modulation followed a complex triphasic pattern consisting of alternating decreases and increases, time-locked to stimulus onset. Third, (i) the magnitude of force modulation was predicted by the amplitude of the cortical activity elicited by the same stimuli, whereas (ii) the modulation of motor parameters was independent of the presence of an evoked response. In summary, we observed a tight coupling between stimulus

induced cortical activity and motor output in the isometric force task, which was not present in the visuomotor task. There, goal-related but stimulus-independent neural activities correlated with behavioural performance. These results suggest that saliency detection is not merely a perceptive but a reactive process, which however has differential effects on motor output, depending on the time proximity between stimulus and action and on action's complexity.

Disclosures: M. Kilintari: None. **R.J. Bufacchi:** None. **G. Novembre:** None. **Y. Guo:** None. **P. Haggard:** None. **G. Iannetti:** None.

Poster

488. Visual Sensory-Motor Processing II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 488.05/II17

Topic: D.08. Visual Sensory-motor Processing

Title: Human egomotion visual areas respond to long-range leg movements

Authors: S. DI MARCO[1,2], C. SERRA[1,2], *C. GALLETTI[3], P. FATTORI[3], G. GALATI[2,4], V. SULPIZIO[2,5], S. PITZALIS[1]
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Abstract: Optic flow constitutes a rich source of essential visual cues for guiding egomotion while moving in the environment. Egomotion perception involves the integration of multiple sensory signals arising from visual as well as vestibular, somatosensory and motor systems (Greenlee et al., 2016). Monkey neurophysiology and human neuroimaging studies have demonstrated that passive viewing of optic flow stimuli activates a large cortical network of temporal, parietal, insular and cingulate visual motion regions (including the well-known areas MST, VIP, V6 and CSv). Although all these regions respond to egomotion-compatible visual stimuli, they are well different in terms of anatomical position and functional properties. Indeed, some of them have a clearly retinotopic organization whereas others show also somatosensory or vestibular responses. Recently it has been also shown that area V6+ is connected with posterior visual regions (Tosoni et al., 2015), while area CSv has strong connections with the medial somatosensory cortex and motor areas (Smith et al., 2017). One possible hypothesis is that posterior egomotion visual regions (as V6+) contribute only to the visual analysis of egomotion signals while anterior egomotion visual regions (as CSv) provide sensory information to the motor system with the aim of guiding locomotion. To test this hypothesis, we used a combined approach of brain mapping methods, task-evoked activity and resting-state functional connectivity by fMRI. We localized with high consistency across 18 subjects a set of six

egomotion visual areas (V6+, V3A, VIP, CSv, pCi, PIC) by using a Flowfields stimulus (Pitzalis et al., 2010). Then, we tested their response to a motor task implying active long-range leg movements. Finally, we examined their pattern of functional connectivity. We found that, among these visually defined areas, only CSv, pCi and PIC responded to leg movements. Functional connectivity analysis showed that the visuomotor areas CSv, pCI and PIC are connected with the cingulate motor areas, the supplementary motor area and notably, with the medial primary somatosensory and motor cortex, which represent the leg and foot. In conclusion, results revealed a gradient of functional specialization and cortical connections, with the most posterior regions dedicated to the analysis of visual attributes of egomotion and the most anterior regions additionally committed to the analysis of motor components of egomotion, likely integrating visual information with locomotion-relevant proprioceptive and vestibular signals. We propose that CSv, pCi and PIC provide a pivotal link between perception and action aimed at locomotion control.

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Poster

488. Visual Sensory-Motor Processing II

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Program #/Poster #: 488.06/DP08/II18

Topic: D.08. Visual Sensory-motor Processing

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Bertarelli Program in Translational Neuroscience and Neuroengineering
NIH Grant R21 NS085320
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Title: Large-scale EM reconstruction of microcircuits supporting sequential activity in parietal cortex

Authors: A. T. KUAN[1], L. N. DRISCOLL[1], C. D. HARVEY[1], *W.-C. A. LEE[2]
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Abstract: Recent work has demonstrated that neurons in posterior parietal cortex (PPC) are activated in temporal sequences corresponding to navigational decisions during a two-alternative forced-choice task. However, it remains unknown how these sequences of activation arise. One approach to understanding the circuit basis of decision-making is to analyze the connectivity of choice-selective neurons. In this project, we combine large-scale serial-section electron microscopy (EM), *in vivo* calcium imaging, and navigational behavior in virtual reality to create

a unified structural and functional map of mouse PPC. We will investigate how connectivity supports task-relevant functional activity, such as whether choice-selective neurons form distinct subnetworks and exhibit synaptic connections consistent with feedforward signal propagation. Here, we present a preliminary EM connectomic dataset centered on functionally characterized PPC. We show correspondence of cell bodies in the EM volume with cells chronically imaged during 30 days of behavior and present preliminary analysis from reconstructions of choice-selective cells. By leveraging methodological innovations, including automated sectioning onto tape substrates and automated reel-to-reel imaging with transmission electron microscopes, we demonstrate the ability to rapidly and comprehensively image the structure of functionally characterized neuronal populations. This technology will enable investigations into the circuit mechanisms underlying complex behaviors.

Disclosures: A.T. Kuan: None. **L.N. Driscoll:** None. **C.D. Harvey:** None. **W.A. Lee:** None.

Poster

488. Visual Sensory-Motor Processing II

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Program #/Poster #: 488.07/JJ1

Topic: D.08. Visual Sensory-motor Processing

Support: NSF BCS-146063

Title: Synchronizing movements to a visual rhythm shifts the neural frequencies of entrainment to lower frequency bands compared to passive perception of visual rhythms

Authors: *D. COMSTOCK, R. BALASUBRAMANIAM
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Abstract: There has been growing evidence that multiple timing systems exist within the brain. Given the evidence linking the motor system to rhythm perception, it is likely that engaging the motor system during a rhythm task will alter the timing mechanisms involved in rhythm perception. While the role of the motor system in auditory rhythm perception has been well studied, the role of the motor system in visual rhythm perception remains relatively unknown. To investigate the role of the motor system in visual rhythm perception we recorded scalp EEG while participants were tasked to passively entrain to a visual flashing rhythm and then to tap in synchrony while entraining with a visual flashing rhythm. Analysis of the neural time-frequency activity at the channel level showed entrainment in alpha and beta bands over motor regions, peaking at flash onset in the passive synchronization condition. During the synchronization condition, that activity shifted so that alpha and beta peaked prior to onset. Additionally, a shift from beta band entrainment in the passive condition to delta band entrainment in the synchronization condition was seen over central and parietal regions. Using ICA and dipole

source localization, we found indication of mu rhythm entrainment in the motor cortex during passive entrainment that, during synchronization, was reduced while entrainment shifted to the beta band. Additional sources in the posterior parietal cortex, temporal parietal junction, and in the pre-motor area showed a shift from beta band entrainment during the passive condition to delta band entrainment in the synchronization condition. The frequency band switching shown in these findings indicate the networks switching to adjust to changing tasks demands, while the presence and modulation of mu rhythms can be seen as an indirect measure of increased coupling between the visual and motor systems. The switching to lower frequency bands may be a result of increased need to share timing information across networks.

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Poster

488. Visual Sensory-Motor Processing II

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Program #/Poster #: 488.08/JJ2

Topic: D.08. Visual Sensory-motor Processing

Support: SFB/TRR 135
IRTG-1901 BrainAct

Title: Effective connectivity during the processing of self-generated movements and their consequences

Authors: *B. ARIKAN, B. VAN KEMENADE, B. STRAUBE, A. JANSEN, T. KIRCHER
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Abstract: Sensory consequences of self-generated movements are often perceived as less intense and generate less neural activity compared to externally-generated stimuli. Such attenuation has been explained as resulting from predictions made regarding the consequences of self-generated movements, which are then compared with actual sensory consequences. Brain areas that have been suggested to be involved in this process include regions of the sensorimotor network as well as cerebellar and parietal areas. However, exact underlying mechanisms are still unclear. Here we used dynamic causal modelling (DCM) for fMRI to assess effective connectivity in the left primary motor cortex (M1), left secondary visual cortex (V5), posterior part of the right cerebellum and left posterior parietal cortex (PPC). 20 participants underwent fMRI as they executed self- vs. externally-generated movements of the wrist while seeing an online recording of their movements in real-time or with a delay. We investigated which area (PPC, M1, cerebellum) was mainly responsible for the observed attenuation in visual cortex. More specifically, we tested on the one hand whether the PPC or M1 plays a central role in the hierarchy of sensorimotor processing during self-generated movements, and on the other hand

the contribution of the cerebellum in attenuating activity in sensory areas during self-generated movements. Bayesian model selection and Bayesian model averaging suggest that the PPC up-regulated activity in M1 while attenuating activity in V5 during self-generated movements. Cerebellar contribution was negligible within this model, possibly because time modulations were not considered. Results provide support for current accounts of PPC as a top-down prediction area in sensorimotor processing.

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Poster

488. Visual Sensory-Motor Processing II

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Topic: D.08. Visual Sensory-motor Processing

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Title: The role of thalamus in the flexible control of timed behavior

Authors: *T. V. PARKS[1], E. D. REMINGTON[1], M. JAZAYERI[2]
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Abstract: Adopting a dynamical systems framework, previous results in our lab have provided evidence that flexible control of covert motor timing might be accomplished by the modulation of initial conditions and inputs associated with the dorsomedial frontal cortex (DMFC) including supplementary eye field and supplementary motor area (Wang et al. 2018; Remington et al. 2018). Currently, the neural circuits that provide the necessary input to DMFC for the control of behavior are not known. Recent studies of sensorimotor function have highlighted the importance of thalamocortical interactions in sensorimotor computations. We thus set out to explore whether thalamus could be the source of this input.
We recorded spiking activity from thalamocortical neurons, putatively in the ventral lateral area and area X, of two macaque monkeys (one female and one male) trained to measure time intervals and subsequently produce timed motor responses according to context-specific stimulus-response rules. In one context, monkeys had to reproduce a measured interval veridically, whereas in the other, the target interval was 1.5 times the measured interval. We

analyzed neural trajectories across the population of thalamic neurons as a function of the context and interval. Within each context, trajectories were structured with respect to the produced interval, similar to that observed previously in DMFC. This corroborated previous results that thalamus through its interactions with DMFC may play a role in the control of motor timing. Next, we asked whether thalamus has an explicit representation of the context information needed to control the behavior. We found that indeed the population activity had a representation of context consistent with thalamus providing a context-dependent input to DMFC. However, this signal was relatively weak suggesting that putative context-dependent signals to DMFC may originate from other, possibly cortical, brain areas.

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Poster

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Title: Neural mechanisms underlying training-based negative compatibility effect

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Abstract: The negative compatibility effects (NCE) is a surprising phenomenon that performance to the targets are faster in incompatible trials (i.e. prime and target indicate opposite responses) than compatible trials (i.e. prime and target indicate the same response) in masked priming paradigm. Previous studies used relevant (composites of perceptual features to target and alternative) and irrelevant (composites of target-irrelevant features) masks to examine the contribution of perceptual updating and motor inhibition to NCE. However, the prime/target used in these studies (e.g. arrow) could induce strong stimuli and response (S-R) link due to long-term experimce during development, which results in the debate about the relative role of perceptual updating and motor inhibition in NCE remains unresolved.
To address this issue, we used short-term training paradigm to establish new S-R link between prime/target and response in the present study. Moreover, BOLD changes with fMRI to investigate the neural mechanism underlying the training-based NCE. Specifically, we examined

the neural substrates that are involved in the generation of NCE with relevant and irrelevant masks before and after S-R link established. Each subject participated in 3 sessions within 8 days: 1-day pre-test fMRI session, 4-day S-R link training session and a 1-day post-test fMRI session. The NCE responses with BOLD index were calculated by contrast each compatible condition against the corresponding incompatible condition.
For relevant mask condition, behavior results showed that NCE was occurred at both pre- and post- training session. We also found brain areas which showed
increased NCE responses in post-test than in pre-test session, including both lower and higher visual areas, SMA, thalamus, posterior cingulate cortex. These results indicated that both perceptual updating and motor inhibition contributed to NCE with relevant mask. In addition, OFC revealed decreased NCE responses in post-test than in pre-test session, which implied that cognitive control demand might decreased after training. For irrelevant mask condition, NCE was only significant at post-test session and only SMA activation showed increased NCE responses at post-test session than in pre-test session. These results suggested that only motor inhibition contribute to NCE triggered by irrelevant mask.
Our findings provide evidence to the neural mechanism underling short training-based NCE. Both perceptual updating and motor inhibition contributes to short training-based NCE triggered by relevant mask, whereas only motor inhibition contributes to short training-based NCE triggered by irrelevant mask.

Disclosures: M. Di: None. **Y. Li:** None. **Y. Wang:** None.

Poster

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Title: Relationship between cortical and striatal activity during visually guided behavior

Authors: *A. J. PETERS, N. A. STEINMETZ, K. D. HARRIS, M. CARANDINI
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Abstract: Corticostriatal interactions are believed to play an essential role in learning and executing stimulus-action transformations. We investigated this relationship by recording the propagation of activity across the cortex and striatum during a visually guided behavior, in which mice reported the position of a visual stimulus by turning a wheel in the correct direction with their forelimbs. Stimulus contrast varied across trials, allowing for easier or harder detection conditions.
To directly relate cortical and striatal activity during behavior, we recorded from both structures simultaneously. We used widefield calcium imaging to record from the dorsal surface of the cortex and a 384-channel electrode array (Neuropixels probe, Jun et al. Nature 2017) to record from a one-dimensional section of the striatum, stretching diagonally from dorsomedial to dorsolateral at 0.2 mm anterior to bregma.
Firing rates in the striatum could be predicted from linear regression of cortical calcium signals, establishing a functional relationship that largely matched anatomical connectivity. Progressing from dorsomedial to dorsolateral striatum, activity was best predicted from visual cortex, then from frontal cortex, and finally from orofacial somatomotor cortex. The boundaries of these representations along the electrode appeared to show sudden transitions rather than a graded shift in predictor location.
During each trial, task-related activity within each striatal domain largely matched that of activity within its corresponding cortical area. Between stimulus onset and movement execution, striatal activity progressed from medial to lateral sites on the electrode. Simultaneously, cortical activity progressed from visual areas to frontal areas and finally to somatomotor areas.
Different cortical and striatal domains exhibited different activity profiles. Activity in visual cortex and dorsomedial striatum aligned best to stimulus onset but included sustained activity during movement. Activity in frontal cortex and dorsocentral striatum aligned best to movement with a peak at movement onset. Finally, activity in somatomotor cortex and dorsolateral striatum aligned best to movement and including sustained activity after movement onset.
By recording activity simultaneously across large areas of the cortex and striatum, we have found that corticostriatal domains can be functionally determined and that task-related activity within each corticostriatal domain is generally consistent. We have also observed that activity profiles across each corticostriatal domain are unique, suggesting a progression of processes that underlie behavior in this task.

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Poster

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PRESTO

Title: Dynamic representation of eye movement direction in mouse frontal cortex

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Abstract: Cortical plasticity is a fundamental process in recovery from motor dysfunction. However, it is not clear how the plasticity is induced at a circuit level. In this study, we investigated motor recovery and underlying neural plasticity upon optogenetic suppression of a cortical area for eye movement. Using visually guided eye movement task in mice, we suppressed a small portion of the secondary motor cortex (MOs) which encodes the contraversive eye movement, i.e., movement toward the contralateral side. We found that optogenetic unilateral suppression severely impaired the contraversive eye movement on the first day. However, repetitive suppression on the following days turned out to be ineffective and the mice restored capability for the contraversive eye movement. Moreover, longitudinal *in vivo* two photon calcium imaging revealed that the regained capability was accompanied by an increased number of neurons encoding for the ipsiversive eye movement in the unsuppressed contralateral MOs. Additional suppression of the contralateral MOs impaired the recovered eye movement again, indicating that the newly-acquired ipsiversive preference was compensatory plasticity responsible for the recovery. Our study directly demonstrates an indispensable contribution of the contralateral hemisphere for the motor recovery and that the directional encoding of eye movement can be dynamic across hemispheres.

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Poster

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Title: Effect of viewing distance on object responses in macaque areas 45B and F5

Authors: *I. CAPRARA, C. STOCKEM, P. JANSSEN
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Abstract: In order to perform real-world tasks like grasping efficiently, the primate brain has to process visual object information so that the grip aperture can be adjusted before contact with the object is made. For this reason, extensive research has been conducted to assess the way in which different brain areas contribute to 3D shape perception and how this is conveyed to the motor cortex. Previous single-cell and monkey fMRI studies have shown that disparity-defined 3D shape is processed in both the ventral (inferior temporal cortex, IT) and the dorsal visual stream. In area AIP and in the anterior subsector of F5 (F5a), 3D shape -selective neurons are also active during object grasping. Moreover, electrical microstimulation of 3D shape-selective clusters in AIP during fMRI activates F5 and area 45B (Premereur E et al., 2015, PLoS Biology *13: e1002072*), indicating that these two frontal areas represent important downstream areas for object processing during grasping. Here, we investigated whether and how F5 and 45B neurons encode object shape and viewing distance during visual fixation of real-world objects. We recorded in two macaque areas, 45B (N = 48) and F5 (N = 32), during a passive fixation and visually- guided grasping task. Using a commercial robot, we presented four real-world objects, two spheres (large - 6cm – small - 3cm), and two plates (large - 6cm – small - 3cm) at two viewing distances, one within reaching distance (28cm) and one outside reaching distance (56cm). Many neurons in area 45B were object-selective (main effect of object in 56% of the neurons, ANOVA $p < 0.05$) and selective for viewing distance (main effect of distance in 50% of the neurons, significant interaction between object and distance in 29% of the neurons, ANOVA, $p < 0.05$). At the population level, the selectivity for viewing distance only emerged in the later epoch of the response (between 200 and 600 ms), with a clear preference for the near viewing distance, whereas in the initial part of the response (0-200 ms), no differences between near and far were observed. In contrast, F5 neurons were less frequently affected by shape (main effect of object in 22% of the neurons) or distance (main effect of distance in 41% of the neurons; significant interaction between object and distance in 16% of the neurons, $p = 0.0086$, z-test). At the population level, F5 neurons did not exhibit any preference for near or far viewing distances, neither in the early epoch nor in the late epoch of the response. In conclusion, contrary to our expectations, neurons in area 45B – but not F5 neurons – prefer objects presented in peripersonal space.

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Poster

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Title: Connections between functional domains in posterior parietal cortex and motor cortex for running or climbing in galagos revealed by microstimulation

Authors: *Q. WANG, C.-C. LIAO, I. STEPNIEWSKA, H. X. QI, M. GABI, J. H. KAAS
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Abstract: Previous studies have demonstrated that posterior parietal cortex (PPC) in prosimian galagos and other primates can be subdivided into up to eight functional domains from which specific types of complex movements (e.g. reach, grasp or hand to mouth) can be evoked by 500 ms long trains of electrical pulses. Studies of some of these domains, mostly within the forelimb representation, have shown their specific connections with premotor and primary motor areas of the frontal cortex and with other areas of parietal and occipital cortex. However, connection patterns of the most medial PPC domain from which combined forelimb and hindlimb movements suggestive of running or climbing behavior can be evoked remain unclear. Here, we investigated the functional organization of this domain and its cortical connections with other brain areas in two adult male galagos (*Otolemur garnetti*). First, we employed 500 ms trains of intracortical microstimulation to map the PPC region above the intraparietal sulcus and identified the climbing/running domain which is located dorsally close to the medial wall. Then we made two injections of different retrograde tracers, cholera toxin B subunit (CTB) and fluoro-ruby (FR), in this domain. Flattened cortices were cut parallel to the surface and divided into series processed for cytochrome oxidase and myelin staining for cortical architecture, and CTB and FR for labeled neurons. Injections in the climbing/running domain revealed that the densest patches of labeled neurons were in the cortex adjacent to injection site and through out most of rostral PPC (PPCr), other dense connections were with primary motor (M1) and premotor cortex (PMC), mostly in dorsal locations from which hindlimb and forelimb movements can be evoked. Other labeled neurons were densely distributed in arm and leg regions of the parietal somatosensory areas (area 3a, 3b, 1/2). Numerous neurons were also labeled in cingulate motor areas
of the medial surface of the hemisphere dorsal to the cingulate sulcus. Less dense connections were with the secondary somatosensory area (S2) and parietal ventral area (PV) in cortex of the upper bank of the lateral sulcus. Occasionally, we observed labeled neurons anterior to the ventral premotor areas (PMV). These preliminary results indicate that the climbing/running movement domain exists in the rostromedial portion of PPC receives dense motor and somatosensory inputs from the hindlimb and forelimb cortical representations. In addition, our microstimulation results provide further evidence for the climbing/running domain in PPC and functionally matched domains in M1 and PMC.

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Poster

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Title: Modulation of cell-type-specific spike-field coherence in posterior parietal cortex during coordinated visual behavior

Authors: *M. F. KHAZALI, Y. WONG, B. PESARAN
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Abstract: Neurons in the intraparietal sulcus (IPS) of the posterior parietal cortex (PPC) are involved in coordinated eye-arm movements to visually-defined targets. Before coordinated visual behaviors, many PPC neurons display elevated activity in spatial response fields. Previous work demonstrates that spike-field coherence (SFC) within and between the lateral and medial banks of the IPS also predicts the properties of upcoming coordinated visual movements and movement choices. Neuronal coherence may reflect cell-specific neuronal morphology and biophysical properties as well as task-dependent functional interactions between populations of neurons. Here, we analyze extracellular recordings of 778 PPC neurons in four macaque monkeys performing coordinated look-reach movements to remembered visual targets to test whether SFC in PPC depends on putative neuronal cell-type (M1:211 neurons, M2:463, M3:68, M4:34). We identified four different populations of neurons based on their spike width (Hartigan's dip test, $p<0.05$; narrowest NS1:133 neurons, second narrowest NS2:141, widest WS1:225; second widest WS2:229). SFC in the beta band (13-30 Hz) was more prominent than SFC at other frequencies. SFC magnitude across the population during both baseline period before the movement target was flashed (Kruskal-Wallis test; $p = 0.027$) and the planning period after the target was flashed ($p=0.007$). NS1 neurons exhibited the greatest magnitude SFC (pairwise rank-sum $p<0.05$) during both epochs. Moreover, WS1 showed higher spike-field coherence during baseline and planning than NS2 (pairwise rank-sum $p<0.05$), but was not different from WS2. Whereas WS2 SFC was higher than NS2 SFC during planning alone (pairwise rank-sum $p<0.05$), as it did not differ from NS2 one during baseline. The spatial extent of SFC also varied with putative cell-type. NS1 cells showed the highest SFC with locally-recorded LFP activity (pairwise rank-sum $p<0.05$) and other putative cell-types expressed similar SFC (pairwise rank-sum $p>0.05$). WS1 and NS1 spikes showed the greatest SFC with LFP activity recorded from different area nearby PPC (same coherence level pairwise rank-sum $p>0.05$) as compared to each of the other neuron-cell-types NS2 and WS2 (pairwise rank-sum $p<0.05$). These results demonstrate that SFC reflects cell-type-specific mechanisms.

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Poster

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Title: Semi-chronic subdural electrocorticography, local field potentials, and spike recordings over posterior parietal cortex during coordinated visual behavior

Authors: *B. PESARAN[1], A. L. ORSBORN[2], V. SANCHEZ[3], M. F. KHAZALI, 10003[2]
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Abstract: Neurons are the basic information encoding units in the brain. However, interpreting individual unit activity alone provides insufficient information about neural processing because the brain operates at multiple scales, from single neurons to interacting brain regions. Monitoring brain activity at different scales can therefore enable better understanding of brain function. Posterior parietal cortex (PPC) activity during coordinated hand and eye movements illustrates the need for multiscale recordings sampled simultaneously across extended cortical areas. Many behavioral aspects of coordinated movements are explained by coherent activity across the lateral and medial banks of PPC. Thus, we performed electrophysiology recordings at different spatial scales over the lateral and medial banks of PPC using a previously developed semi-chronic recording system (Orsborn 2015). The system allows both subdural micro-electrocorticography (μECoG), local field potential (LFP) and single-unit recordings in the same tissue volume. We apply tuning analysis of single unit, multi-unit, and LFP responses recorded by microdrive at different cortical depths and μECoG arrays from a rhesus macaque (Monkey M) performing a variety of coordinated reach and saccade tasks. Each trial began with a baseline period in which M was required to maintain touch and fixation on a central cue. A peripheral target appeared then for 0.3s (memory trials) or for the whole period (delay trials). The central cue then switched from yellow to gray, signaling a “go” cue, after which M made coordinated hand and eye movements to a peripheral target. M was trained on task variations to fully dissociate reaches and saccade. He performed variations with coordinated reach and saccades to the same location, reach and saccade to different locations, reaching while holding fixation, and saccading while holding center touch. He performed delay and memory trials for each task variation. Preliminary results show that all forms of signals (spikes, multiunit and LFPs) indicate visual response after presenting visual target over the receptive field of the recording sites. We similarly observed sustained activity after the visual response in all signal types. Sustained

activity was spatially localized to different anatomical areas depending on task, with responses in the lateral bank during saccade trials and in the medial bank during reach trials. LFPs recorded from different depths with microdrive or from the surface activities of μECoG showed similar sustained activity in Beta band. This sustained activity was observed on the lateral and medial banks during memory saccades and reaches, respectively.

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Poster

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Title: Clarifying the anatomical organization and cortical projections of multiple major white matter tracts associating the human temporal and parietal lobes

Authors: *D. BULLOCK[1], H. TAKEMURA[4], C. F. CAIAFA[5,6], L. KITCHELL[2], B. MCPHERSON[2], B. CARON[3], F. PESTILLI[1]
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Abstract: Traditionally, norms of neuroscientific attention have caused researchers to primarily study larger white matter tracts that are aligned to the rostral-caudal axis. These tracts include the superior longitudinal fasciculus, the arcuate fasciculus, the inferior fronto-occipital fasciculus, and the inferior longitudinal fasciculus. More recently, modern in-vivo imaging studies have begun elucidating several tracts in the posterior of the human brain that are instead aligned perpendicular to the rostral-caudal axis. These tracts transfer information directly between the dorsal and ventral aspects of the posterior human cortex. Here we examine several of these tracts, namely, the temporal-parietal connection, the posterior arcuate, and the two components of the middle longitudinal fasciculus.In this work, we compare the anatomical features, volumes,

and connectivity patterns of the rostro-caudal aligned and rostro-caudal perpendicular tracts using diffusion-weighted magnetic resonance data from the Human Connectome Project (1.25 mm, b=2000 mm^2/s), modern tractography methods (ensemble tractography), and statistical validation techniques (LiFE). Furthermore, we developed an automated segmentation method to identify these four tracts along with the more studied rostro-caudal tracts. Our results indicate a significant degree of interconnectivity between the ventral and dorsal streams of the human brain. We find that the rostro-caudal perpendicular tracts can be reliably segmented across subjects. Their statistical evidence, volume, and fiber length are generally smaller than those of the more well established rostro-caudal aligned tracts. We also report that the collective architecture of these four vertical tracts instantiate a dual set of parallel white matter structures, conducting information directly between the parietal and temporal lobes. These tracts constitute an important but understudied set of connections in the human brain, which are fundamental in linking cortical areas involved in face recognition, object and word perception, and controlling or planning eye and limb movements. As such, this pattern of connectivity suggests that theories of visual perception and action may need to expand their accounts to incorporate models of cortical function with direct information flow between the posterior dorsal and ventral cortex.

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Poster

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Support: Wellcome Trust 101092/Z/13/Z

Title: Mapping response properties in lateral intraparietal area (LIP) of the rhesus macaque

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Abstract: Primate sensorimotor area LIP is thought to have a central role in visual attention, saccade guidance and decision-making. Anatomically, it is divided in dorsal and ventral LIP. LIP neurons may exhibit a visual receptive field or a saccade target response field or both. The nature of the visual receptive field, the distribution of these properties and the relationship between maps are not fully understood.
Using a guidance grid and maps from structural MRI, we carried out multiple penetrations orthogonal to the cortical surface to map systematically neuronal response properties across LIP in one Rhesus macaque. We screened cells for activity during a delayed saccade task to targets

across the visual screen. If cells showed delay-period activity, we tried to establish a visual receptive field with a patch of moving dots. We collected complete data sets from 24 single cells that both responded significantly to a visual stimulus such as moving dots and also responded in a delayed saccade task in comparison with fixation task on a blank screen. LIP neurons usually had both a clear response field and a receptive field, but sometimes the visual receptive field was ill-defined. As previously reported, visual receptive fields were found generally in the contralateral visual hemifield; response fields could be either contra- or ipsilateral. Cells recorded more posteriorly and ventrally tended to have lower visual receptive fields, progressing upwards with penetrations moving anteriorly.
The visual receptive fields of these neurons were tested for direction and disparity tuning with patches of coherently moving random dots positioned over the receptive field. 29% (7/24) of cells showed significant direction tuning and 38% (9/24) significant disparity selectivity (ANOVA, $p < 0.05$). At sites with significant visual tuning for the isolated single unit (SU), multi-unit activity was usually also tuned. We then studied the combination of stereo and motion information to investigate how LIP cells process this cue combination during a relevant perceptual decision. We presented a structure-from-motion cylinder over the receptive field of the cell and one of two response targets on the response field. The other target was presented symmetrically in the opposite hemifield. The monkey was trained to discriminate the rotation direction of the cylinder by making a saccade to the appropriate target in a reaction time task. 38% (9/24) of cells were tuned to cylinder disparities (ANOVA, $p<0.05$) and many responded to choices about the cylinder.
In sum, LIP contains at least one crude map of the contralateral visual field and many cells show tuning for direction of motion and binocular disparity.

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Poster

488. Visual Sensory-Motor Processing II

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Title: Mapping functional connectivity between layers of the superior colliculus

Authors: A. L. SMOULDER, *U. K. JAGADISAN, N. J. GANDHI
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Abstract: The superior colliculus (SC) is a laminar structure involved in visual stimulus detection and eye movement generation. Superficial layer neurons respond most strongly to visual stimulus onset, whereas intermediate/deep layer neurons are active both after target onset and immediately before a saccade. While anatomical connectivity between layers has been extensively studied, functional connectivity across the layers has not been thoroughly characterized. Mapping the functional connectivity of SC in vivo will contribute to our understanding of sensorimotor transformations and related phenomena such as visual input suppression during saccades. Additionally, spectral decomposition of effective information transfer can elucidate the frequency content of interactions between layers.
We sought to determine this circuit of information flow by using a laminar multi-contact electrode to record from all layers of a macaque SC during a delayed saccade task. This paradigm dissociates the neural activity into two epochs: target onset (visual response) and saccade onset (motor response), with a delay period in between. We used conditional Granger Causality to compute the temporal dynamics and spectral content of functional connectivity within SC. This quantifies the directed (asymmetric) correlation between SC layers while conditioning on the signals from other layers to exclude redundant connections.
Preliminary results indicate bidirectional information flow across layers. During the visual epoch, superficial layer activity Granger causes intermediate layer response, most prominently in beta band frequencies. Beta band activity has been shown to decrease during movements, so it is feasible that the increase in activity observed is reflective of eye movement suppression. Also, during this epoch, intermediate layers show ascending information transfer to superficial layers at sub-alpha frequencies, and to a lesser extent, in the beta band. In contrast, little Granger Causality was observed during the delay, pre-, and peri-movement periods, indicating a lack of inter-layer communication while hinting at intra-layer processing and/or influences from outside SC. Immediately following saccade onset, two patterns emerge. First, superficial-to-intermediate Granger Causality is observed similar to target onset, indicative of target reafference. Second, intermediate layer activity Granger causes both superficial and deep SC layer responses in alpha band frequencies. These interactions, along with further analysis of data, help illustrate the effective information transfer within SC during an oculomotor task.

Disclosures: A.L. Smoulder: None. **U.K. Jagadisan:** None. **N.J. Gandhi:** None.

Poster

488. Visual Sensory-Motor Processing II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 488.20/KK6

Topic: D.08. Visual Sensory-motor Processing

Support: F31 NS103305-01A1
R01NS079518-06A1

Title: Functional circuits for goal-directed behavior in the superior colliculus

Authors: *J. ESSIG[1], G. FELSEN[2]
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Abstract: The midbrain superior colliculus (SC) is a conserved sensorimotor structure essential for spatial attention and orienting behaviors. Experiments in mice, cats and primates demonstrate a topographical representation of contralateral space along the horizontal axis of the SC whereby increased neural activity at specific sites in the collicular network predictably elicit behaviors to distinct spatial targets. In natural environments with many stimuli available for attention, it is hypothesized that behaviorally salient targets are selected in the SC via competitive interactions, however the functional circuitry underlying competition in the SC, and the mode of competition, is unknown. Here, we measure how intrinsic inhibition in the SC shapes neural activity during target selection and acquisition by recording and manipulating optogenetically-identified inhibitory SC neurons in mice performing an odor-guided spatial choice task. Trained GAD2-Cre mice expressing channelrhodopsin-2 (ChR2) in GABAergic neurons via a Cre-dependent viral strategy were implanted with an "optetrode" drive, an optic fiber surrounded by four tetrodes, in the rostral or caudal SC to enable light delivery to and extracellular recordings from the same population of neurons. GABAergic neurons were identified based on short-latency light responses (i.e., "optotagging") before and after each behavioral session. We hypothesized that caudal GABAergic neurons locally influence SC activity by inhibiting outputs representing contralateral choices, and therefore predicted that activity in these neurons would promote ipsilateral choices. However, we instead found that the activity of these neurons was higher during the selection of and movement towards the contralateral reward port, and that optogenetically activating these cells during target selection biased choices contralaterally. Notably, we obtained similar results in the rostral SC. These results suggest that GABAergic SC neurons mediate target selection through functionally long-range, as opposed to local, connections to shape intercollicular dynamics and suppress output representing competing targets. We are currently incorporating these findings into biologically relevant attractor network models to examine inter- and intra-SC circuit motifs underlying the neural dynamics for goal-directed behavior.

Disclosures: J. Essig: None. **G. Felsen:** None.

Poster

488. Visual Sensory-Motor Processing II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 488.21/KK7

Topic: D.08. Visual Sensory-motor Processing

Support: NIH Grant EY024831

NIH Grant EY022854
GAANN Fellowship P200A150050

Title: Population dynamics of delay period activity during a saccade task

Authors: *M. R. HEUSSER[1,2], U. K. JAGADISAN[1,2], B. R. COWLEY[3,2], N. J. GANDHI[1,2]
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Abstract: The superior colliculus (SC) is a midbrain structure crucial for the generation of fast eye movements, or saccades. SC neurons are known to encode multiple types of signals. For instance, aptly named visuomotor SC neurons increase their firing rates following stimulus onset and when generating a motor command. This multiplexing of visual and motor information is most apparent in the activity of SC neurons during a delayed saccade task. The paradigm temporally dissociates the visual and motor epochs and consequently reveals two distinct bursts of activity that are widely thought to be visual- and movement-related, respectively. However, the structure of population activity during the delay period, i.e., between visual target onset and eye movement onset, is not as well characterized. SC activity during the delay period likely reflects cognitive processes, transformations of signals from a sensory to motor reference frame, and movement preparation. To investigate the structure of neural activity during the delay period, we recorded SC activity from two male rhesus macaques (Macaca mulatta) with a multi-contact laminar probe while they performed a standard delayed saccade task to a target placed either in the population's response field or in the diametrically opposite direction. We sought to characterize the evolution of SC activity throughout the trial with clustering and decoding techniques. We first performed a clustering analysis of population activity, seeking any systematic trends across the delay period, and used this clustering approach to inform our decoding analyses. Population spike counts in sliding windows during the delay period were fed into a logistic regression classifier trained on predefined activity windows (baseline, visual, delay, motor, or other), and the decoder returned the most likely category to which the neural activity belonged. A general trend emerged: activity early in the delay period was often classified as visual, but late in the delay period as motor, with a smooth transition between the two categories. Overall, this preliminary analysis shows that SC population activity during the delay period is not static, but rather reflects a dynamic transition between two multiplexed signals.

Disclosures: M.R. Heusser: None. **U.K. Jagadisan:** None. **B.R. Cowley:** None. **N.J. Gandhi:** None.

Poster

489. Multisensory Integration: Cross-Modal Processing in Humans I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 489.01/KK8

Topic: D.09. Multisensory Integration

Support: Funded by UEA

Title: Decoding the sound of hand-object interactions in primary somatosensory cortex

Authors: *K. M. BAILEY[1], B. L. GIORDANO[2], A. KAAS[3], F. W. SMITH[1]
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Abstract: Neurons, even in earliest sensory regions of cortex, are subject to a great deal of contextual influences from both within and across modality connections. Such connections provide one way for prior experience and the current context to shape the responses of early sensory brain areas. Recently we have shown that cross-modal connections from vision to primary somatosensory cortex (S1) transmit content-specific information about familiar but not unfamiliar visual object categories. In the present work, we investigated whether hearing sounds depicting familiar hand-object interactions would also trigger such activity in S1. In a rapid event-related functional magnetic resonance imaging (fMRI) experiment, right handed participants (*N*=10) listened to five exemplars from each of three categories of auditory stimuli: hand-object interactions (e.g. bouncing a ball), animal calls (e.g. dog barking), and pure tones (unfamiliar control). Participants listened attentively, and performed a one-back repetition counting task, which eliminated any need for a motor response during scanning. An independent finger-mapping localizer was completed afterwards, and used to define finger-sensitive voxels within anatomically drawn masks of the right and left post-central gyrus (PCG). Multivariate pattern analysis revealed significant decoding of different hand-object interactions within bilateral PCG, whilst no significant decoding was found for either control category. Crucially, in the finger-selective voxels, decoding accuracies were significantly higher for decoding hand-object interactions compared to both control categories in left PCG. Further analyses also revealed significant decoding in pre-motor cortex (PMC) for familiar hand-object interactions. Our findings indicate that hearing sounds depicting familiar hand-object interactions elicit different patterns of activity in PCG, despite the complete absence of tactile stimulation. Thus cross-modal connections from audition to early somatosensory cortex transmit content specific information about familiar hand-object sounds. This finding is consistent with Predictive Coding models, which suggest that the key goal of even the earliest sensory brain areas is to use the current context, together with prior knowledge, to predict forthcoming stimulation.

Disclosures: K.M. Bailey: None. **B.L. Giordano:** None. **A. Kaas:** None. **F.W. Smith:** None.

Poster

489. Multisensory Integration: Cross-Modal Processing in Humans I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 489.02/KK9

Topic: D.09. Multisensory Integration

Support: DARPA N66001-15-C-4038
Cleveland VA Medical Center

Title: Visual and proprioceptive inputs affect the location of evoked somatosensory percepts in amputees

Authors: *B. CHRISTIE[1,2], H. CHARKHKAR[2], D. J. TYLER[1], R. TRIOLO[2]
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Abstract: Cross-modal links between vision, somatosensation, and proprioception play an important role in fine motor control, balance, and locomotion. For instance, orientation of the eyes to a body site enhances tactile acuity [Pierson 1991], and visuo-proprioceptive conflicts can modify reaction time to tactile stimuli [Folegatti 2009]. However, the impact of visual and proprioceptive inputs on the spatial location of tactile perception is not well established.
By utilizing cuff electrodes to apply electrical stimulation to the residual peripheral nerves of two trans-tibial amputees, we have elicited tactile sensations referred to their missing limbs. This unique opportunity enabled us to evoke somatosensation without physical contact, decoupling somatosensation from vision and proprioception.
Participants were asked to draw the location of stimulation-evoked percepts on a diagram of an intact foot. Experimental conditions included baseline, seated, and upright standing. While seated, an experimenter touched plantar regions of the participant's prosthetic foot while he observed. During upright standing, the participants were instructed to put pressure on plantar areas of their prostheses. Standing conditions were repeated while participants looked at their prostheses or closed their eyes.
Preliminary results suggest that both proprioception and vision can change the spatial location of a somatosensory percept. When the baseline percept was located in the residuum, incongruent proprioceptive inputs affected percept location more strongly than vision. However, incongruent visual inputs had a stronger influence when the baseline sensation was located in the phantom heel. Visual and proprioceptive inputs made approximately equal contributions for baseline sensation in the toes.
In conclusion, proprioception appears to have a stronger influence on somatosensory location than vision in the residuum, which may represent the prioritization done in able-bodied individuals. In the phantom limb, amputees appear to rely more strongly on vision than

proprioception from the residuum. This may be due to the missing proprioceptive ankle information and a disrupted body schema. Continued testing will allow us to examine cross-modal integration in a manner that has never been possible before.

Disclosures: B. Christie: None. **H. Charkhkar:** None. **D.J. Tyler:** None. **R. Triolo:** None.

Poster

489. Multisensory Integration: Cross-Modal Processing in Humans I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 489.03/KK10

Topic: D.09. Multisensory Integration

Support: Wellcome Trust 098433
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Wellcome Trust 107802

Title: Representational interactions during audiovisual speech entrainment: Redundancy in left posterior superior temporal gyrus and synergy in left motor cortex

Authors: *H. PARK[1], R. I. I. INCE[2], P. G. SCHYNS[2], G. THUT[2], J. GROSS[3]
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Abstract: Integration of multimodal sensory information is fundamental to many aspects of human behavior, but the neural mechanism underlying these processes remain mysterious. For example, during face-to-face communication we know that the brain integrates the dynamic auditory and visual inputs but we do not yet understand where and how such integration mechanisms support speech comprehension. Here we quantify representational interactions between dynamic audio and visual speech signals and show that different brain regions exhibit different types of representational interaction. With a novel information theoretic measure, we found that theta (3-7 Hz) oscillations in the posterior superior temporal gyrus/sulcus (pSTG/S) represent auditory and visual inputs redundantly (i.e. represent common features of the two) whereas the same oscillations in left motor and inferior temporal cortex represent the inputs synergistically (i.e. the instantaneous relationship between audio and visual inputs is also represented). Importantly, redundant coding in the left pSTG/S and synergistic coding in the left motor cortex predict behavior - i.e. speech comprehension performance. Our findings therefore demonstrate that processes classically described as integration can have different statistical properties and may reflect distinct mechanisms that occur in different brain regions to support audiovisual speech comprehension.

Disclosures: R.I.I. Ince: None. **P.G. Schyns:** None. **G. Thut:** None. **J. Gross:** None.

Poster

489. Multisensory Integration: Cross-Modal Processing in Humans I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 489.04/KK11

Topic: D.09. Multisensory Integration

Support: Experimental Psychology Society Small Grant

Title: Examining the size-weight illusion with visuo-haptic conflict in immersive virtual reality

Authors: *G. BUCKINGHAM
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Abstract: When we experience our environment, we do so by combining our sensory inputs with our prior knowledge. This combination of top-down and bottom-up information causes surprising perceptual effects such as the size-weight illusion (SWI), were small objects feel heavier than equally-weighted large objects. This powerful illusion is thought to occur because the experienced heaviness reflects a contrast to the lifter's prior expectation that the large object will outweigh the small object. Interestingly, there is evidence that the strength of the SWI varies depending on the modality the lifter uses to experience the size differences. Ellis and Lederman (1993) showed that the SWI experienced by individuals lifting blindfolded (i.e., experiencing only haptic the size cues was substantially larger than that induced when lifting with a string (i.e., experiencing only visual size cues), and that adding visual size cues added nothing over and above haptic size cues. It is, however, unclear whether these findings are due to the reliability of the sensory modality removal used to experience the size difference, or a consequence of removing one sensory input. To further investigate multisensory contributions to the SWI, I placed vision and touch cues to size in conflict with one another using immersive virtual reality. An Optitrak motion capture system tracked the positions of SWI-inducing stimuli in real time, and images of the objects were displayed to participants in Unity through and Oculus Rift head-mounted display. With this setup, 22 participants lifted and judged the heaviness of identically-weighted cylinders across three within-subject conditions: (1) objects appeared different sizes but were physically the same size, (2) objects were physically different sizes but appeared to be the same size, or (3) objects both looked and actually were different sizes from one another. Consistent with prior work, size differences experienced with the hands induced a larger SWI than that induced with visual size differences. In contrast to prior work, however, congruent vision and haptic size cues yielded a larger-still SWI. These findings not only add to our understanding of how different modalities combine to influence our hedonic perception, but also highlight the value of cue conflict paradigms for studies of multisensory integration and showcase how immersive virtual reality can develop experimental cue-conflict paradigms with high ecological validity.

Disclosures: G. Buckingham: None.

Poster

489. Multisensory Integration: Cross-Modal Processing in Humans I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 489.05/KK12

Topic: D.09. Multisensory Integration

Support: R15 HD093086
Whitaker International Program Grant
National Science Foundation under an Individual Research and Development Plan
Erasmus+ KA 107 action (USA-ITALY)

Title: Influence of age and practice on the discrimination of sequential and simultaneous vibrotactile stimuli

Authors: *L. A. MROTEK[1], V. SHAH[1], M. CASADIO[2], K. A. NIELSON[1], R. A. SCHEIDT[1,3,4]
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Abstract: Sensory augmentation via vibrotactile feedback (VTF) can be used in body-machine interfaces to enhance the precision of movement in healthy individuals and in patients with impaired proprioception (e.g., some survivors of stroke). However, learning to use limb state information encoded within VTF to plan and control goal-directed movements requires considerable cognitive effort. To what extent can interpretation of vibrotactile stimuli improve with practice? We examined the capability of healthy people in two groups, Middle Age (40-55 yr) and Older Age (65-90 yr), to discriminate vibrotactile stimuli applied sequentially or simultaneously within and across dermatomes, as well as the extent to which vibrotactile discrimination changes with practice. Stimuli were applied using vibration motors (ERM tactors) taped to the forearm. We tested locations in dermatome C7 (posterior proximal forearm) and dermatome T1 (anterior middle forearm). Stimuli were applied in one location sequentially (C7 **or** T1), in two locations sequentially (C7/T1 or T1/C7), or two locations simultaneously (C7+T1). We used a two-alternative, forced choice approach and the method of constant stimuli to estimate the just noticeable difference in the magnitude/frequency of vibratory stimuli within each condition. In all cases, a "standard stimulus" was presented at 186 Hz and a "probe stimulus" was presented within a range of 100Hz to 235Hz (5 frequencies above and 5 below the standard). Each probe was presented 10 times in each condition. The presentation order of standard and probe stimuli and testing locations was pseudorandomized and counterbalanced. Probability that the subject would declare the probe stimulus greater than the standard was computed in each condition and fit with a cumulative Gaussian distribution function. The Middle

Age group was better at discriminating vibrotactile stimulation than the Older Age group. Within the Middle Age group, we found sensory discrimination to be better in the C7 and T1 sequential conditions vs. the C7+T1 simultaneous condition. The Middle Age group did not improve appreciably with practice, except for in the C7+T1 simultaneous condition. Discrimination performance in the Older Age group was highly variable: some (but not all) members initially struggled with discriminating the vibration stimuli, especially in the C7+T1 simultaneous condition. However, the performance in the Older Age group improved over 3 days of practice. This evidence of perceptual learning is encouraging, suggesting that interpretation of sequential and simultaneous vibrotactile cues can be improved with extended practice, even in older individuals.

Disclosures: L.A. Mrotek: None. **V. Shah:** None. **M. Casadio:** None. **K.A. Nielson:** None. **R.A. Scheidt:** None.

Poster

489. Multisensory Integration: Cross-Modal Processing in Humans I

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Topic: D.09. Multisensory Integration

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Erasmus+ KA 107 action (USA-ITALY)

Title: Vibrotactile feedback guided reaching during single and dual-task conditions

Authors: *V. SHAH[1,2], L. A. MROTEK[1], M. CASADIO[2,1], R. SCHEIDT[1,3,4]
[1]Dept. of Biomed. Engin., Marquette Univ., Milwaukee, WI; [2]Dept. Informatics, Bioengineering, Robotics and Systems Engin., Univ. of Genova, Genova, Italy; [3]Feinberg Sch. of Med., Northwestern Univ., Chicago, IL; [4]Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Vibrotactile feedback (VTF) is a non-invasive and inexpensive way to augment sensation or display useful information in body-machine interfaces. The initial learning of VTF cues requires significant cognitive resources, but may eventually transition into an autonomous phase requiring less overt attention (c.f., Fitts & Posner, 1973). Our long-term goal is to enhance control of upper limb movements with the real-time use of VTF, thus requiring users to integrate VTF cues into the planning and ongoing control of movements. To advance this goal, we used a dual-task condition to determine the effects of cognitive load on VTF-guided reaching, and the extent to which VTF-guided reaching can improve across 5 days of training. We hypothesized

that VTF training improves reach performance in a way that is impervious to dual-task interference, and that 5 days of training suffice to increase expertise of VTF-guided reaching such that secondary task learning can also occur. Ten young participants with no neurological impairment gave written consent to 5 days of experiments wherein they held the handle of a planar manipulandum with the dominant hand. Four eccentric rotating mass motors were used to create a vibrotactile display that encoded information about the {X, Y} position of the handle. The vibrotactile display was attached to the non-moving arm. Each participant performed two tasks, individually and simultaneously (the dual-task condition). The primary task asked participants to make goal-directed reaches under three different feedback conditions: visually-guided, VTF-guided, and none (i.e., proprioception alone). We analyzed target capture error and target capture time. The secondary task required participants to perform a cued, choice reaction time task. We analyzed choice accuracy and reaction time. Participants received 30 minutes of VTF-guided reach training on each of 5 days; we assessed single and dual-task performance before training (Day 1) and after training (Days 1, 3, & 5). Repeated measures ANOVA and post-hoc t-test found significant ($p < 0.05$) pre-to-post-training improvements in single-task reach performance (~17 % target capture error reduction) that were largely preserved in the dual-task condition (~14% target capture error reduction). These results support the hypothesis that VTF training improves reach performance despite dual-task loading. By contrast, we found no significant improvements in target capture time or in secondary task performance. Lack of improvement in these variables suggests that 5 days of training did not suffice to bring VTF-guided reaching into the autonomous phase of learning.

Disclosures: V. Shah: None. **L.A. Mrotek:** None. **M. Casadio:** None. **R. Scheidt:** None.

Poster

489. Multisensory Integration: Cross-Modal Processing in Humans I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 489.07/LL2

Topic: D.09. Multisensory Integration

Support: Wenner-Gren Scholarship UPD2017-0172

Title: a new psychophysical paradigm to directly quantify the perception of body ownership during the rubber hand illusion

Authors: *M. CHANCEL, H. H. EHRSSON
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Abstract: Introduction: The perception of limbs as one's own is referred to as the sense of body ownership (BO). This bodily experience depends on the integration of signals from multiple sensory modalities (Ehrsson, 2012). However, a major shortcoming of the current literature is the

lack of a sensitive psychophysics method to adequately register BO while controlling for cognitive bias. To fill this gap, we developed a new discrimination task for a more precise and direct measurement of BO based on a version of the Rubber Hand (RH) Illusion. **Method**: The participants' right hand lies hidden beneath a table. On this table two identical right RHs are placed in parallel with the same orientation as the real hand (the real hand lays between the RHs). Three robot arms repeatedly apply taps to the two RHs and to the participants' real hand. Each RH is touched repeatedly for 12 sec (1 Hz); either synchronously with the other RH and the participants' hand or with a delay that is systematically varied (50, 100, or 200 ms, the longer the delay the weaker the BO for that RH). The participants then have to decide which of the two RHs that feels more like their own. In experiment 1 (N=24 participants), we manipulated the distance between the real hand and the two RHs in the horizontal plane: both RHs were placed 5 cm away from the real hand or one was 10 cm away from the real hand (projection on the horizontal plan). In experiment 2 (N=22 participants), we manipulated the texture congruency between the visual and tactile stimuli (plastic versus foam tubes). **Results**: The proportion of "the right RH feels more like mine" for each delay was efficiently fitted by cumulative Gaussian curves (fitting performed with the Palamedes toolbox). This fitting did not work under conditions known to abolish the RHI (e.g. rotating the RHs 90º) as demonstrated in separate control experiments. By performing ANOVAs the psychometric curves' means under different distance conditions we found that participants favoured the RH that was closer to their real hand (Exp1: $F(2, 46) = 55.7$, $p < .001$, $\eta^2 = 0.71$), which is in line with the previous literature. The results from the second experiment showed how incongruency between the seen and felt tactile properties of the objects touching the RHs and the real hand led to a significant reduction in BO (Exp2: $F(2, 42) = 26.26$, $p < .001$, $\eta^2 = .56$). This demonstrates the sensitivity of our method and solves a controversy in the previous literature. **Discussion**: Taken together, our results show that BO constitutes a genuine perceptual multisensory phenomenon that can be quantified with psychophysics. This has important bearings on theoretical models of BO and future empirical studies on the rubber hand illusion.

Disclosures: M. Chancel: None. **H.H. Ehrsson:** None.

Poster

489. Multisensory Integration: Cross-Modal Processing in Humans I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 489.08/LL3

Topic: D.09. Multisensory Integration

Support: Swedish Research Council

Title: Unconscious body ownership during continuous flash suppression

Authors: *B. VAN DER HOORT[1,2], N. RADZIUN[2], H. H. EHRSSON[2]
[1]Univ. of Amsterdam, Amsterdam, Netherlands; [2]Karolinska Insitute, Stockholm, Sweden

Abstract: Body ownership is traditionally defined as the conscious sensation that our body is our own. However, the implicit assumption that body ownership requires consciousness has never been directly tested. In the rubber hand illusion, body ownership is induced through simultaneous stroking of the rubber hand (in view) and the participant's real hand (out of view). In the current study, we combined the rubber hand illusion with continuous flash suppression, which prevented conscious visual perception of a stranger's hand and an object stimulating it, while participants' real hand was stimulated synchronously.
In Experiment 1a (n = 40), continuous flash suppression successfully rendered the rubber hand invisible. However, despite the absence of visual awareness of the rubber hand, participants displayed a significant increase of ownership for the masked hand after a period of synchronous stimulation. To be more specific, their skin conductance responses to physical threats towards the location of the masked hand were increased (Z = 2.25, n = 30, p = 0.024), and their felt hand position drifted towards the masked hand (Z = 3.07, n = 40, p = 0.002).
In Experiment 1b (n = 40), continuous flash suppression was removed, rendering the hand clearly visible. As expected, when the hand was visible, the ownership measures remained significant (skin conductance response: Z = 2.252, n = 30, p = 0.024; proprioceptive drift: t(39) = 2.21, p = 0.033). In fact, visibility of the hand did not even alter the magnitude of the objective ownership measures (skin conductance response: U = 414, p = 0.75: proprioceptive drift: U = 674, p = 0.22), which suggests that, for the measures used in this study, visual awareness of the rubber hand does not increase ownership.
In a final experiment (Experiment 2, n = 30*)*, we found that the 'unconscious body ownership' as described by Experiment 1a, has a promoting effect on visual awareness. The time needed for the masked hand to break through continuous flash suppression was decreased when unconscious ownership was induced (t(29) = 3.17, p = 0.004).
Taken together, our results show that ownership can be induced for a hand that is not consciously perceived, which is probably driven by unconscious multisensory integration. These results emphasise the importance of subconscious processes in body ownership, and in doing so, might call for a re-evaluation of how body ownership is defined.

Disclosures: B. Van Der Hoort: None. **N. Radziun:** None. **H.H. Ehrsson:** None.

Poster

489. Multisensory Integration: Cross-Modal Processing in Humans I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 489.09/LL4

Topic: D.09. Multisensory Integration

Support: Swedish Research Council

Title: The supernumerary hand illusion revisited: Disambiguating ownership of one and two right rubber hands

Authors: *C. FAN[1], H. EHRSSON[2]
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Abstract: Can we experience that we have three arms? Some previous experiments have successfully adopted a modified version of the rubber hand illusion to elicit a supernumerary hand illusion, in which participants felt two rubber hands as their own hands. However, some other studies have provided conflicting results suggesting only one fake hand can be owned and incorporated into body representation. Thus, it is still unclear if we can truly experience ownership over extra limbs.

To address this issue, we studied the supernumerary hand illusion with a modified experimental design that allowed us to disambiguate ownership of one or two rubber hands. The participant's real right hand was hidden under a platform while two identical right rubber hands were placed adjacently above. The participant's real right hand was placed directly under the right rubber hand. After 2 minutes of stroking of the two rubber hands and real hand, participants answered a questionnaire (Experiment 1; N = 40, 14 males, mean±SD age: 27.9±7.29 years). The questionnaire included separate statements about ownership and referral of touch to each of the two rubber hands and to both hands simultaneously. We used a two-by-two factorial design where we applied synchronous strokes to both rubber hands (SS), synchronous strokes to one and asynchronous to the other (AS and SA) or asynchronous strokes to both fake hands (AA). In Experiment 2 (N = 24, 12 males, mean±SD age: 29.3±9.58 years), we applied a "syringe threat" to the right rubber hand after one-minute of strokes while recording participant's skin conductance response (SCR) as objective physiological evidence of ownership. Here we threatened the right rubber hand in the SS, SA and AA conditions, which allowed us to directly contrast dual versus single hand ownership.

Questionnaire results of Experiment 1 demonstrated that participants felt both referral of touch and ownership over both rubber hands in the critical SS condition when both fake hands were stroked synchronously with the real hand (S5: $\chi 2$ (3) = 43.629, $p < 0.001$; S6: $\chi 2$ (3) = 56.867, $p < 0.001$). SCR results of Experiment 2 confirmed the participants respond more intensely when threatening the right rubber hand in SS condition compared to the SA and AA conditions (SS > SA: t (23) = 3.009, p = 0.006; SS > AA: t (23) = 2.353, p = 0.028).

Taken together, these results demonstrate that the rubber hand illusion can be used to induce the true sense of ownership over supernumerary hands. These findings emphasize the dynamic flexibility of body representation and bring new perspectives into current engineering studies of supernumerary robotic limbs and advanced prostheses for amputees.

Disclosures: C. Fan: None. **H. Ehrsson:** None.

Poster

489. Multisensory Integration: Cross-Modal Processing in Humans I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 489.10/LL5

Topic: D.09. Multisensory Integration

Support: European Commission - MSCA fellowship to P.T.
James S. McDonnell Foundation
Torsten Söderbergs Stiftelse
StratNeuro
Swedish Research Council

Title: Fluidity of gender identity induced by illusory body sex change

Authors: *P. TACIKOWSKI, J. FUST, H. EHRSSON
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Abstract: Introduction: Gender identity is a subjective sense of being male, female, both, or neither. It remains unknown how stable or fluid gender identity is over time. Here, we induced a perceptual illusion of having the opposite-sex body to test the hypothesis that the perception of one's own masculine or feminine physical characteristics shapes gender identity dynamically.
Methods: In four behavioral studies, 205 healthy adults (102 females; age: 26±5) wore head-mounted displays and observed a stranger's body (male or female) from a first-person perspective. The stranger's body was continuously stroked with a ball attached to a stick and the experimenter applied synchronous touches on the corresponding parts of the participant's body. We expected that this visuotactile synchrony (sync) would induce a perceptual illusion that the stranger's body is one's own, whereas asynchrony (async) would break the illusion and serve as a near-perfect control. Thus our 2-by-2 within-subject design included the "body-sex-change" condition (sync-opposite-sex) and three control conditions (sync-same-sex, async-same-sex, async-opposite-sex). We measured the illusion psychometrically and objectively by recording skin-conductance stress responses when the stranger's body was physically threatened. Gender identity was measured with objective behavioral tests (Implicit Association Task) and self-report questionnaires. These measures were applied during each condition which allowed us to track changes in gender identity across different embodiment contexts.
Results: As expected, psychometric and skin-conductance data showed that the body-sex-change illusion was successfully induced in all our studies. With regard to the main research question, we found that participants who experienced a strong body-sex-change illusion balanced their implicit associations between the self and both genders (Study I: ρ_{64}=0.31; P=0.014) and shifted their subjective sense of masculinity/femininity toward the opposite gender (Study II: r_{33}=0.46; P=0.007). We also found that the illusion led to less stereotypical beliefs about oneself (Study

III: r_{44}=0.35; P=0.022) and reduced implicit gender-stereotypes (Study IV: ρ_{64}=0.46; P=0.008). Importantly, updating of gender identity was enhanced for participants who generally had a strong gender-bias, which suggests that an internal conflict between pre-existing attitudes and ongoing body perception underlies fluidity of gender identity.
Conclusions: These findings show that body perception dynamically shapes gender identity and that the sense of own gender is more fluid than commonly assumed.

Disclosures: P. Tacikowski: None. **J. Fust:** None. **H. Ehrsson:** None.

Poster

489. Multisensory Integration: Cross-Modal Processing in Humans I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 489.11/LL6

Topic: D.09. Multisensory Integration

Support: Swedish Research Council

Title: Investigating the multisensory mechanisms of full-body ownership using the illusion of owning an entire artificial body

Authors: *S. H. O'KANE[1], H. EHRSSON[2]
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Abstract: Introduction: The notion we each experience ownership for the single, entire body we call our own resonates fascination across diverse academic fields. In cognitive neuroscience, the use of the full-body ownership illusion has led to significant advancements in knowledge. However, how multisensory information across the body gives rise to a unified percept remains elusive. We investigated whether increasing the number of body parts involved in the illusion promotes enhanced perceived full-body ownership.
Methods: 48 healthy adults (28 males, mean age 26.9 ± 6.2) wore head-mounted displays providing a first-person perspective of a mannequin's body. Whilst observing tactile stimulation applied to the mannequin, temporally synchronous or asynchronous tactile stimulation was applied to their real bodies, involving 1, 2 or 3 body parts simultaneously (trunk; trunk and right arm; trunk, right arm and leg). We collected questionnaire, illusion onset (sec) and threat-evoked skin conductance (SCR) (μS) data and hypothesized that our measures would differentiate the synchronous from asynchronous conditions, but also potentially varying degrees of illusion intensity related to the number of body parts stimulated.
Results: As expected, illusion scores derived from the questionnaire were significantly increased for synchronous versus asynchronous stimulation ($Z = 5.460$, $p < .001$; $Z = 5.349$, $p < .001$; $Z = 5.423$, $p < .001$). However, post-hoc analyses revealed no significant differences depending on the number of sites receiving synchronous stimulation ($Z = 0.993$, $p = .320$; $Z = 2.012$, $p = .044$;

Z = 2.377, p = .017). No significant differences in illusion onset time (sec) were found ($\chi 2(2)$ = 0.424, p = .809), suggesting this aspect also remained stable. Interestingly, only items specific to illusory ownership of the mannequin's right arm and leg revealed significant differences across the synchronous manipulation. Highlighting the essential role of multisensory integration, ownership ratings for these parts were significantly higher during conditions in which they were stimulated than not (Z = -2.850, *p* = .004; Z = -3.500, *p* < .001; Z = -2.930, *p* = .003; Z = -3.283, *p* = .001). Finally, a significant difference in the magnitude of SCRs was identified for 1 body part (synchronous) versus 3 body parts (asynchronous) (Z = 2.322, *p* = .020), whilst there was no significant difference for 1 versus 3 body parts (both synchronous) (Z = -1.218, *p* = .223). **Conclusions**: These findings are consistent with the notion that full-body ownership is mediated by generalization from part-to-whole, a percept that is only subtly enhanced by converging multisensory input across multiple body segments.

Disclosures: S.H. O'Kane: None. **H. Ehrsson:** None.

Poster

489. Multisensory Integration: Cross-Modal Processing in Humans I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 489.12/LL7

Topic: D.09. Multisensory Integration

Support: David and Astrid Hagelén Foundation
Swedish Research Counsil
Söderbergs Stiftelse

Title: Incongruent visuo-tactile-vestibular stimulation leads to body disownership and feelings of depersonalisation and derealisation

Authors: *N. PREUSS, H. H. EHRSSON
Neurosci., Karolinska Institutet, Stockholm, Sweden

Abstract: Introduction: Vestibular sensations are often reported when individuals experience a loss of ownership such as during out-of-body illusions or dissociative experiences. The purpose of the present study was to investigate whether incongruent multisensory information results in a decreased perception of ownership over one's own body and, moreover, if this additionally results in feelings of depersonalization and derealization. A depersonalization experience concerns the feeling of 'the self being detached from the own body' whereas a derealization experience concerns the experiences of the world around us as being 'unreal'. **Methods:** Participants (N=30) saw their own body from a first-person perspective through a head-mounted display showing a live 3D-video stream during six different conditions. In these conditions they were exposed to direct current galvanic vestibular stimulation (DC-GVS), no stimulation or

sham stimulation, where the electrodes were attached to the neck and DC stimulation was applied. At the same time, touches were applied to their abdomen and upper legs using a wooden stick. These touches were either synchronous or temporally delayed for one second, i.e. asynchronous. Each block lasted for three minutes and afterwards they filled out a questionnaire concerning ownership ('I felt as if the body I saw was my body') and depersonalization and derealization experiences (Likert-scale 0-4). **Results:** As predicted, Wilcoxon signed-rank test and Bayesian t-tests showed that asynchronous visuo-tactile stimulation resulted in a decreased ownership rating ($p<0.009$, $BF>6$). Importantly, Bayesian mixed models revealed that both DC-GVS and asynchronous visuo-tactile stimulation increased depersonalization ratings (DC-GVS mean increase=0.2, SD=0.1, CI: 0-0.4; visuo-tactile asynchronous mean increase =0.2, SD =0.1, CI= 0-0.3). Moreover, the derealization ratings were affected by asynchronous visuo-tactile stimulation (visuo-tactile asynchronous mean increase=0.2, SD =0.1, CI= 0.1-0.4). **Discussion**: We conclude that weak sensations of depersonalization and derealization can be elicited in healthy participant through incongruent visual, tactile and vestibular signals in a full-body disownership paradigm. This finding is important because it provides a new mechanistic multisensory framework to investigate depersonalization and derealization in cognitive neuroscience and cognitive psychiatry.

Disclosures: N. Preuss: None. **H.H. Ehrsson:** None.

Poster

489. Multisensory Integration: Cross-Modal Processing in Humans I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 489.13/LL8

Topic: D.09. Multisensory Integration

Support: Yamagishi Student Project Support Program

Title: Effect of vestibular information on early visual processing: An EEG study

Authors: *T. UENO[1], K. MATSUSHITA[2], M. OGAWA[2], A. AOYAMA[2]
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Abstract: The vestibular system has a critical role in sensing body tilt, gravity direction, and acceleration input, and receives information from other sensory systems such as the visual system. Because of the technical difficulty in designing a neuroimaging experiment for testing the vestibular system in humans, however, little is known about the interaction between vestibular and visual information. Here, we tested the visual-vestibular interaction using EEG with two apparatuses: a virtual reality head-mounted display and an inversion table. Videos of falling scenes in either upward or downward direction were randomly displayed by the VR

device, while a participant's body tilt was alternately manipulated for every eight video plays in either an upright or inverted manner by the inversion table. Therefore, four combinational conditions were established with regard to the orientation of retinal images and the direction of gravity. Event-related potential analysis revealed that continuous attenuation of visual activity was observed from 100-200 ms after the start timing of falling in the inverted body condition as compared with the upright condition, irrespective of the visual falling direction. Moreover, Granger causality analysis showed feedback connection from the temporoparietal vestibular area to the visual area.These findings indicate that visual activity is suppressed by unusual vestibular information and that visual-vestibular interaction begins at a relatively early stage of visual processing.

Disclosures: K. Matsushita: None. **M. Ogawa:** None. **A. Aoyama:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 490.01/LL9

Topic: E.02. Cerebellum

Support: Evangelisches Studienwerk Villigst

Title: The calcium-gated chloride channel anoctamin 2 as a modulator of inhibitory transmission in the cerebellum

Authors: F. AUER, D. FLEISCHHAUER, L. SCHÜSSLER, L. SCHÜLE, F. MÖHRLEN, *S. FRINGS
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Abstract: Neuronal networks process incoming signals through excitatory and inhibitory synapses. Both methods of passing information can be modulated independently, which is particularly important for learning processes and memory formation. Severe problems may occur when these mechanisms of plasticity are impaired. We observed such a dysfunction in a mouse line lacking Anoctamin 2 (ANO2), a calcium-gated channel that conducts chloride and bicarbonate. These mice show motor coordination deficits as well as impaired motor learning, indicating an important role of ANO2 in the cerebellum. Previous studies have provided initial evidence that spontaneous inhibitory postsynaptic currents (IPSCs) are transiently reduced after climbing fiber activity. This form of short-term synaptic plasticity, which has been named *depolarization-induced depression of inhibition* (DDI), is supposed to be dependent on a diminished chloride gradient at the GABAergic synapses on Purkinje cell dendrites. Our initial data suggested that DDI was decreased in $ANO2^{-/-}$ mice but the precise role of ANO2 could not be established. The present exploratory study aims to further elucidate this mechanism of

synaptic plasticity.
We performed whole-cell patch clamp recordings on Purkinje cells in acute cerebellar slices of adult male mice, both wildtype (C57Bl/6) and ANO2$^{-/-}$. We stimulated inhibitory interneurons to monitor evoked IPSCs in Purkinje cells. Then a train of depolarizing pulses was given via the patch pipette to mimic a climbing-fiber signal. This way, DDI can be induced through opening of dendritic voltage-gated calcium channels without climbing fiber activity. During the recording, the Purkinje cells are loaded with the fluorescent pH-sensitive dye HPTS to measure IPSCs and changes in pH simultaneously. In addition, we investigated the localization of ANO2 by immunohistochemistry and by single-cell PCR. Moreover, we examined density and arrangement of synapses by climbing fibers and interneurons on the dendritic arbor of Purkinje cells.
First results indicate that DDI is indeed reduced in ANO2$^{-/-}$ mice. This supports the assumption that ANO2 is expressed in Purkinje cells and is necessary for this type of synaptic plasticity, which could explain the symptoms of ataxia in ANO2$^{-/-}$ mice. The changes in pH during the measurements seem to be similar for wildtype and ANO2$^{-/-}$ mice, suggesting that ANO2 is not a major player in bicarbonate homeostasis. Furthermore, immunohistochemical stainings of ANO2 also indicate the localization of ANO2 in Purkinje cell dendrites. The data suggest that ANO2 is an important modulator of inhibitory transmission in the cerebellum.

Disclosures: F. Auer: None. **D. Fleischhauer:** None. **L. Schüssler:** None. **L. Schüle:** None. **F. Möhrlen:** None. **S. Frings:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 490.02/LL10

Topic: E.02. Cerebellum

Title: The interaction of Purkinje cell firing rate-dependent phase response curves and cerebellar network oscillations

Authors: *Y. ZANG, E. DE SCHUTTER
Computat. Neurosci. Unit, Okinawa Inst. of Sci. and Technol., Okinawa, Japan

Abstract: Phase response curves (PRCs), describing the response of spiking neurons to brief external stimuli, have been widely used to study biological oscillations. The shapes of PRCs are variable between different neurons and even differ for the same cell under different states. In mammalian neurons, Purkinje cells are unique because of their phase-independent PRCs at low firing rates. Positive peaks of Purkinje cell PRCs get larger and broader with increasing firing rates. However, none of the existing models or theories can reproduce this phenomenon, leaving the underlying mechanisms undetermined.

We have developed a new morphologically detailed Purkinje cell model, which is constrained by a plethora of available experimental data (https://doi.org/10.1101/284026). Our new model reproduces the transition from phase-independent integrator to a phase-dependent mode by increasing the simple spike firing rate. This model highlights the critical regulatory role of dendrites in Purkinje cell somatic firing properties and PRC. In our model without dendrites, the PRC peaks get smaller and narrower at higher firing rates.
We further test the role of the firing rate-dependent PRC in the synchronization of Purkinje cells. Purkinje-to-Purkinje inhibitory connections have been well documented in recent years. We have built a sparsely connected network including 200 Purkinje cells with 0.2 connection probability. In the network model, we find that the network can exhibit "spike-to-spike synchrony" under a *in vitro* condition at high cellular firing rates but not at low firing rates. With larger background synaptic input noise, the coefficients of variation (CVs) of interspike intervals increase, and the network is gradually dominated by high-frequency oscillations (~ 160 Hz). In agreement with previous findings (de Solages *et al*. 2008), the oscillation power can be reduced by larger noise, but the oscillation frequency is relatively insensitive to the noise level. At higher cellular firing rates, the network oscillation power increases when the CVs of interspike intervals are the same. This increased oscillation power is due to the larger and broader PRCs at high cellular firing rates. Given the fact that cerebellar nuclear neurons preferentially relay the spike timing of synchronized Purkinje cells, the firing rate-dependent PRC may be a critical property of the cerebellum to organize its output.

Disclosures: Y. Zang: None. **E. De Schutter:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 490.03/LL11

Topic: E.02. Cerebellum

Support: NIH Grant NS083127 (MJR)
NIH Grant NS083894 (JC)

Title: The role of local inhibitory circuits in expression of cerebellar-dependent motor memories

Authors: *M. J. ROWAN, J. CHRISTIE, A. BONNAN
Max Planck Florida Inst., Jupiter, FL

Abstract: The cerebellum plays a key role in motor learning using multiple sites of plasticity within its circuitry. A major component of the cerebellar circuit are molecular layer interneurons (MLIs). MLIs provide feedforward inhibition onto Purkinje Cells (PCs) thereby controlling the output of the cerebellar cortex. Thus, plasticity within this inhibitory circuitry could play a major

role in the expression of motor memories. In acute cerebellar slices, we observed potentiation of MLI feedforward inhibition onto PCs following conjunctive stimulation of parallel fibers and climbing fibers. This complemented LTD at parallel fiber-PC synapses. Thus convergent forms of plasticity work in unison to weaken the ability of parallel fibers to excite PCs. To assess the role of MLIs in the expression of learning, we used fiberphotometry to directly measure population-level calcium activity of MLIs *in vivo* during vestibulo-ocular reflex (VOR). The VOR is a compensatory eye movement in response to head rotation that is subject to re-calibration through cerebellar dependent plasticity. MLI activity was measured both before and after VOR learning. In naïve animals, MLIs displayed a phasic response to vestibular stimuli. Interestingly, the phase of the MLI response was shifted following gain increase learning indicating a dramatic change in the organization of their activity following adaptation. In a second set of experiments, we manipulated MLI activity using optogenetics to inhibit MLIs before and after VOR gain-increase training. Although inhibiting MLIs had no effect on baseline VOR performance, we found that optogenetic suppression of MLI activity after learning resulted in near-elimination of the learned increase in VOR gain. Together our results suggest that MLIs are an important site of memory storage necessary for rapid expression of motor learning.

Disclosures: M.J. Rowan: None. **J. Christie:** None. **A. Bonnan:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 490.04/LL12

Topic: E.02. Cerebellum

Title: MLI disinhibition relieves gating of climbing fiber-mediated learning in the cerebellum

Authors: *K. ZHANG[1], G. G. GROSS[2], D. B. ARNOLD[2], J. M. CHRISTIE[1]
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Abstract: The cerebellum has emerged as a key model system to study motor learning**.** However, the mechanisms underlying the regulation and encoding of adaptive movements in its cortex are poorly understood. Our previous work indicates that inhibition from molecular layer interneurons (MLIs) is sufficient to override the ability of climbing fibers (CFs) to instruct learning during adaptation of the vestibular-ocular reflex (VOR). However, to assess for the necessity of MLIs in gating learning, we used a genetically encoded toolkit to manipulate the activity of floccular MLIs during the performance of the VOR. Suppressing MLI activity with halorhodopsin during a normally non-adapting visual-vestibular stimulus produced an increase in the VOR. This adapted response resembled the learned change in the VOR induced by CFs during retinal slip errors. This result suggests that MLI inhibition prevents CFs from instructing learning when adaptation is unnecessary or inappropriate. It also implies that inhibition from

MLIs must be suppressed for CF-mediated learning to occur. In support of this hypothesis, we found that mice with ablated inhibition between MLIs were unable to adapt their VOR during opposite direction visual-vestibular pairing. However, learning could be rescued in these mice by optogenetic suppression of MLI activity during visual-vestibular pairing. Thus, disinhibition of CF-evoked Purkinje cell signaling appears to be accomplished by an MLI-MLI microcircuit. These findings point to a decisive role for MLIs in regulating how and when learning is implemented in the cerebellum.

Disclosures: K. Zhang: None. **G.G. Gross:** None. **D.B. Arnold:** None. **J.M. Christie:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

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Program #/Poster #: 490.05/LL13

Topic: E.02. Cerebellum

Support: MEXT KAKENHI Grant Number 2643009
MEXT KAKENHI Grant Number 17K07049
MEXT Hetero-Manycore Project

Title: Development of large-scale artificial cerebellum and its petaflops simulation on PEZY-SC2 processor

Authors: *W. FURUSHO, T. YAMAZAKI
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Abstract: The cerebellum is a repeated structure of a corticonuclear microcomplex, which is considered as a functional unit of the cerebellum. Because the structure of the cerebellum is known clearly, many numerical cerebellar models have been built on workstations, accelerators such like graphics processing units (GPUs) and supercomputers. In this study, we built a numerical model of the cerebellum on a supercomputer Gyoukou developed by PEZY Computing K.K. and ExaScaler Inc. Gyoukou is composed of 10,000 PEZY-SC2 processors. A PEZY-SC2 processor contains 2,048 processing elements and hierarchical cache memory We implemented a spiking network model of a corticonuclear microcomplex composed of 1 million neurons on a PEZY-SC2 processor, where neurons were modeled as leaky integrate-and-fire units. Using 7,920 out of 10,000 PEZY-SC2 processors on Gyoukou, we built a network model of the cerebellum composed of 8 billion neurons. As a cerebellar learning mechanism, we implemented synaptic plasticity at parallel fiber-Purkinje cell synapses called long-term depression and long-term potentiation on this model. We optimized our program by using local memories on processing elements and hierarchical cache memory to achieve realtime simulation. As a benchmark test, we carried out a computer simulation of a typical form of cerebellar

learning on eye movement reflex called gain adaptation of optokinetic response (OKR). We confirmed that our model could perform the simulation in realtime. In fact, a 6-sec simulation completed within 2.2 sec of wall clock time. Next, we measured performance of our program. We achieved 1.85 petaflops in single precision floating points in the OKR simulation, indicating 2.9 percent of the effective performance. Finally, we examined a weak scaling property in computational time. We confirmed that the execution time was almost constant while increasing the number of used prosessors and the number of neurons simultaneously. This weak-scaling property allows us to build a human-scale artificial cerebellum with online learning capability if we could use more processors. In summary, our artificial cerebellum will provide a means to gain better understanding of what the cerebellum computes.

Disclosures: W. Furusho: None. **T. Yamazaki:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 490.06/LL14

Topic: E.02. Cerebellum

Support: Wellcome Trust
EMBO

Title: Dynamic coordination of climbing fiber input to Purkinje cell populations during goal-directed action

Authors: *D. KOSTADINOV, M. BEAU, M. B. POZO, M. HAUSSER
Wolfson Inst. for Biomed. Res., Univ. Col. London, London, United Kingdom

Abstract: The activity of cerebellar Purkinje cells (PCs) is important for motor execution and learning. Activation and suppression of PCs can inhibit and drive movements, respectively, and coactivation of climbing fiber and parallel fiber inputs to PCs drives parallel fiber synaptic plasticity that is a major locus of cerebellar learning. In this framework, climbing fibers, which trigger complex spikes (CSs) in PCs, carry error signals and drive trial-by-trial adaptation, but do not modify behavior in real time. However, in some behavioral contexts, complex spiking can precede movement and cannot therefore solely encode errors. These complex spikes may serve as a timing signal for movement initiation. Our goal is to reconcile how predictive and reactive CS signals are represented in PC populations during motor execution, learning, and predictive sensory processing.
To address this question, we used 2-photon microscopy to image CS-evoked dendritic calcium transients across 200-300 PCs expressing GCaMP6f while mice performed a virtual-reality based sensorimotor integration task. Mice were head-fixed and trained to use a steering wheel with

their forepaws to translate a virtual object from eccentric visual positions to the midline to obtain a delayed reward.
PC dendrites in the simplex lobule and adjacent vermis exhibited diverse and spatially clustered CS signals in our task. PCs fired complex spikes just prior to movement onset, during the delay between the end of movement and reward, and in response to the audible click associated with reward. Vermis PCs showed prominent motor-related signals, the amplitude and timing of which were predictive of trial outcome. Many were also activated by the reward click. In contrast, simplex PCs exhibited less prominent motor signals, while responses during the delay period and at reward delivery were more reliably observed. Co-activation of adjacent microzones was dynamic and task-related. In both simplex and vermis, reward click responses were contextually modulated: random rewards evoked large responses, task-related rewards evoked moderate responses, and tone-cued rewards evoked negligible responses. However, omissions of expected reward evoked well-timed error responses in simplex PCs but not vermis PCs.
Our results illustrate regional differences in predictive and reactive CS signals: medial cerebellar regions preferentially signal movement kinematics and more lateral regions preferentially signal learned associations and errors. These findings help resolve two opposing views of the role of climbing fiber input for cerebellar function.

Disclosures: D. Kostadinov: None. **M. Beau:** None. **M.B. Pozo:** None. **M. Hausser:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 490.07/MM1

Topic: E.02. Cerebellum

Support: PAPIIT UNAM 206616
CONACYT grant 220224
Severo Ochoa SEV-2015-0522

Title: Response to hypoxic preconditioning of glial cells from the roof of the fourth ventricle

Authors: *M. BECERRA GONZÁLEZ[1], E. GUALDA[2], P. LOZA-ALVAREZ[2], A. MARTÍNEZ-TORRES[1]
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Abstract: Recent evidence shows that the cerebellar surface that contacts the ventricular cavity possesses a peculiar diversity of cellular populations, which contrasts with the idea that the organization of cerebellum is highly stereotyped. This population includes oligodendrocytes,

glial and neuronal lineages, and probably progenitor cells. On the surface of the lobe I, a novel structure was found and named the Ventromedial cord (VMC). It is composed by GFAP+ and nestin+ glial cells. Cells positive for these markers and in contact with the cerebrospinal fluid are known to respond to hypoxic preconditioning (HPC) through proliferation and differentiation, therefore we explored whether the VMC maintains this ability.
Analysis of the VMC was performed using adult (P25) transgenic mice (n = 3-6), expressing the green fluorescent protein under the GFAP promoter (GFAP-GFP). Clarified brains analyzed by light sheet microscopy revealed a reduction in the number of cells of different lobes of cerebellum. By day 4 after HPC, GFP expression decreased in the VMC. Cryoprotected coronal sections showed displacement of Bergmann glia (BG) somas, and a gradual retraction of their processes; furthermore, Golgi staining disclosed a decrease in the area of the soma of BG and a rise in the length of protrusions. Western blots showed a decrease in expression of glial identity markers and an increase in the markers for mature neurons NeuN, microglia Iba1 and stem cells nestin. Immunofluorescence for Iba1 indicated that HPC induces morphological changes in the soma of microglial cells, which is a feature of these cells in the "activated" state. A slight incorporation of BrdU was found in the roof of the fourth ventricle and a screen of behavioral tests for motor coordination showed a tendency to lower performance.
We conclude the VMC exerts a homeostatic response after HPC that is evidenced by changes in the expression of glial markers and morphology.

Disclosures: M. Becerra González: None. **E. Gualda:** None. **P. Loza-Alvarez:** None. **A. Martínez-Torres:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

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Program #/Poster #: 490.08/MM2

Topic: E.02. Cerebellum

Support: National Institutes of Health Grant NS083894 (JMC)

Title: Mechanisms of Purkinje cell-dependent instructive signaling in the cerebellum

Authors: *A. BONNAN[1], M. J. M. ROWAN[1], C. A. BAKER[2], M. BOLTON[1], J. M. CHRISTIE[3]
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Abstract: The cerebellum is known to play a crucial role in motor learning. Purkinje cells (PC) give rise to the sole output of the cerebellar cortex and are therefore pivotal in this process. PCs can fire two different types of spikes: simple spikes (SS) in response to parallel fiber (PF)

stimulation and complex spikes (CS) as a result of climbing fiber input. The CS is a multicomponent response that includes a burst of sodium spikes at the soma and a dendrite-wide Ca^{2+} transient. A classic theory of cerebellar function postulates that CFs carry instructive signals to PCs that guide learning. However, recent findings indicate that learning may occur independent of CF activity suggesting the existence of other candidate instructive signals. To study the mechanistic basis of instructive signaling, we used the vestibulo-ocular reflex (VOR), a compensatory eye movement in response to head motion that is subject to re-calibration through cerebellar-dependent plasticity. We used optogenetics to selectively manipulate PC activity during vestibular stimulation and probe for the consequences of this activity by examining the gain of the VOR. Using subcellular targeting motifs to limit expression of channelrhodopsin to the PC soma and different intensities of stimulation, we were able to evoke activity with large, small or no dendritic Ca^{2+} influx during vestibular stimulation. We found that PC activity associated with dendritic Ca^{2+} was sufficient to induce a transient memory in the VOR and that the direction of this memory depended on the amplitude of the evoked Ca^{2+} signal. However learning did not occur when Purkinje cells were activated without a dendritic Ca^{2+} transient. Our results suggest that Ca^{2+} influx in PC dendrites is necessary for learning and determines the direction of learning.

Disclosures: A. Bonnan: None. **M.J.M. Rowan:** None. **C.A. Baker:** None. **M. Bolton:** None. **J.M. Christie:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 490.09/MM3

Topic: E.02. Cerebellum

Support: Simons Collaboration on the Global Brain 543031
UC Davis Ophthalmology Research to Prevent Blindness
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Title: Systems consolidation without replay? Learning rules and circuit architectures for consolidation in cerebellar learning

Authors: *B. J. BHASIN[1], M. S. GOLDMAN[2], J. L. RAYMOND[3]
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Abstract: A common feature of learning and memory systems is that the neural circuitry required for the expression of long-term memory is distinct from that required for the expression of memory soon after acquisition. Whereas this transformation has been clearly demonstrated at

the level of phenomenology—for example, from hippocampus-dependent to hippocampus-independent storage of declarative memories—the mechanism by which changes supporting consolidation are orchestrated across synaptic sites is not well understood.
We explored this problem in a well-characterized system: the gaze-stabilizing cerebellar and brainstem circuitry underlying the vestibulo-ocular reflex (VOR). When the head rotates in space, the eyes reflexively counter-rotate so that image motion on the retinas is minimized. Experience in a virtual environment where the visual feedback is manipulated to suggest that head movements are eliciting erroneously large or small eye movement responses induces an adaptive adjustment of the amplitude of the VOR. Initially, the expression of learning depends on the cerebellar cortex, but over time becomes cerebellum-independent, presumably reflecting a transfer of the synaptic changes supporting the memory to a site downstream.
We constructed a circuit model of VOR learning that includes empirically motivated plasticity rules at synaptic sites in the cerebellar cortex and brainstem. In the cerebellar cortex, we used an error-driven rule consistent with the Marr-Albus-Ito theory. In the brainstem, the hypothesized target of consolidation, we used two candidate learning rules based on previous studies: a heterosynaptic rule, and a Hebbian rule with a sliding threshold. During simulated VOR training, our model with either brainstem rule was able to consolidate learned increases in eye movement amplitude, *without* replay of training signals in the post-training period. In both cases, the dynamics of the brainstem synapse integrate changes in the cortical synapse, and therefore require fine-tuning for stability. Our results suggest that the storage of an analog connection weight for long-term memory is analogous to the maintenance of persistent analog activity in working memory networks; hence, continuous attractor dynamics may also be important for memory consolidation.

Disclosures: B.J. Bhasin: None. **M.S. Goldman:** None. **J.L. Raymond:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 490.10/MM4

Topic: E.02. Cerebellum

Support: ANR-14-CE17-0006
ANR-11-LABX-0015

Title: Supralinear Ca^{2+} signals in cerebellar Purkinje neurons associated with concomitant parallel fibre and climbing fibre inputs: mGluR1-dependent and mGluR1-independent distinct components

Authors: *K. AIT OUARES[1], M. CANEPARI[2]
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Abstract: In cerebellar Purkinje neurons (PNs), the concomitant activation of parallel fibre (PF) synapses and of the climbing (CF) input produce a Ca^{2+} signal larger than the linear summation of the signals associated with the PFs and the CF (supralinear Ca^{2+} signal). This phenomenon, strictly dependent on the delay between the PF and the CF inputs, is associated with short-term and long-term PF synaptic plasticity. Using ultrafast membrane potential (V_m) and Ca^{2+} imaging techniques, we explored the supralinear Ca^{2+} signals at different delays between a train of five local PF-EPSPs and a CF-EPSP. These techniques included the use of Ca^{2+} indicators of different affinities and the pharmacological inhibition of specific molecular targets. We found that when the CF-EPSP occurs with ~10 ms from the end of the PF train, the supralinear Ca^{2+} signal is independent of type-1 metabotropic glutamate receptors (mGluR1) and is due to two mechanisms: the increased Ca^{2+} influx through P/Q-type Ca^{2+} channels enabled by PF-depolarisation inactivating A-type K^+ channels; and a transient saturation of endogenous Ca^{2+} buffers amplifying free Ca^{2+} concentration. At longer delays (~100 ms), the supralinear Ca^{2+} signal is mGluR1-dependent and correlated with an increase in mGluR1-dependent Ca^{2+} influx via cation channels. In this case, the supralinear Ca^{2+} signal is not associated with larger depolarisation since the additional V_m transient produced by the cation current is compensated by a slow dendritic hyperpolarisation preventing activation of P/Q-type Ca^{2+} channels. These results shed new light on one of the most important phenomenon in cerebellar physiology.

Disclosures: K. Ait Ouares: None. **M. Canepari:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

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Program #/Poster #: 490.11/MM5

Topic: E.02. Cerebellum

Support: NS083894

Title: Purkinje cell dendrites encode graded information dependent on the level of climbing fiber activity

Authors: *J. M. CHRISTIE, S. B. AMAT, M. A. GAFFIELD
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Abstract: Climbing fibers excite Purkinje cells producing dendritic Ca^{2+} signals useful for instructing plasticity and learning. Experimental evidence indicates that climbing fiber-evoked

responses in Purkinje cells encode a range of behaviorally relevant information. The mechanisms that contribute to graded responses in Purkinje cells aren't currently known. Excitation from parallel fibers and inhibition from molecular layer interneurons have the potential to modulate climbing fiber-mediated Ca^{2+} signaling in Purkinje cells contributing to the dynamics of the integrated, dendritic response. It also remains possible that the level of presynaptic climbing fiber activity itself conveys information pertinent for determining the amplitude of the postsynaptic Ca^{2+} signal. We sought to examine these possibilities by directly monitoring the activity of Purkinje cells, climbing fibers, and molecular layer interneurons in cerebellar Crus I of awake mice to a range of unexpected sensory stimuli. Graded Ca^{2+} signals were produced in Purkinje cell dendrites; the amplitude of the response changing with the type and intensity of the stimulus. Interestingly, the presynaptic activity level of climbing fibers was altered in a likewise manner. In contrast, molecular layer interneurons responded opposite to what would be expected for these neurons if suppressive inhibition was directly responsible for determining Ca^{2+} signal amplitude (i.e., MLI activity increased with the size of the evoked response in Purkinje cells). These results demonstrate that the amplitude of climbing fiber-evoked Ca^{2+} signals in Purkinje cell dendrites is a largely determined by the firing level of climbing fibers.

Disclosures: J.M. Christie: None. **S.B. Amat:** None. **M.A. Gaffield:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

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Program #/Poster #: 490.12/MM6

Topic: E.02. Cerebellum

Support: NINDS NS088567

Title: Optogenetic stimulation of amygdala central nucleus specific to conditioned stimulus is sufficient to modulate cerebellar learning

Authors: *S. J. FARLEY[1,2], J. H. FREEMAN[2,1]
[1]Iowa Neurosci. Inst., Iowa City, IA; [2]Psychological and Brain Sci., The Univ. of Iowa, Iowa City, IA

Abstract: Pharmacological inactivation of the amygdala central nucleus (CeA) in rats impairs delay eyeblink conditioning (dEBC), a well-known cerebellum-dependent task (Farley 2016, 2018). In order to better understand amygdala modulation of cerebellar learning, we used gain-of-function and loss-of-function optogenetic techniques in the CeA with adult rats during dEBC. For gain-of-function, channelrhodopsin (AAV-hSyn-hChR2(H134R)-EYFP) in the CeA was stimulated with 473nm (blue) light. Archaerhodopsin (AAV-hSyn-eArch3.0-EYFP) in the CeA was used as the loss-of-function opsin, stimulated by 561nm (green) light. Control animals

received AAV-hSyn-EYFP to their CeA. After recovering from optical implant surgery, rats commenced training in five, 100-trial sessions of dEBC. Trials consisted of tone (CS) - shock (unconditioned stimulus [US]) pairings. Blue light was illuminated at 20 Hz (5 ms pulses) for the ChR2 animals, and green light was constant for Arch animals. In all cases, laser stimulation was limited to the duration of the conditioned stimulus (CS) period only (400 ms). Animals trained with Arch stimulation showed impaired learning relative to controls, whereas animals trained with ChR2 stimulation showed a slightly enhanced learning curve. The rate of conditioned responses for ChR2 animals was only slightly enhanced compared to controls. However, CR onset latency was significantly lower during acquisition with ChR2 stimulation compared to controls and Arch animals. CR amplitude and CR area were also significantly increased for the ChR2 animals. Similar to our previous findings (Farley 2016, 2018), no metrics pertaining to the unconditioned response (peak, latency, area, etc) revealed group differences or interactions across opsin groups. This finding suggests that amygdala modulation during cerebellar associative learning may not be occurring through the US pathway. Since all of the statistically significant findings were across CR characteristics, it may be that perturbations to the CeA effect the sensory input of the CS to the cerebellum (Farley 2016, 2018; Pochiro 2015; Siegel 2015; Taub 2010). Thus, the CeA may have a modulatory role for gating sensory information in pre-cerebellar areas, e.g. the pontine nucleus.

Disclosures: S.J. Farley: None. **J.H. Freeman:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

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Program #/Poster #: 490.13/MM7

Topic: E.02. Cerebellum

Support: NIH Grant F31NS103425

Title: Cerebellar climbing fibers signal reward expectation in both voluntary and classically conditioned behaviors

Authors: *W. E. HEFFLEY, Z. XU, C. HULL
Duke Univ., Durham, NC

Abstract: Classical models of cerebellar learning posit that climbing fibers operate according to a supervised learning rule to instruct changes in motor output by signaling the occurrence of movement errors. However, recent evidence has challenged this view by demonstrating that climbing fiber-driven complex spiking can signal a different type of error consistent with a temporal difference (TD) reinforcement learning rule after the acquisition of learning in an aversive conditioning paradigm. To test whether sensory prediction error provides a

generalizable model to explain the behavior of climbing fibers in other regimes and across other cerebellar regions, we have measured complex spiking in head-fixed mice during two reward-driven behavioral paradigms. First, we trained mice to associate a visual cue with an upcoming reward and measured complex spiking both at the population level and within individual Purkinje cell dendrites before and after learning. These data suggest that individual climbing fibers can signal distinct task features before and after learning in a manner that is consistent with reward expectation. However, we do not find evidence that climbing fibers can signal negative prediction error in this task, and thus our data are not strictly consistent with a TD learning rule. We also trained mice on a second task that requires a properly timed forelimb movement to receive reward. Population and single dendrite Purkinje cell calcium imaging revealed similar climbing fiber driven responses as observed in the classical conditioning paradigm. Specifically, climbing fiber activity scaled with reward expectation. Again, however, we did not observe activity consistent with negative reward prediction errors as required by TD reinforcement learning models. Instead, we observed elevated complex spiking when reward expectation was high but no reward was delivered, consistent with climbing fibers signaling an unsigned prediction error related to violated expectation. Results from these two behavioral paradigms thus suggest that climbing fibers can both report and evaluate predicted task outcomes, consistent with the hypothesis that the cerebellum operates according to a forward model. However, these results also suggest that such predictive instructional signals are not driven exclusively by motor errors.

Disclosures: W.E. Heffley: None. **Z. Xu:** None. **C. Hull:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 490.14/MM8

Topic: E.02. Cerebellum

Title: Sensory and motor representations in the inferior olive

Authors: *D. MARKOV[1], R. FELIX[2], M. ORGER[2], R. PORTUGUES[1]
[1]Max Planck Inst. of Neurobio., Martinsried, Germany; [2]Champalimaud Ctr. for the Unknown, Lisbon, Portugal

Abstract: The olivo-cerebellar system plays a pivotal role in sensory-motor control and coordination in vertebrates. According to the classical theory of cerebellar cortex, the inferior olive (IO) provides Purkinje cells with error information which drives motor learning in the cerebellum. Even though this process has been extensively studied over the last five decades, it remains unclear whether the nature of IO signals is more sensory, motor or both. Therefore, our aim in this study is to characterize sensory and motor representations in the IO and investigate

their potential interactions and spatial organization. In our experiments, we presented a set of different sensory stimuli (monocular and binocular translational and rotational motion) to larval zebrafish, while simultaneously tracking their eye and tail movements and recording calcium activity in genetically identified IO neurons with a 2-photon microscope. We found direction-selective sensory responses that formed a spatially-organized functional map. Interestingly, directional tuning properties of the IO neurons were predictive of their morphological characteristics, obtained with single-cell labeling, with different functional types projecting to distinct regions of the cerebellum. To isolate sensory-related responses from motor-related activity and their interactions we employed a virtual reality behavioral assay. Although we found few purely motor representations, a subpopulation of the IO neurons modulated their response depending on behavioral output and its visual feedback. These data add evidence that IO signals provide Purkinje cells with a combination of sensory and motor related information.
*DM and RF contributed equally to this work and will both present the poster.

Disclosures: D. Markov: None. **R. Felix:** None. **M. Orger:** None. **R. Portugues:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

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Topic: E.02. Cerebellum

Support: Simons Collaboration on the Global Brain (SCGB)
NIH R01 NS104926
UC Davis Ophthalmology Research to Prevent Blindness grant

Title: An adaptive control theory for cerebellar mediated tuning of the oculomotor neural integrator

Authors: *A. ALEMI[1], E. R. F. AKSAY[2], M. S. GOLDMAN[3]
[1]Ctr. for Neurosci., Univ. of California, Davis, Davis, CA; [2]Weill Cornell Med. College, Cornell Univ., New York, NY; [3]Ctr. for Neurosci., Univ. of California Davis, Davis, CA

Abstract: Neural systems need to adapt and tune their dynamics in the face of changes in the environment. For tuning of the dynamics of motor outputs, the cerebellum is thought to be a key locus of adaptive plasticity. Here, we formulate this idea in the language of adaptive control theory. We focus on a specific cerebellar mediated motor control function: the maintenance of stable eye position by the oculomotor neural integrator brain region. This circuit is responsible for accurately holding the eyes at a given position by temporally integrating transient eye velocity input commands and keeping the resulting eye position commands in short-term memory in the format of persistent activity. Experimental evidence (Major et al 2004) suggests

that the cerebellum is necessary for the tuning of the oculomotor integrator; however, a general theory for how the oculomotor system can use biologically plausible synaptic plasticity rules to stably tune and consolidate this tuning is missing.
We construct a circuit model in which the oculomotor neural integrator is recurrently connected to the cerebellum. Retinal slip error signals are separately conveyed via the climbing fibers to the cerebellar Purkinje cells. We consider two potential sites for synaptic plasticity: one site is at the parallel fiber to Purkinje cell synapses and is guided by the retinal slip error; the other site is at the neural integrator recurrent connections and is guided by the Purkinje cell output. We find a set of local, correlation-based, synaptic plasticity rules such that a cost (Lyapunov) function consisting of squared deviations from optimal tuning is non-increasing. Our results demonstrate that the system gets tuned as long as the plasticity within the cerebellum occurs faster than the plasticity at the neural integrator recurrent connections. This suggests a justification from first principles for the common assumption that the cerebellum performs fast learning that is consolidated more slowly by cerebellar target circuits. This work may provide a general framework for understanding cerebellar mediated adaptation of motor commands.

Disclosures: A. Alemi: None. **E.R.F. Aksay:** None. **M.S. Goldman:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 490.16/MM10

Topic: E.02. Cerebellum

Support: University of Otago, Division of Health Sciences Summer Research Scholarship

Title: Short duration voluntary exercise does not alter cerebellar morphology or motor performance in a mouse model of human spinocerebellar ataxia type 1

Authors: *E. DEENEY, R. EMPSON
Physiol., Univ. of Otago, Dunedin, New Zealand

Abstract: Individuals that suffer from spinocerebellar ataxia type 1 (SCA1) exhibit motor coordination deficits that progressively worsen and to date there is no effective treatment for SCA1. The climbing fibre-Purkinje neuron (CF-PN) synapse is a critical cerebellar synapse that shows abnormalities in both human SCA1 patients and in a mouse model of SCA1, and could be a site for therapeutic intervention. Exercise increases longevity in SCA1 (154Q) mice and has mixed benefits in human ataxia patients, but the beneficial effects of exercise for PN morphology and motor performance are not known. Here, we tested the hypothesis that a short period of voluntary exercise rescues PN morphology and motor performance in SCA1 mice.
Twelve-week-old ataxic SCA1 and non-ataxic wild-type (WT) mice were sub-divided into

exercising (E) and non-exercising (NE) groups for three weeks. Mice were individually housed in smooth-walled cages to encourage voluntary wheel running. Thereafter, we examined their fore-limb and hind-limb base-of-support (Catwalk, Noldus). After completion of testing, we prepared sagittal cerebellar sections (30 μm) for fluorescence immunohistochemistry and confocal microscopy using calbindin (Cb) to identify PNs and measure molecular layer height (MLH) within folia III, VI, VIII and X of the cerebellar cortex.
SCA1 NE mice exhibited PN dendritic atrophy throughout all folia compared to WT NE mice and this was not altered in SCA1 or WT E mice (interaction $P<0.05$, column $P<0.001$, two-way ANOVA, n = 6 per group, for both measurements). Gait analysis revealed a significant difference between fore-limb and hind-limb base-of-support between WT and SCA1 mice ($P<0.01$, two-way ANOVA, WT: n = 6 and SCA1: n = 5), similarly this was not influenced by exercise ($P>0.05$, two-way ANOVA, SCA1 NE: n = 7 and SCA1 E: n = 5).
These findings indicate that a short period of voluntary exercise is insufficient to alleviate symptoms in SCA1 mice. Instead, forced exercise, or motor learning activities of a more challenging nature, may be more beneficial for treating SCA1.

Disclosures: E. Deeney: None. **R. Empson:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 490.17/MM11

Topic: E.02. Cerebellum

Support: MEXT KAKENHI Grant Number 17H06310

Title: Purkinje cells in a cerebellar neural network model acquire climbing fiber driven activity modulation for accurate movements

Authors: *H. YAMAURA, T. YAMAZAKI
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Abstract: The cerebellum plays an important role in accurate movements. Purkinje cells that are the only output cells of the cerebellar cortex project to deep cerebellar nucleus cells and inhibit them. Burst activity of the deep cerebellar nucleus cells is related to movements. Previous studies demonstrated that suppression of Purkinje cells activity can activate deep cerebellar nucleus cells and cause limb movements. However, plasticity mechanism of Purkinje cells activity modulation and effect on motor control have not been fully elucidated. In order to understand these mechanism, we built a neural network model of the cerebellum. First, we investigated how modulation of Purkinje cells activity is acquired. Purkinje cells receive input from parallel fibers (granule cell axons) and climbing fibers. Long term plasticity of Purkinje cells occurs by

correlated the parallel fibers activity with the climbing fibers activity. By conducting computer simulations, we demonstrated that the cerebellar model can acquire pauses in Purkinje cell activity depending on the climbing fiber inputs. Next, we investigated how do the modulation in Purkinje cell activity contribute to motor control. In experimental study, lever-pull task in mouse is used. In the task, mouse has to pull and hold the lever. We consider that motor commands to pull and hold are needed in order to execute the task accurately. The experimental study demonstrated that Purkinje cells receive climbing fiber inputs at various periods during the task. We conducted computer simulations based on the experimental data. We demonstrated that the Purkinje cells in the neural network model acquire various activity modulation depending on the spike timing in climbing fiber. Further, we simulated as Purkinje cells showing various modulation patterns project to deep cerebellar nucleus cell. Assuming that motor commands correspond to neural activity, we demonstrated that combination of various modulation patterns of Purkinje cells activity can generate desired activity of the deep cerebellar nucleus cell. The results indicate Purkinje cells acquire various modulation patterns depending on the climbing fiber inputs and combination of various modulation patterns of Purkinje cells activity contribute to accurate movements.

Disclosures: H. Yamaura: None. **T. Yamazaki:** None.

Poster

490. Cerebellum: Plasticity and Climbing Fibers

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 490.18/MM12

Topic: E.02. Cerebellum

Support: KAKENHI 17H03543
KAKENHI 17H06313

Title: Activity of cerebellar climbing fibers represents forelimb movements during voluntary lever-pull task in mice

Authors: *N. HIDAKA[1,2], S. TSUTSUMI[2], K. IKEZOE[1], Y. ISOMURA[3], M. KANO[2], K. KITAMURA[1,2]
[1]Univ. of Yamanashi, Chuo, Yamanashi, Japan; [2]Dept. of Neurophysiol., Univ. of Tokyo, Tokyo, Japan; [3]Tamagawa Univ., Machida, Tokyo, Japan

Abstract: Execution of voluntary movements depends critically on the cerebellum. The Purkinje cell (PC), which provides a sole output from the cerebellar cortex, plays a central role in motor control and learning. Decades of studies suggest that climbing fiber (CF) inputs to PCs represent errors in movements and are considered to function as teaching signals for motor learning. However, it is still unclear what components of signals for voluntary movements CFs convey,

and how they contribute to motor control and learning. Here, we performed *in vivo* two-photon calcium imaging in mice preforming forelimb lever-pull task in order to investigate activity patterns of CFs during execution of a voluntary movement.
Mice were trained to pull and hold a mechanical cantilever voluntarily using their left forelimb. Each successful lever-pulling/holding (> 400 ms) was rewarded by a drop of water (6-8 µl). Since Ca^{2+} transients in PC dendrites *in vivo* report complex spiking, i.e., PC responses to CF inputs, a genetically-encoded calcium indicator GCaMP6f was expressed in PCs located in the forelimb area of lobule V of the cerebellar vermis/paravermis.
We observed GCaMP fluorescence signals from a population of PCs while monitoring the lever trajectory induced by forelimb movements, and analyzed correlation between population CF signals and lever-movements. We found activation or suppression of CF signals to PCs corresponding to lever pull/hold movement, and that average activity patterns could be classified into three distinct categories. (i) Large and transient increase at the onset of lever-pull movement, (ii) high activity that was maintained during lever-holding period, and (iii) suppression of CF signals during lever-pull and -holding period. We also found that PCs that showed similar activity patterns tended to be spatially clustered, which presumably corresponds to the cerebellar microzones.
These results suggest that activity patterns of cerebellar CFs represent the information about forelimb movements and that CFs projecting to PCs in the same cerebellar microzone have similar properties. Therefore, it is possible that the combination of these distinct types of PCs, which converge on deep cerebellar nuclei neurons, could fully represent motor commands or trajectories for forelimb movements.

Disclosures: N. Hidaka: None. **S. Tsutsumi:** None. **K. Ikezoe:** None. **Y. Isomura:** None. **M. Kano:** None. **K. Kitamura:** None.

Poster

491. Basal Ganglia Systems in Acquired Behaviors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 491.01/MM13

Topic: E.03. Basal Ganglia

Support: The government of Japan

Title: Impaired reach-to-grasp responses in mice depleted of striatal cholinergic interneurons

Authors: *N. ABUDUKEYOUMU, M. GARCIA-MUNOZ, Y. NAKANO, G. W. ARBUTHNOTT
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Abstract: Cholinergic interneurons (ChIs) are sparsely distributed within the striatum, a nucleus that plays important role in voluntary motor control, associated learning, procedural memory, action selection and planning and execution of movement. Sparsely distributed ChIs are 1-3% of all striatal neurons and the main source of striatal acetylcholine.
Here we report the effect of depletion of ChIs in the dorsolateral striatum in a reach-to-grasp task. To selectively deplete ChIs, we used the saporin ribosome-inactivating-immunotoxin that targets choline acetyltransferase. C57BL/J male mice, 21 days old, received a stereotaxic unilateral infusion of the toxin (0.3µl/3min), and sham control group was injected with saline. Following one week postsurgery recovery, animals were food deprived for 12 h everyday and trained for 12 days at night during their active circadian cycle.
The mean percentage ± SEM of successful performance in the reach-to-grasp task for the last 6 training sessions was 51.11 ± 4.09% (n = 25), 48.79 ± 7.7% (n = 9) and 26.28 ± 5.19% (n = 13) for intact control, sham control and ChIs-depleted mice, respectively. These results indicate that striatal depletion of ChIs impair reaching accuracy, whereas no significant differences were observed in control or sham operated mice. Moreover, a positive correlation between loss of ChIs and performance in the reach-to-grasp task was observed. Our results suggest that the participation of ChIs in striatal mediated motor learning impact on the function of interneurons and projection neurons of the whole striatal microcircuitry (*Abudukeyoumu, N., Hernandez-Flores, T. et al. Eur. J. Neuroscience, in press*).

Disclosures: N. Abudukeyoumu: None. **M. Garcia-Munoz:** None. **Y. Nakano:** None. **G.W. Arbuthnott:** None.

Poster

491. Basal Ganglia Systems in Acquired Behaviors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 491.02/MM14

Topic: E.03. Basal Ganglia

Title: Distinct roles for cortico- and thalamo-striatal projections in motor skill learning and execution

Authors: *S. B. WOLFF, A. K. DHAWALE, R. KO, B. P. ÖLVECZKY
Harvard Univ., Cambridge, MA

Abstract: The remarkable capacity of the brain to acquire and execute motor skills depends on a distributed motor network. While many individual components have been identified, less is known about their specific roles and how they interact during learning and execution of motor skills.
To address this, we train rats in a lever-pressing task which results in spatiotemporally precise movement patterns. Our previous finding that motor cortex is necessary for learning, but not for

execution of this motor skill, suggests that motor cortex may act as a tutor for subcortical motor circuits during learning. A main candidate to receive this tutoring is the dorsolateral striatum, a major target of motor cortical projection neurons. In line with this hypothesis, we show that the striatum is indeed necessary both for the acquisition and execution of the motor skills we train. Furthermore, chronic and selective silencing of motor cortex's direct projections to the striatum, by viral and molecular strategies, prevented animals from learning the motor skill. In line with our previous lesion experiments, the same silencing did not affect skill execution when it was done after learning. We next tested the contribution to skill execution of striatum's other main input, that from thalamus. We found that chronic silencing of thalamo-striatal projections disrupted both skill execution and learning. These findings identify the striatum as a central player and suggest distinct roles for its cortical and thalamic inputs during motor skill acquisition and execution.

Disclosures: S.B. Wolff: None. **A.K. Dhawale:** None. **R. Ko:** None. **B.P. Ölveczky:** None.

Poster

491. Basal Ganglia Systems in Acquired Behaviors

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Program #/Poster #: 491.03/NN1

Topic: E.03. Basal Ganglia

Support: MH101697
NS078435

Title: The firing rate of external globus pallidus neurons is modulated by proactive, selective behavioral inhibition

Authors: *B.-M. GU, M. A. FARRIES, J. D. BERKE
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Abstract: The basal ganglia are critically involved in behavioral control, including both the initiation and inhibition of actions. In a reactive "Stop-signal" task - in which an instructed action must be abruptly cancelled - the STN and GPe appear to be involved in rapidly pausing, then cancelling, actions respectively (Schmidt et al., 2013; Mallet et al., 2016; Schmidt & Berke 2017). However, behavioral inhibition can also be proactive - being prepared in advance to stop if needed. We have been testing the hypothesis (Aron 2011) that the indirect pathway (striatum to GPe) mediates the proactive inhibition of specific actions. We first modified our prior rat stop-signal task to assay proactive inhibition. Distinct starting nosepoke locations were associated with either 1) no possibility of needing to stop; 2) a 50% probability of a Stop cue, but only if the Go cue instructed left, or 3) a 50% probability of a Stop cue, but only if the Go cue instructed right. Well-trained rats (n=5) demonstrated proactive inhibition by selectively longer reaction

times for the movement that might be followed by the Stop cue. In ongoing single-unit recordings from GPe during this task we found that a substantial proportion of GPe neurons (68/209 cells) show changes in firing rate that reflect the engagement of proactive inhibition. Especially, GPe cells were modulated when proactive inhibition was engaged to the contralateral direction to the recording site. Furthermore, most of these modulated cells show response selectivity when the animal makes choice. These results support the hypothesis that GPe is selectively involved in being prepared to stop specific actions if needed.

Disclosures: B. Gu: None. **M.A. Farries:** None. **J.D. Berke:** None.

Poster

491. Basal Ganglia Systems in Acquired Behaviors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 491.04/NN2

Topic: E.03. Basal Ganglia

Support: R01 DA045783
R01 MH101697
R01 NS078435

Title: Striatal fast-spiking interneurons help guide learning from disappointments and restrain unrewarded actions

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Abstract: Successful action selection often involves weighing evidence for and against each alternative. The dorsal striatum is thought to facilitate this process by storing such evidence in the synaptic weights of spiny projection cells (MSNs) and using it to make choices. MSN activity can be strongly shaped by inhibitory input from nearby parvalbumin-positive (PV) fast-spiking interneurons (FSIs). We have previously shown that FSIs preferentially increase their activity during choice execution, and that adjacent MSN-FSI pairs have opposite action preferences. Yet it remains unclear what information FSIs specifically convey to MSNs in the context of adaptive decision making. To better understand this we have been recording from, and precisely manipulating, FSIs and MSNs in a trial-and-error "bandit" task. We report three observations. First, we have employed an optogenetic "tagging" procedure in transgenic knock-in PV-Cre and PV-Flp rats to record from identified PV+ striatal FSIs. We confirm prior suggestions that observing a transition to erratic bursting during slow-wave sleep provides a highly accurate method of identifying PV+ neurons (9/9 tagged cells to date). Second, using silicon probes and drivable tetrodes (n=6 rats, 143 MSN/103 FSI) we observe that FSIs fire more

during choice execution when the previous trial was unrewarded. Comparing activity to model-derived action values, we find that the firing rate of ~25% of the FSI population specifically correlates with evidence against performing an action. Third, we expressed the inhibitory archaerhodopsin in PV-Cre rats (n=7) to transiently suppress FSIs during key task events. Suppressing FSIs before movement onset increased the likelihood of repeating a previously unrewarded contralateral choice, consistent with a diminished ability to utilize negative evidence. In addition to this immediate effect on using values for decision-making, we also found that FSIs are important for updating values. Inhibiting FSIs during reward feedback blocked the normal shift in reaction time that accompanies updated reward expectations. These combined effects on performance and learning suggest an active role for FSIs in learning from unrewarded choices, and restraining them in the future.

Disclosures: J.R. Pettibone: None. **A. Mohebi:** None. **R. Hashim:** None. **J.D. Berke:** None.

Poster

491. Basal Ganglia Systems in Acquired Behaviors

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Topic: E.03. Basal Ganglia

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NIH Grant U01 NS094375 03

Title: Forebrain dopamine value signals arise independently from midbrain dopamine cell firing

Authors: *A. MOHEBI[1], J. R. PETTIBONE[1], A. HAMID[2], J.-M. WONG[3], R. KENNEDY[3], J. D. BERKE[1]
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Abstract: The mesolimbic dopamine projection from the ventral tegmental area (VTA) to nucleus accumbens (NAc) is a key pathway for both reward-driven learning and motivation. In head-fixed animals, brief changes in VTA dopamine cell firing can encode reward prediction errors (RPEs), vital learning signals in computational theories of adaptive behavior. However, in unrestrained animals NAc dopamine release more closely resembles reward expectations (values), motivational signals that invigorate approach behaviors. This discrepancy might be due to distinct behavioral contexts, changes in the tonic firing of dopamine cells, or a fundamental dissociation between firing and release. To resolve this, we directly compared dopamine cell firing with dopamine release in the same adaptive decision-making task. With microdialysis

(n=19 rats, 58 probe locations across 7 subregions), we found that dopamine release covaries with reward expectation in two specific forebrain hotspots, NAc core and ventral prelimbic cortex. The dopamine input to NAc core is provided by lateral VTA neurons. Yet the firing rates of optogenetically-identified lateral VTA dopamine cells (n=29, from 4 TH-Cre rats) showed RPE-like responses to reward-predictive cues and did not vary with reward expectation. We conclude that critical motivation-related changes in NAc dopamine release are unlikely to arise from VTA dopamine cell firing but may instead reflect local influences over forebrain dopamine varicosities.

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Poster

491. Basal Ganglia Systems in Acquired Behaviors

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Topic: G.02. Motivation

Support: R01 MH106689-02

Title: Dopamine neurons targeting dorsomedial striatum are modulated by reward and choice independently

Authors: *R. S. LEE, M. G. MATTAR, N. F. PARKER, I. B. WITTEN, N. D. DAW
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Abstract: Dopaminergic (DA) neurons in the midbrain are essential both for learning and for generating movements, but most physiological studies have primarily examined a correlate of the former function: reward prediction error signals. In a previous study, Parker et al. (Nature Neuroscience, 2016) found that two projection-defined DA subpopulations have dissociable properties: in rodents performing a “two bandit” reward learning task, calcium activity in DA terminals in the ventral striatum more strongly encoded reward prediction error. Conversely, DA terminals in the dorsomedial striatum (DMS) were activated during contralateral, relative to ipsilateral choices, potentially reflecting a correlate of movement in DA neurons. However, a major question remains unresolved; these putative movement-related responses may also reflect a prediction error signal, the temporal-difference error for the value of the contralateral action. A lateralized prediction error signal arises in some reinforcement learning algorithms that maintain separate state-related versus action-related decision variables, updated with distinct decision variables. Such a signal would be correlated with contralateral choices, since animals will tend to choose the higher-valued action.
Thus, to determine whether choice encoding in DMS is better viewed as a value-related decision

variable rather than a movement signal, we examine the time course of DMS responses over the course of a trial, and as a function of previous events. We find two indications that the contralateral choice selectivity reflects the direction of movement and not a value-related decision variable. First, although modulation of responses by expected value is present (as assessed through the identity and reward status of the immediately preceding choice), its influence on DA responses reflects an orthogonal reference frame - reward modulates the encoding of the chosen action, rather than the contralateral action-which is separable from the simultaneously present movement effects. Second, the average movement-related modulation reverses polarity immediately following the animals' leverpress, likely reflecting a reversal in the animals direction of movement immediately upon pressing the lever and then returning to harvest reward. Together these results demonstrate that choice encoding is separable from reward encoding in the dopamine system.

Disclosures: R.S. Lee: None. **M.G. Mattar:** None. **N.F. Parker:** None. **I.B. Witten:** None. **N.D. Daw:** None.

Poster

491. Basal Ganglia Systems in Acquired Behaviors

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Topic: E.03. Basal Ganglia

Support: NIH Grant 5R01NS094667-03
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Klingenstein Fellowship

Title: Movement-related activity in ventral basal ganglia and dopaminergic midbrain is gated by behavioral state

Authors: *R. CHEN, P. A. PUZEREY, V. GADAGKAR, J. H. GOLDBERG
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Abstract: Dopamine (DA) neurons and their inputs from the ventral basal ganglia (vBG) exhibit both reward and movement related firing, but it remains unknown if these signals can be differentially gated by behavioral state. For example, movement-related dopamine signals have been observed in some studies but not others. One possibility is that some neurons are movement related and others are not. Yet another possibility is that a single neuron can be movement related under certain behavioral states but not others. We recorded single DA and vBG neurons in birds transitioning between singing and non-singing states while monitoring body movement with microdrive-mounted accelerometers. The activity of many vBG neurons was locked to body movements with millisecond time-scale precision but only during non-singing states. During

singing, these neurons ‘switched’ their tuning and became precisely time-locked to specific song syllables, and not to body movement. Similarly, many DA neurons exhibited phasic movement related activity but only during non-singing states; during singing these neurons lost their movement related signaling and instead encoded singing-related performance error. Changes in neuronal tuning could occur on 10 millisecond timescales at state boundaries. Our findings demonstrate that movement related activity in single neurons can dramatically change with behavioral context.

Disclosures: R. Chen: None. **P.A. Puzerey:** None. **V. Gadagkar:** None. **J.H. Goldberg:** None.

Poster

491. Basal Ganglia Systems in Acquired Behaviors

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Title: Social context-dependent modulation of dopaminergic performance error

Authors: *V. GADAGKAR, P. A. PUZEREY, J. H. GOLDBERG
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Abstract: Dopamine (DA) neurons encode phasic error signals that both modulate striatal plasticity for learning and also control the vigor of ongoing behavior. It remains poorly understood how DA subserves these two functions. Songbirds provide a tractable model for studying the dual roles of dopamine. First, songbird DA neurons encode song performance error signals - necessary and sufficient for learning - characterized by suppression following worse-than-predicted song syllable outcomes and activation by better-than-predicted ones. Curiously, striatal DA signaling is also thought to control the variability of ongoing song. Specifically, songbirds sing in two distinct DA-dependent motor states. (1) Undirected song is produced while alone and is associated with vocal variability and low levels of striatal DA. (2) Female-directed song is associated with a reduction in variability and higher levels of striatal DA. To investigate how DA may implement these dual functions, we recorded from antidromically identified, striatal projecting DA neurons as we controlled perceived error (with distorted auditory feedback) and behavioral state (with female present or absent). Performance error-encoding DA

neurons exhibited no change in tonic firing rate or pattern between undirected and directed singing. Yet singing-related performance error signals observed during undirected singing were significantly reduced or even gated off in the presence of the female. Our findings suggest a spiking-independent mechanism for the previously reported increase in striatal DA during directed song. Further, they demonstrate that dopaminergic error signals can be gated off by social context.

Disclosures: V. Gadagkar: None. **P.A. Puzerey:** None. **J.H. Goldberg:** None.

Poster

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CONACyT PhD fellowship: 620172

Title: Calcium signals of the striatal pathways during the performance of a chain of sequences

Authors: *I. LINARES-GARCIA, J. RAMÍREZ-JARQUÍN, F. TECUAPETLA
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Abstract: The striatal activity have an important role in the generation sequences of actions. Different contributions have been attributed to the two types of striatal projection neurons (SPNs), the striatonigral “direct”, and the “indirect” striatopallidal pathway. An increase in the activity of the striatonigral pathway have been implicated in the increase of movements, while an increase in the activity of the striatopallidal in the reduction of movements, suggesting that the former is required in producing action while the latter is important in ending it. To evaluate this possibility in this study we ask: How the SPNs of the two striatal pathways are recruited throughout the generation of a chain of sequences to achieve a goal?
To address this question, we recorded the activity of striatonigral and striatopallidal neurons through the green calcium indicator GCaMP6f in striatonigral (D1-Cre) and striatopallidal (A2A-Cre mice) in a head-fixed behavioral task where mice learn to do chain of two sequences of lever press in a restricted period of time. We recorded the neuronal activity at the different phases of learning of the chain of sequences.
Our preliminary results show three findings: 1) both pathways are recruited at the onset, the end and the development of the chain of sequences. 2) The striatopallidal cells show a preferential

modulation during the transition between the two sequences in the chain. 3) Calcium signals related to individual sequences in the chain were found in the two pathways.
Our data will be discussed on the light of the current striatal-basal ganglia models.
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Poster

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Topic: E.03. Basal Ganglia

Support: HHMI
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Title: Encoding of sequential context in a songbird cortical-basal ganglia circuit important for context-specific learning

Authors: *L. TIAN, M. S. BRAINARD
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Abstract: Motor skills depend on the reordering of individual gestures into a larger set of sequences; skilled performance of sequences requires the ability to appropriately modify gestures depending on sequential context. The neural mechanisms underlying these context-dependent modifications are poorly understood. Bengalese finch song is a motor skill consisting of variable sequences of discrete gestures, or “syllables.” Bengalese finches can modify the spectral structure of a given syllable in a context-specific manner in order to escape disruption of singing-related sensory feedback (Hoffmann & Sober 2014; Tian & Brainard 2017). Localized inactivation studies indicate that this context-specific learning depends on the anterior forebrain pathway (AFP), a cortical-basal ganglia circuit specialized for song. The AFP adaptively biases syllable structure with high specificity for sequential context (Tian & Brainard 2017). This specificity suggests that during learning the AFP undergoes modifications that reflect the conjunction of signals representing sequential context and performance feedback. Here we test whether there are signals in the AFP encoding context by recording from the AFP during production of individual syllables in different sequential contexts. We found that neural activity in LMAN, the cortical output nucleus of the AFP, depends on sequential context, as measured by the ability to decode the sequence in which a given rendition of a syllable is embedded. We

further hypothesized, based on previously reported effects of AFP inactivation on context-specific learning (Tian & Brainard 2017), that while activity in the AFP depends on both sequential context and syllable identity, activity in downstream motor circuitry depends more strongly on syllable identity and relatively weakly on sequential context. To test this possibility, we leveraged the fact that the AFP contributes to syllable structure by biasing activity in the downstream motor nucleus RA (Kao et al. 2005; Olveczky et al. 2005; Andalman & Fee 2009). This predicts that context-dependent variation in AFP activity should contribute to context-dependent variation in syllable structure. Indeed, we found that blocking AFP output decreases context-dependent variation in syllable structure. These results support a hierarchical organization in which context-specificity of syllable modifications may reflect the learned association between contextual signals and motor biasing activity in the AFP, while syllable structure that is similar across contexts reflects syllable-specific activity in downstream motor circuitry.

Disclosures: L. Tian: None. **M.S. Brainard:** None.

Poster

491. Basal Ganglia Systems in Acquired Behaviors

Location: SDCC Halls B-H

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Program #/Poster #: 491.11/NN9

Topic: E.03. Basal Ganglia

Title: Dynamic shifts of striatal activation pattern during acquisition of an auditory discrimination task

Authors: *S. SETOGAWA[1], T. OKAUCHI[2], D. HU[2], M. SHIGETA[2], E. HAYASHINAKA[2], K. ONOE[2], Y. WADA[2], K. HIKISHIMA[3], H. ONOE[4], Y.-L. CUI[2], K. KOBAYASHI[1]
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Abstract: Associative learning is the process in which a new response associates with particular stimulus throughout trial and error. The neural mechanisms underlying associative learning related to the striatum has been studied extensively using sensory discrimination task. Lesion and electrophysiological studies in rats have suggested that different striatal regions, such as the dorsomedial and dorsolateral parts of striatum, associate with the discrimination learning task. However little is known how the pattern of striatal activation changes during acquisition of associative learning. Therefore, we performed a small-animal neuroimaging with 2-deoxy-2-[^{18}F] fluoro-D-glucose (FDG)-PET to assess dynamic changes in patterns of brain activation in an auditory discrimination task with Long Evans rats. Serial FDG-PET scans were performed before and after the start of the learning (2, 6, 10 and 24 days). Under freely-moving condition,

FDG was intravenously injected just before the starting of a 30-min behavioral task. Fifty-five minutes after the FDG injection, a 30-min static PET scan was performed under anesthesia. Voxel-based statistical parametric mapping analysis revealed that the neural activities in the posterior region of the dorsolateral striatum increased at day 6, then turned to decrease at day 10. Meanwhile, the dorsomedial striatum was deactivated at day 24 as compared with either of day 2, 6 or 10. These findings suggest that the associative learning evokes dynamic shifts of neuronal activation pattern in sub-regions in the striatum. Moreover, this study demonstrates that small animal FDG-PET enables us to provide a useful information on the regional neural activity in the entire brain during the acquisition of operant conditioning task.

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Poster

491. Basal Ganglia Systems in Acquired Behaviors

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Topic: E.03. Basal Ganglia

Support: KBRI basic research program 18-BR-01-06

Title: Night-time sleep does not play a major role in consolidation of basal ganglia-dependent vocal learning in adult songbirds

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Abstract: Birdsong is a complex motor skill that songbirds develop by learning from other individuals. This song learning critically depends on a basal ganglia-thalamo-cortical circuit called the anterior forebrain pathway (AFP), which is discrete and specialized for song learning. Although in many songbird species song learning depends on age and does not naturally occur in adult birds, small changes in a specific feature of song, such as pitch of a song syllable, can be experimentally induced by training adult birds to avoid aversive noise playback (Tumer & Brainard 2007). Recent studies have demonstrated that the initial expression of this pitch-shift learning is driven by an instructive signal from the AFP that biases song structure to avoid noise playback (Andalman & Fee 2009; Warran et al. 2011). It is still unclear and controversial, however, how this "AFP-bias" of song structure is consolidated in the song motor pathway during song learning. Here, we investigated this issue by examining AFP-bias at different times of a day. AFP-bias was estimated by pharmacologically blocking the synaptic transmission from

the AFP output nucleus LMAN to the song motor nucleus RA and by measuring magnitudes of reversions of learned changes in the pitch of a target syllable as reported in previous studies. We found that birds learning to change the pitch have substantial AFP-bias in the morning and that its magnitude is comparable with that in the previous evening. These results do not support the hypothesis that AFP-bias is consolidated in the motor pathway during night-time sleep and thus disappears by the next morning, and instead suggest that consolidation of AFP-bias occurs predominantly during daytime. In support of this conclusion, pharmacological inactivation of RA during a night-time period did not significantly affect learning (pitch changes) on the following day. Our results contrast sharply with previous studies demonstrating the importance of sleep for consolidation of learned motor behavior, and thus provide new insight into the mechanisms of motor learning and memory.

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Poster

491. Basal Ganglia Systems in Acquired Behaviors

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Program #/Poster #: 491.13/NN11

Topic: E.03. Basal Ganglia

Support: Jane Coffin Childs Fellowship

Title: Basal ganglia modulation of motor thalamus

Authors: *A. D. LIEN[1], A. C. KREITZER[2]
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Abstract: The ability to accurately plan and execute movement is fundamental. In the mammalian brain, the basal ganglia-thalamo-cortical circuit is believed to be important for initiating and suppressing movement. Anatomically, the output nuclei of the basal ganglia form inhibitory synapses on neurons in the motor thalamus which sends excitatory projections to motor cortex. Motor cortex in turn projects to brainstem and spinal cord circuits that control the musculoskeletal system. It has long been hypothesized that increases and decreases in basal ganglia inhibition of motor thalamus can suppress and enhance thalamic activity and in turn reduce or promote movement however direct evidence is lacking. Here we tested these hypotheses by recording the spiking of motor thalamus neurons in awake mice during optogenetic manipulation of basal ganglia circuitry or during performance of a forelimb movement task. We demonstrate that spiking in a distinct region of motor thalamus is suppressed during optogenetic activation of striatal indirect pathway medium spiny neurons (iMSNs). Spiking of these same thalamic neurons was modulated around the time of lever movement in a

task where mice used their forelimb to pull a lever for reward. The cortical projection targets of these thalamic neurons are currently being identified.

Disclosures: A.D. Lien: None. **A.C. Kreitzer:** None.

Poster

491. Basal Ganglia Systems in Acquired Behaviors

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Title: Multiple viral tracings reveal an anatomical hierarchy in cortico-basal ganglia loops

Authors: *S. AOKI[1,2,3,4], J. B. SMITH[1], M. IGARASHI[2,4], P. COULON[5], J. R. WICKENS[2], X. JIN[1], T. J. H. RUIGROK[3]
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Abstract: Controlling action involves hierarchical steps, decision-making, planning and execution. Cortico-basal ganglia circuits are critical for appropriately enacting these processes. Across cerebral cortex and basal ganglia, limbic, associative and sensorimotor information are thought to be processed in parallel, segregated closed loops. Indeed, cortico-striatal projections show a clear topography; dorsolateral striatum (DLS) receives input from sensorimotor cortex, whereas dorsomedial (DMS) and ventral striatum (VS) have input from prefrontal and limbic areas. However, structure of striatal output through substantia nigra pars reticulata (SNr), thalamus, and ultimately to cortex remains obscure. Furthermore, whether they form parallel closed loops or interlace open loops has yet to be determined in rodents. To address this question, we first performed retrograde transsynaptic wildtype rabies tracing (RABV) combined with anterograde tracing by cholera-toxin b subunit (CTb) from three cortical areas of rats, by which cortico-striatal input and striatal output neurons tri-synaptically connecting to each cortical area were identified. RABV/CTb injections in primary or secondary motor cortex

yielded RABV+ neurons and CTb+ terminals in DLS, indicating a closed loop between them. Surprisingly, we also found RABV+ neurons in VS, DMS and tail of striatum (TS) without CTb+ terminals, suggesting that VS, DMS and TS can target motor cortex despite the absence of its direct input. Conversely, RABV/CTb injections in medial prefrontal cortex showed an essentially closed loop since RABV+ and CTb+ labeling were only found in VS and DMS but not in DLS or TS. To determine whether and how such striatal connections to motor cortex were mediated by thalamus/SNr, we performed Cre-dependent monosynaptic modified RABV tracing from nigro-thalamic neurons specifically projecting to motor thalamus, and analyzed RABV+ striatal neurons. This revealed an identical distribution of RABV+ neurons to our transsynaptic RABV tracing from motor cortex; VS, DMS, DLS, and TS have output to motor thalamus and in turn to motor cortex. These results unveiled a previously unidentified hierarchy of cortico-basal ganglia output, whereby limbic/associative VS and DMS can access motor cortex through thalamus, but sensorimotor DLS cannot do so to prefrontal cortex. Further experiments are conducted to map the topography of striato-nigral, nigro-thalamic, and thalamo-cortical projections. We propose a revised framework for the organization of cortico-basal ganglia circuits, which are not segregated closed loops, but interact in a one-way hierarchical manner for controlling action.

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Poster

491. Basal Ganglia Systems in Acquired Behaviors

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Program #/Poster #: 491.15/NN13

Topic: E.03. Basal Ganglia

Support: HHMI

Title: Mapping the Basal Ganglia output projection

Authors: *J. LEE[1], W. WANG[2], B. SABATINI[2]
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Abstract: Basal ganglia is a phylogenetically old and evolutionary conserved set of structures important for reinforcement learning and movement control. Although a lot of work have focused on the corticostriatal pathway, very little is known about the substantia nigra reticulata(SNr) output to different target regions. Using a combination of dual anterograde tracing, retrograde tracing and optogenetics with slice physiology, we show that SNr target different thalamic, collicular and brain stem regions in a topographical manner. Different regions of SNr, which receive inputs from different striatal sectors, targeted different sectors of VM and

Pf, consistent with the segregated closed loop model for thalamostriatal and thalamocortical loops. Our data provides a framework to investigate the function of different BG pathways as well as different SNr projections to distinct target areas.

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Poster

491. Basal Ganglia Systems in Acquired Behaviors

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Topic: E.03. Basal Ganglia

Support: Israel Science Foundation (ISF)

Title: Processing of competing cortical inputs in the basal ganglia

Authors: *M. ISRAELASHVILI[1], I. BAR-GAD[2]
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Abstract: The basal ganglia are a group of interconnected sub-cortical nuclei that are involved in motor, associative and limbic functions. They receive information from most areas of the cerebral cortex and the thalamus, and project back to frontal cortical areas through the thalamus, thus forming the cortico-basal ganglia-cortico loop. Currently, the main network level model of the basal ganglia is the action selection model. This model emphasizes the role of the basal ganglia, within the cortico-basal ganglia-cortical loop, in choosing one or more actions out of a multitude of such actions presented by the cortex. According to this model, projections from the cortex to the striatum, the main input nucleus of the basal ganglia, excite a subset of striatal neurons that leads to a release of the selected action. The selection process of the action within the striatum involves both feedback and feedforward inhibition that inhibits all other potential actions. Currently, there is limited physiological support for the functional role of the striatal inhibitory network and for the validation of action selection hypothesis. In this study we examine the processing of competing cortical input in the basal ganglia of freely behaving rats. We use optical stimulation of cortical areas in conjunction with somatosensory input while performing extracellular recordings from the striatum and globus pallidus. Characterization of the neuronal activity that occurs during separate as well as simultaneous stimulation of different cortical areas was performed. We observed both synergistic and antagonistic interactions between cortical inputs, supporting a complex representation of the cortical activity by the basal ganglia in general and the striatum in particular. This remapping of cortical information suggests that the study of cortico-basal ganglia information processing requires the progression to a study of the interaction between multiple sources of input to this pathway.

Disclosures: M. Israelashvili: None. **I. Bar-Gad:** None.

Poster

491. Basal Ganglia Systems in Acquired Behaviors

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 491.17/NN15

Topic: F.01. Neuroethology

Support: NIH 5R01DC002524-20
NIH F30 NS096871
Inscopix DECODE award

Title: Identifying a learning role for the songbird basal ganglia

Authors: *J. SINGH ALVARADO[1], M. BEN-TOV[2], M. G. KEARNEY[2], R. D. MOONEY[3]
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Abstract: The basal ganglia (BG) plays a key role in the acquisition and execution of complex behaviors. Reinforcement learning (RL) models have been extensively proposed as an appealing framework for understanding BG function, yet demonstrating RL implementations in neural circuits has remained challenging. Two factors contribute to this difficulty: the diversity of behaviors the mammalian BG contributes to, and the limited understanding of how the BG contributes to a specified behavior. The songbird is an experimentally tractable platform where these issues can be addressed; an anatomically and functionally segregated network of specialized brain nuclei selectively control the acquisition and execution of song, enabling the direct linkage of neural circuits and a single behavior. Furthermore, the RL framework has been extended to songbird learning, where it posits the BG striatal spiny neuron (SN) as a critical locus of plasticity. Despite their influence, little experimental evidence exists to test these hypotheses. To bridge this gap, we combined genetic ablation, optogenetic inactivation, and single-photon deep brain imaging of SNs in the songbird BG homologue Area X. Genetic ablation of SNs in adult zebra finches leads to progressive loss of spectral features, stuttering, and failure to initiate song. In contrast, rapid optogenetic inactivation of SNs had no outstanding acute effects, but prevented adaptive plasticity when precisely triggered during an experimental RL paradigm. Imaging from populations of Area X neurons over multiple months revealed heterogeneous and spatiotemporally biased activity, with the majority of neurons firing during one part of a motif. While we observed highly stereotyped and reliable SNs, the majority were recruited during the minority of song trials. Current analysis is focusing on SN dynamics during RL, as well as the context dependence of SN activity. These results begin to test implementations of RL in a specialized circuit during an innately learned behavior, as well as provide evidence for a highly temporally precise role of SNs in learning.

Disclosures: J. Singh Alvarado: None. **M. Ben-Tov:** None. **M.G. Kearney:** None. **R.D. Mooney:** None.

Poster

492. Voluntary Movements: Finger and Grasp Control: Age, Pathology, and Physiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 492.01/NN16

Topic: E.04. Voluntary Movements

Support: NYS Spinal Cord Injury Board Grant 31291GG

Title: Enhanced neuromodulation with paired brain and spinal cord stimulation in a large animal of cervical contusion injury

Authors: *P. T. WILLIAMS[1], J. R. BRANDENBURG[2], D. Q. TRUONG[3], A. DE PAOLIS[3], H. BORGES-DESOUZA[3], D. RYAN[2], J. WONG[2], S. AMBIA[2], H. ALEXANDER[2], L. CARDOSO[3], M. BIKSON[3], J. H. MARTIN[1,4]
[2]Molecular, Cell. and Biomed. Sci., [1]CUNY Sch. of Med., New York, NY; [3]Biomed. Engin., City Col. of New York, New York, NY; [4]CUNY Grad. Ctr., New York, NY

Abstract: Regaining hand function is the highest priority for people with cervical SCI. Our lab is developing therapeutic neuromodulation using brain and spinal cord stimulation to promote recovery of hand function in a large-animal model of SCI that can be scaled to patients. We use patterned cortical electrical stimulation (intermittent theta burst stimulation; iTBS), shown in the rat to strongly activate the corticospinal tract (CST), the principal pathway for hand control, to promote recovery of skill and dexterity. We combine this with transcutaneous spinal direct current stimulation (tsDCS) to further strengthen connections and improve function after SCI.
Our goal was to produce a moderate C4 contusion using the IH Spinal Impactor. Simulations using the finite element method (FEM) were run on a segmented model of the spinal column based on MR and microCT scans in order to compare probe shapes and force magnitudes on the distribution of stress and strain during contusion. Predictions of lesion extent were corroborated in pilot studies to induce a mild, moderate, or severe lesion.
We determined if the paired therapy augments the efficacy of motor cortex activation of muscle. In separate sessions we compared MEPs before, during, and after iTBS or tsDCS alone, and in combination. In line with the findings in the rat studies, iTBS alone, c-tsDCS alone, and the combination, augmented the period of post-stimulation MEP facilitation.
Our next goal was to evaluate the effect of stimulation therapy after SCI. We induced a moderate lesion revealed by MR-scans (3.5 mm spherical probe hit at 800 kDyn force with a 1 s dwell) in one animal. Assessments of upper-limb control showed more severe motor impairments on the left side, so iTBS was delivered with an epidural electrode to the contralateral motor cortex. We paired this with tsDCS (4 mA cathodal), as in the rat studies, using montages guided by FEM

models of current density, to target the cervical enlargement. We delivered the paired therapy for 30 min/day on 10 consecutive days in the chronic phase, after spontaneous recovery had plateaued.
We tested the neuromodulation of MEP amplitudes with iTBS or tsDCS alone, and in combination, and found greater MEP enhancement after therapy compared to before. Importantly, we also found improvements in reaching accuracy with the limb receiving the iTBS component of the therapy.
These encouraging results show a strengthening of motor cortex-to-muscle activation, facilitation of motor cortex-mediated MEP potentiation, and an improvement in motor skill. These preliminary findings point to a neuromodulatory strengthening of the corticospinal system for improved motor control after cervical injury.

Disclosures: P.T. Williams: None. **J.R. Brandenburg:** None. **D.Q. Truong:** None. **A. De Paolis:** None. **H. Borges-DeSouza:** None. **D. Ryan:** None. **J. Wong:** None. **S. Ambia:** None. **H. Alexander:** None. **L. Cardoso:** None. **M. Bikson:** None. **J.H. Martin:** None.

Poster

492. Voluntary Movements: Finger and Grasp Control: Age, Pathology, and Physiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 492.02/OO1

Topic: E.04. Voluntary Movements

Support: Dementia program of the Norwegian Health Association

Title: Can changes in manual dexterity and white matter integrity identify mild cognitive impairment from normal aging?

Authors: *C. RODRIGUEZ-ARANDA[1], S. A. CASTRO-CHAVIRA[2], V. K. BYRE[2], A. EVJEN[2], O. VASYLENKO[2], M. M. GORECKA[1], K. WATERLOO[1], E. KAMYCHEVA[3], S. H. JOHNSEN[3], T. R. VANGBERG[3]
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Abstract: Epidemiological research has demonstrated that manual dexterity deteriorates early in degenerative diseases and that changes in hand function may be a useful, non-invasive indicator of dementia. However, no experimental data corroborating this assumption exist. In healthy elderly, hand dexterity declines have been associated with deterioration in the microstructure of cerebral white matter. Thus, the present study aims to examine whether specific dexterity declines exist in individuals with mild cognitive impairment (MCI) as compared with healthy age-matched controls and whether these differences are associated with cerebral white matter degeneration. Two specific tracts were explored: corticospinal (CST) and uncinate fasciculus

(UF). The former underlies motor dexterity and the latter has been found to differentiate MCI from normal aging. **Material:** 26 right-handed MCI patients (*M* age = 71.2 y) and 29 right-handed healthy elderly (*M* = age 70.9 y) were tested with the Purdue Pegboard test and video recorded with Vicon Motus to calculate movement times (MT) and kinematic parameters during task performance. Reaching, grasping, transport and inserting were analyzed separately with each hand. Movement times and kinematics including path length, angle and linear and angular velocities were calculated. Significant group differences on dexterity were selected and correlated with white matter indices. MRI data were acquired on a 3T MR scanner. Tract-based analysis using FreeSurfer's TRACULA was used to extract FA and MD measures from the selected tracts. Correlations between DTI metrics and dexterity measures were conducted. **Results:** Group differences were found on MT only for left hand during reaching and grasping. For kinematic data, several group differences were found in both hands. For the *right han*d, lower mean values of angular and linear velocities characterized the patient group. Variability of movements (CoVs) with right hand shows low variability for linear velocity but high variability for hand rotation (angular velocity) suggesting disturbed hand rotation. Kinematics for the left hand differed in all actions. Though, results for grasping showed a distinctive pattern in MCI. Associations with DTI indices showed various significant interactions between group and MTs during reaching and grasping. Specifically, reaching times were positively associated with MD in the left UF and CST. **Conclusions:** Patients showed significant differences in MTs and kinematics with left hand, which were further correlated uniquely with DTI indices. The present data offer empirical support to the suggestion that dexterity changes are a characteristic of MCI.

Disclosures: C. Rodriguez-Aranda: None. **S.A. Castro-Chavira:** None. **V.K. Byre:** None. **A. Evjen:** None. **O. Vasylenko:** None. **M.M. Gorecka:** None. **K. Waterloo:** None. **E. Kamycheva:** None. **S.H. Johnsen:** None. **T.R. Vangberg:** None.

Poster

492. Voluntary Movements: Finger and Grasp Control: Age, Pathology, and Physiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 492.03/OO2

Topic: E.04. Voluntary Movements

Support: Wellcome Trust grant 101002 to SNB

Title: A novel wearable device for motor recovery of hand function in chronic stroke survivors

Authors: S. CHOUDHURY[1], R. SINGH[1], A. SHOBHANA[1], D. SEN[1], S. S. ANAND[1], S. SHUBHAM[1], M. R. BAKER[2], H. KUMAR[1], *S. N. BAKER[2]
[1]Inst. of Neurosciences Kolkata, Kolkata, India; [2]Newcastle Univ., Newcastle upon Tyne, United Kingdom

Abstract: We have previously demonstrated in monkey that reticulospinal connections to hand and forearm muscles are strengthened following corticospinal lesion, contributing to recovery of function (Zaaimi et al, 2012). Reticulospinal neurons can be activated by auditory click stimuli, probably partially via the vestibular apparatus (Fisher et al 2012). Pairing clicks with electrical stimulation of a muscle induces plastic changes in motor pathways (probably the reticulospinal tract) via spike timing-dependent plasticity mechanisms (Foysal et al 2016). In this study, we tested whether pairing clicks with muscle stimulation could improve hand function in stroke survivors. Clicks were delivered via a miniature earpiece, and electrical stimuli at motor threshold were given over the forearm extensor muscles. Stimulation was delivered using a wearable electronic device, as in Foysal et al (2016), which allowed the patient to receive stimulation at home while performing normal daily activities. We recruited 95 patients who had suffered a cortical or sub-cortical stroke at least 6 months previously. Patients were randomised to three groups: 1) wearable device stimulation at ~0.67Hz, where muscle stimuli were given 12 ms before click, 2) wearable device stimulation, where click and shock occurred independently at random, also at 0.67 Hz, 3) standard care. Those allocated to the device used it for at least 4 hours per day, every day for 4 weeks. Hand function was assessed at baseline (week 0), and weeks 2, 4 and 8, using the Action Research Arm Test (ARAT) which has four domains - Grasp, Grip, Pinch and Gross. Severity across three groups were comparable at baseline (mean total ARAT in three groups- 18.09, 10.75, 17.25, p= 0.513). Group 1 improved in the total ARAT (mean week 0: 18.09; week 8: 19.77, p= 0.019) unlike the other two groups. The Grasp sub-score also improved significantly (mean week 0: 5.84, week 8: 7.18, p= 0.004) only in Group 1. Other ARAT sub-domains showed no significant changes in any groups. Only one device related adverse event occurred, which was a contact dermatitis associated with the adhesive surface electrodes; this improved with topical steroid cream with no interruption of treatment. We conclude that a wearable device delivering paired clicks and shocks can produce a significant improvement in hand function in stroke survivors, probably via an action on the reticulospinal tract. References Fisher et al (2012) *J Physiol,* 590**,** 4045-60. Foysal et al (2016) *Journal of Neuroscience,* 36**,** 10823-10830. Zaaimi et al (2012) *Brain,* 135**,** 2277-89.

Disclosures: S. Choudhury: A. Employment/Salary (full or part-time):; Institute of Neuroscience Kolkata. **R. Singh:** A. Employment/Salary (full or part-time):; Institute of Neuroscience Kolkata. **A. Shobhana:** A. Employment/Salary (full or part-time):; Institute of Neuroscience Kolkata. **D. Sen:** A. Employment/Salary (full or part-time):; Institute of Neuroscience Kolkata. **S.S. Anand:** A. Employment/Salary (full or part-time):; Institute of Neuroscience Kolkata. **S. Shubham:** A. Employment/Salary (full or part-time):; Institute of Neuroscience Kolkata. **M.R. Baker:** A. Employment/Salary (full or part-time):; Institute of Neurosciences, Newcastle, United Kingdom. **H. Kumar:** A. Employment/Salary (full or part-time):; Institute of Neuroscience Kolkata. **S.N. Baker:** A. Employment/Salary (full or part-time):; Institute of Neurosciences, Newcastle, United Kingdom.

Poster

492. Voluntary Movements: Finger and Grasp Control: Age, Pathology, and Physiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 492.04/OO3

Topic: E.04. Voluntary Movements

Title: Aging impairs the use of explicit cues for anticipatory modulation of digit placement for dexterous manipulation

Authors: *P. J. PARIKH[1], N. RAO[2]
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Abstract: Dexterous manipulation depends on our seamless ability to control digit contact points and digit forces. Young adults demonstrate anticipatory modulation of their digit contact points and digit forces based on explicit verbal or visual cues about object property such as weight and center of mass (CM). Older adults, in contrast, demonstrate an impaired ability to use explicit color cues about object property for anticipatory modulation of digit forces. However, whether older adults are able to modulate their digit contact points based on explicit color cues about object CM remain to be known. Five older adults (65+) and six young adults performed a novel visuomotor task that required them to identify object center of mass using a color cue and to apply appropriate torque on the object at lift onset to minimize tilt over 60 trials. The application of CM-appropriate torque required fine modulation of digit contact points and digit forces. We found that older adults were slower in acquiring novel color-torque associations, a finding consistent with previous studies. Further analysis found that older adults failed to demonstrate anticipatory modulation of digit contact points based on the color cues about object CM when compared with young adults. Older adults were also impaired in applying CM-appropriate digit forces when compared to young adults. These finding suggest that the slower rate of arbitrary visuomotor learning in older adults resulted from impaired anticipatory modulation of both digit contact points and digit forces based on explicit color cues about object CM.

Disclosures: P.J. Parikh: None. **N. Rao:** None.

Poster

492. Voluntary Movements: Finger and Grasp Control: Age, Pathology, and Physiology

Location: SDCC Halls B-H

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Program #/Poster #: 492.05/OO4

Topic: E.04. Voluntary Movements

Support: NIH 1R03HD0773566-01
American Heart Association/American Stroke Association 15MCPRP25700312

Title: Forced aerobic exercise paired with motor task practice optimizes upper extremity motor recovery post-stroke

Authors: *S. LINDER[1], A. ROSENFELDT[2], S. DAVIDSON[3], N. ZIMMERMAN, 44195[3], J. LEE, 44195[3], A. PENKO, 44195[2], J. L. ALBERTS[2]
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Abstract: OBJECTIVE: To determine the effects of forced- and voluntary-rate aerobic exercise on the recovery of motor function in individuals with hemiparesis due to stroke.
BACKGROUND: The effects of aerobic exercise (AE) training in improving cardiovascular function post-stroke is well-documented. The potential role of AE in facilitating motor recovery following stroke, however, has not been systematically evaluated. Aerobic exercise is known to induce neurophysiologic responses in the brain, some of which may be exploited to enhance motor recovery. It has been shown in healthy adults that intensive AE administered immediately prior to motor task practice enhances motor skill acquisition. We have conducted preliminary studies investigating whether AE can enhance the motor learning benefits associated with task practice to improve motor recovery post-stroke. Two modes of AE, voluntary and forced, were evaluated and compared to a time-matched control group. Forced exercise (FE) is a mode of AE in which the participant's voluntary exercise rate during lower extremity cycling is augmented; thus, FE was used to overcome the deficits in motor and cardiovascular output commonly seen post-stroke.
DESIGN/METHODS: Two prospective, three-arm randomized clinical trials were conducted in which each group underwent a 45-min session of upper extremity repetitive task practice. Immediately preceding task practice, one group completed a 45-min session of forced aerobic exercise (FE, n=16), one group completed a 45-min session of voluntary aerobic exercise (VE, n=16), and one group completed a 45-min session of stroke-related education (EDU, n=8). Participants attended 3 times per week for 8 weeks. Outcomes included the Fugl-Meyer Assessment (FMA), Wolf Motor Function Test (WMFT), and Action Research Arm Test (ARAT).
RESULTS: The FE, VE and EDU groups improved significantly on the FMA from baseline to end of treatment by a mean of 11, 5, and 9 points, respectively. Post-hoc analysis revealed that change in the FMA was greater for the FE group compared to VE and EDU ($p=0.001$). On the WMFT, the FE group demonstrated significant improvement on all outcomes (total time, fine motor, gross motor, and functional ability score), while the VE group improved in two of the scores and the EDU group improved only in the functional ability score. All 3 groups improved significantly on the ARAT, with only the FE group improving significantly in all 4 subscales.
CONCLUSIONS: FE preceding motor task practice resulted in greater improvements in upper extremity motor recovery. Pairing AE training with task practice may enhance motor recovery and should be incorporated into stroke rehabilitation.

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Poster

492. Voluntary Movements: Finger and Grasp Control: Age, Pathology, and Physiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 492.06/OO5

Topic: E.04. Voluntary Movements

Support: VA Rehabilitation Research & Development - Research Career Scientist Award (F7823S, Patten)
VA Brain Rehabilitation Research Center of Excellence (B6793C)
University of Florida Fellowship (Ding)

Title: Non-paretic hand exercise to task-failure increases functional connectivity to paretic hand in chronic stroke

Authors: *Q. DING, T. MCGUIRK, P. S. ELLIOTT, C. PATTEN
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Abstract: We previously observed acute neural adaptations in the ipsilesional hemisphere of chronic stroke survivors in response to non-paretic hand exercise to task failure (ETF). These robust adaptations were sustained for up to four hours and accompanied by facilitation of paretic hand maximal voluntary contraction (MVC) and improved dexterity. These behavioral effects are consistent with the phenomenon known as 'cross-transfer'. Here we sought to determine the locus of these adaptations and how ETF affects functional connectivity between the central nervous system and non-exercised paretic limb. Intermuscular coherence (IMC) has been used to assess the strength of functional connectivity between the central nervous system and effector muscles. Activity in specific frequency bands is argued to arise from different neural loci (e.g., alpha (range 8-12 Hz): spinal reflexes; beta (range 15-30 Hz): corticospinal tract, subcortical & cortical; gamma (range 30-60 Hz): cortical). We investigated IMC using surface EMG from first dorsal interosseous and opponens pollicis in 12 individuals with chronic stroke (upper-extremity Fugl-Meyer assessment: 28-64/66, age: 65±7 (53-79) years, 11 males) who performed ETF with repeated submaximal non-paretic hand isometric power grip. Powergrip MVC, dexterity (Box and Blocks Test, BBT), and IMC were tested at baseline, immediately post-ETF, and every 45 min until 4 hours post-ETF. IMC in beta and gamma bands at baseline was significantly lower in the paretic than non-paretic hand ($p's<0.05$). IMC in alpha, beta and gamma bands increased in the exercised non-paretic hand immediately revealing peaks at 0 (alpha) and 45 (beta, gamma) min after ETF ($p's<0.05$). In the non-exercised paretic hand, IMC increased significantly only in

beta and gamma bands, revealing peaks at 90 and 135 min after ETF, respectively (p's<0.05). Paretic hand BBT improved (4-24%) in 10/12 participants at ≥1 point post-ETF. The magnitude of increased paretic hand beta band IMC correlated positively with paretic hand BBT facilitation (r^2=0.47, p=0.02). These parallel increases in paretic hand beta band IMC and BBT were greater in higher-functioning individuals (p's<0.05). In response to ETF functional connectivity to the exercised, non-paretic hand increased from all levels of the central nervous system. Crossed-effects in the non-exercised paretic hand, however, reveal increased functional connectivity primarily from supraspinal levels which are associated with behavioral facilitation. Our findings suggest that non-paretic hand ETF could potentially be an alternative rehabilitative intervention for motor recovery post-stroke.

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Poster

492. Voluntary Movements: Finger and Grasp Control: Age, Pathology, and Physiology

Location: SDCC Halls B-H

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Program #/Poster #: 492.07/OO6

Topic: E.04. Voluntary Movements

Support: NIH Grant NS 097450
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Title: Forced-use therapy after sensorimotor cortex lesions restores contralesional hand preference in macaca mulatta

Authors: *W. G. DARLING[1], K. S. STILWELL-MORECRAFT[3], J. GE[3], D. L. ROTELLA[1], M. A. PIZZIMENTI[2], R. J. MORECRAFT[3]
[1]Dept. of Hlth. and Human Physiol., [2]Anat. and Cell Biol., Univ. of Iowa, Iowa City, IA; [3]Basic Biomed. Sci., Univ. of South Dakota, Vermillion, SD

Abstract: We previously showed that after unilateral lesions to the arm/hand area of M1, lateral premotor cortex (LPMC), S1 and rostral part of the superior parietal lobule, fine digit motor function of the more affected hand recovers to variable levels. This recovery occurred despite reductions in strength of the corticospinal projection from spared ipsilesional supplementary motor cortex (M2) (Morecraft et al. 2015 J Comp Neurol 523:669). The lesion was always induced in the hemisphere contralateral to the preferred hand as identified using a hand preference test (Nudo et al. 1992, J Neurosci 12:2918). When allowed to choose, monkeys with these lesions would primarily use the ipsilesional (less affected) hand when picking up small food objects even after good recovery, demonstrating a form of learned nonuse (LNU) of the contralesional hand. We now test the hypothesis that forced-use therapy of the more affected hand can restore this hand to preferred hand status for a fine motor task. Six monkeys received

unilateral sensorimotor cortex (F2P2) lesions contralateral to the preferred hand. Two monkeys (SDM93, SDM94) received forced-use therapy beginning two weeks after the lesion. Therapy was provided three days/week using a device that allowed only the contralesional hand to successfully acquire small food objects without any constraint of the ipsilesional limb. On average, each animal successfully grasped and retrieved 400-450 small food treats during each rehabilitation session. Similarly, two motor testing devices were used that allowed testing of both hands for the duration of the survival period (Morecraft et al. 2015). A LNU test was performed on the same post-lesion schedule in four lesioned monkeys that did not receive therapy and hand preference was computed based on the last 3 post-lesion LNU tests. The two monkeys receiving therapy performed a hand preference test during the last post-lesion month for comparison to the pre-lesion hand preference test. Both monkeys that received forced-use therapy during recovery showed a stronger post-lesion hand preference to the contralesional hand than in the pre-lesion test (i.e., handedness index increased from 26.4 to 32 in one case and from 0.4 to 4 in the other). In contrast, the monkeys that did not receive therapy all strongly preferred the ipsilesional, less impaired, hand (average handedness index of 78.7) in the last 3 LNU testing sessions. Thus, forced use therapy restored hand preference after impairment by sensorimotor cortex lesion. Future research will establish whether the descending projections from ipsilesional M2 are maintained by this type of therapy.

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Poster

492. Voluntary Movements: Finger and Grasp Control: Age, Pathology, and Physiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 492.08/OO7

Topic: E.04. Voluntary Movements

Title: Lack of interlimb transfer following visuomotor adaptation in a person with congenital mirror movements

Authors: *S. BAO, A. M. MORGAN, J. WANG
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Abstract: Learning a motor adaptation task can generalize across the arms, although the extent of interlimb transfer is typically limited (30-50%). In this exploratory study, we examined the extent of interlimb transfer following visuomotor adaptation in an individual with congenital mirror movements (MM), which refer to contralateral involuntary movements that mirror voluntary movements. To confirm our subject's condition, we provided transcranial magnetic stimulation (TMS) on the primary motor cortex (M1) and recorded electromyographic activity from the first dorsal interosseous (FDI) muscle of both hands. We observed motor-evoked

potentials (MEPs) elicited in response to TMS in the FDIs both ipsilateral and contralateral to the stimulated M1, although the magnitude observed on the ipsilateral FDI was substantially smaller than that observed on the contralateral FDI. Following that, we had the subject perform targeted reaching movements first with the left arm under a novel visuomotor condition in which the visual display was rotated 30 degrees counterclockwise about the start circle, and then with the right arm under the same visuomotor condition. The results showed that initial adaptation with the left arm did not facilitate subsequent performance with the right arm at all, in terms of either the initial amount of transfer or the rate of adaptation. This finding is surprising, given that neurologically intact adults have demonstrated approximately 50% of transfer from the left to the right arm under the same visuomotor condition (cf. Lei and Wang, 2014). Based on the finding that the magnitude of ipsilateral MEPs was substantially smaller than that of contralateral MEPs, this subject seems to have adapted to his condition (i.e., MM) by learning to unconsciously inhibit ipsilateral corticospinal projection, so that he can perform activities of daily living that requires asymmetrical bilateral movements. Indeed, this subject is capable of performing asymmetrical bilateral movements without too much difficulty. Such adaptation to the given condition, in turn, may have influenced the way information is transferred between the two limb/hemispheric systems, thus resulting in lack of interlimb transfer.

Disclosures: S. Bao: None. **A.M. Morgan:** None. **J. Wang:** None.

Poster

492. Voluntary Movements: Finger and Grasp Control: Age, Pathology, and Physiology

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Title: Effect of coil orientation on motor evoked potentials examined during grasping

Authors: *H. JO[1,2], M. A. PEREZ[1,2]
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Abstract: We recently showed that the latency of corticospinal responses elicited by different orientations of the transcranial magnetic stimulation (TMS) coil change after spinal cord injury (SCI). The extent to which these differences are preserved during behaviorally relevant motor

behaviors after the injury remains unknown. Here, we used TMS over the hand representation of the motor cortex to elicit motor evoked potentials (MEPs) in an intrinsic finger muscle during precision grip and power grip in humans with and without (controls) cervical incomplete SCI. The TMS coil was oriented to induce currents in the brain in the latero-medial (LM) direction to activate corticospinal axons directly and in the posterior-anterior (PA) and anterior-posterior (AP) directions to activate the axon indirectly through synaptic inputs. We found prolonged MEP latencies in individuals with SCI in all coil orientations and in both tasks compared with controls. The latencies of MEPs elicited by AP relative to LM stimuli were consistently longer during power grip compared with precision grip in controls but not in SCI participants. PA relatively to LM MEP latencies were shorter in SCI than controls but similar between tasks across groups. Our results demonstrate that differences between corticospinal responses elicited by AP and PA induced currents during grasping behaviors were not preserved in humans with SCI and suggest that neural structures activated by AP currents, which are particularly relevant for power grip in uninjured controls, changed largely after the injury.

Disclosures: H. Jo: None. **M.A. Perez:** None.

Poster

492. Voluntary Movements: Finger and Grasp Control: Age, Pathology, and Physiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 492.10/OO9

Topic: E.04. Voluntary Movements

Support: NIH Grant R01NS076589-01
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VA Grant I01RX001807

Title: Changes in the silent period evoked by transcranial magnetic stimulation during different coil orientations

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Abstract: A motor evoked potential (MEP) elicited by transcranial magnetic stimulation (TMS) during voluntary activity is followed by a silent period (SP). Although it is known that the duration of the SP is prolonged in humans with spinal cord injury (SCI), the neural mechanisms contributing to this effect remain unknown. To address this question, we used TMS over the hand representation of the primary motor cortex to generate input-output MEPs recruitment curves in an intrinsic finger muscle using posterior-anterior (PA) and anterior-posterior (AP)

induced currents in the brain during isometric index finger abduction in humans with and without chronic cervical incomplete SCI. We found that the duration of the SP elicited by PA and AP currents was prolonged in SCI compared with control subjects in the ascending part of the recruitment curve but similar at higher stimulus intensities. The size of MEPs elicited by PA and AP currents was positively correlated with the duration of the SP in both groups in the ascending part of the recruitment curve but not at higher intensities. MEPs elicited by AP compared with PA currents have longer SP duration in controls but not in humans with SCI, regardless of the stimulus intensity. Our findings show that differences in SP duration elicited by AP and PA induced currents were not preserved in humans with SCI, supporting the view that neural structures activated by AP currents largely change after SCI.

Disclosures: F.D. Benavides: None. **M.A. Perez:** None.

Poster

492. Voluntary Movements: Finger and Grasp Control: Age, Pathology, and Physiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 492.11/OO10

Topic: E.04. Voluntary Movements

Support: NIH Grant UL1 TR002014 and KL2 TR002015
Social Science Research Institute at Penn State Grant
Young Investigator Award from the Brain & Behavior Research Foundation

Title: Grip force output is related to somatosensation and self-reported ADHD symptoms in young women with and without ADHD

Authors: *J. TUCKER[1], A. N. MERIDA, 16802[2], C. R. N. DAHM, 16802[3], A. J. N. GROFF, 16802[3], D. DIMERCURIO, III[4], N. ETTER[4], K. A. NEELY[5]
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Abstract: The goal of this work was to examine how grip force output is related to tactile somatosensation in young women with and without Attention-Deficit/Hyperactivity Disorder (ADHD). Previous work involving young women with ADHD is limited, possibly because many women are not diagnosed until late adolescence or adulthood. This work is motivated by previous investigations from our group that demonstrate that adults with ADHD produce more force than adults without ADHD during visually guided grip force (Neely et al., 2016; Neely et al., 2017). Here, we extend that work by evaluating visually guided grip force at seven force amplitudes in concert with tactile somatosensation at the finger, thumb, and palm. Consistent with our previous work, we hypothesized that women with ADHD would produce more force

than women without ADHD. We further hypothesized that those that produced more force would have reduced tactile somatosensation. Thirty-nine female participants (19 ADHD), were recruited from a larger ongoing study. Participants produced force during four 30-second blocks. Within each force block, participants produced force for 4s separated by 2s of rest, for a total of five trials within each block. Participants completed seven force amplitude conditions ranging from 5% to 50% of their precision grip maximum voluntary contraction. Somatosensory assessments included tactile detection and discrimination threshold estimates, as well as two-point discrimination. The results demonstrated that women with ADHD produced more force than women without ADHD in 6 of the 7 amplitude conditions. A trend was observed such that women with ADHD had a slower rate of force production compared to females without ADHD. We then evaluated bivariate correlations between mean force, the rate of force production, tactile somatosensation, and self-reported ADHD symptoms. Participants with a slower rate of force production in the 5% MVC condition had larger two-point discrimination thresholds for the right index finger. Similarly, participants that produced higher force in the 10, 30, and 40% MVC conditions had larger two-point discrimination thresholds for the right index finger. Further, slower rates of force production, and larger overall force output, were associated with more severe ADHD symptoms. These findings suggest that a slower rate of force production and greater force production may be due to reduced tactile somatosensation in the index finger. Additionally, slower rates of force production and higher overall force output may be reliable quantitative measures to indicate the severity of ADHD in young women.

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Poster

492. Voluntary Movements: Finger and Grasp Control: Age, Pathology, and Physiology

Location: SDCC Halls B-H

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Topic: E.04. Voluntary Movements

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Title: Functional brain mechanisms of sensorimotor control in individuals with autism spectrum disorder

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Abstract: Background: Socio-communicative deficits and restricted, repetitive behaviors and interests comprise the core diagnostic features of autism spectrum disorder (ASD). However, abnormalities in sensorimotor behavior are also present in the majority of individuals with ASD and associated with a variety of clinical issues, including social and cognitive deficits. Cortico-cerebellar and cortico-striatal networks that control sensorimotor behavior have been implicated in ASD, but little is known about the functional alterations that contribute to these atypicalities. The purpose of this study was to identify differences in patterns of neural activation during feedback-guided motor behavior in ASD compared to typically developing controls.
Methods: Individuals with ASD (11-30 years; N = 18) and age-matched controls (N = 15) completed a visuomotor task of feedback-guided precision gripping during fMRI. Participants pressed with thumb and forefinger on a force transducer while viewing a white FORCE bar on a screen that moved upwards with increased force toward a fixed green TARGET bar and were instructed to maintain FORCE at TARGET level for 24 seconds. Force levels were set at 20% and 60% of the participant's maximum voluntary contraction (MVC).
Results: Participants with ASD showed increased force variability compared to controls only at 60% MVC (p = .049, d = .74). Across force conditions, ASD participants showed increased activity in the cortico-cerebellar visuomotor network for regions involved in sensory (S1, PPC), motor (M1), and sensory-feedback (cerebellum) processes, even in the absence of increased motor error (20% MVC), suggesting hyper-reactivity of this circuit to visual sensory information. ASD participants also showed greater activation in regions supporting internally-guided motor behavior (putamen, SMA).
Conclusions: Increased force variability during force output in ASD suggests impaired processing of visual sensory feedback to guide precision motor behavior, converging with imaging results that suggest hyper-responsivity of sensory processing and sensory feedback cortico-cerebellar circuits. This dysregulation of cortico-cerebellar circuitry may result in a decreased ability to effectively utilize sensory feedback information and therefore greater reliance on internally-generated mechanisms, including those supported by fronto-striatal brain systems. Our findings that brain mechanisms involved in continuous sensory processing are hyper-active during basic precision motor behaviors indicates sensory hyper-reactivity in ASD also may contribute to deficits of more complex motor and non-motor mechanisms.

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Poster

492. Voluntary Movements: Finger and Grasp Control: Age, Pathology, and Physiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 492.13/OO12

Topic: E.04. Voluntary Movements

Support: Young Investigator Award from the Brain & Behavior Research Foundation
NIH Grant UL1 TR002014 and KL2 TR002015

Title: Brain morphometry differences associated with sex and ADHD symptom severity in young adults

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Abstract: Previous work examining brain structure in Attention-Deficit/Hyperactivity Disorder (ADHD) is inconsistent and focuses mainly on children and adolescents. Further, work examining adults often uses a large age range. The current work examines brain structure and symptom severity in young adults ages 18 to 25. The goals of this project were to examine 1) potential atypicalities in the volumetric properties of motor and sensory cortical regions in young adults with ADHD; 2) whether such atypicalities are associated with self-reported ADHD symptoms; 3) if these effects are modulated by biological sex. ADHD was confirmed using a semi-structured interview and the Connors' Adult ADHD Rating Scale (CAARS). Ninety-six participants (49 ADHD, 47 non-ADHD controls) were scanned with MRI to generate T1-weighted high-resolution structural images (192 volumes, 1 mm^3 voxels). The images were reconstructed, preprocessed, and parcellated using Freesurfer. We extracted volume, thickness, and area for cortical regions, and total volume of subcortical structures. We conducted a 2 (Male, Female) by 2 (ADHD, CTRL) multivariate analysis of variance to identify possible interactions between sex and diagnosis. Volumes in the left pallidum and medial orbitofrontal cortex and right pars opercularis were larger in adults with ADHD than adults without ADHD. Critically, there was a positive association between volume in the left medial orbitofrontal cortex and symptom severity as indexed by the CAARS subscales for Inattention/Memory Problems, Hyperactivity/Restlessness, and ADHD Index. Unlike previous findings, non-ADHD controls exhibited greater thickness in right medial orbitofrontal cortex and volume across all subcortical regions measured than ADHD adults. This is relevant because there was a negative relation between subcortical volume and symptom severity as measured by the three subscales of the CAARS. We observed an interaction between diagnosis and sex for left pars orbitalis thickness, right frontal pole volume, and right frontal pole area. Independent samples t-tests for sex differences within diagnostic groups revealed that frontal pole volume and area were greater for

females than males, only among adults with ADHD. In contrast, left pars orbitalis volume was greater for males than females in adults without ADHD. This work reveals notable differences in volumetric properties of regions related to motor and sensory function, which may be indicative of symptom severity. Most important, this work demonstrates the need to include males and females to evaluate the interaction between sex and diagnosis in ADHD.

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Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 493.01/OO13

Topic: E.04. Voluntary Movements

Title: piReach: An open source, automated skilled reaching task platform

Authors: *S. LEEMBURG
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Abstract: ***Aims:*** Skilled reaching tasks, such as single pellet reaching and the pasta matrix, are widely used to assess fine motor function in rodents. These tasks reliably show motor deficits in rodent models of brain damage and neurodegeneration, but training and testing the animals and performing detailed, objective quantification of their forelimb movements is very labor intensive. piReach is a low-cost, open source system for automated and standardized testing and quantification of rat forelimb function in these tasks.
Methods: piReach consists of a wifi-enabled module that houses of a pasta matrix or single pellet reaching task and 3 cameras for high-speed video recording of forelimb movements. This module is connected to a PC serving as a control hub for multiple reaching modules, showing real-time training results for each cage. A separate software package can then be used for offline quantification of reaching movements.
Results: The system automatically detects successful or failed reaching attempts and blocks access to the reaching target when a predetermined number of trials is completed or when the maximum training duration has been reached. Reaching success, forelimb trajectories, speed and accuracy are then calculated for each trial.
Conclusions: piReach enables transparent and replicable behavioral analyses, as well as high-throughput training and testing in rodent skilled reaching tasks. The system allows researchers to perform sophisticated quantification of forelimb movements, without requiring extensive computational experience or expensive equipment.

Disclosures:

Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 493.02/OO14

Topic: E.04. Voluntary Movements

Support: NSF CRCNS #1308159 (RW)
NIH R01 NS091010A (TK)
McKnight Scholar Award (TK)

Title: Heterogeneous correlation between neural activity in motor cortex and aspects of movement reorganizes during learning

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Abstract: Neural circuits in motor cortex are known to reorganize during motor learning. Such reorganization raises important questions concerning (i) the dynamics, coordination, and stability of neural activity in recurrent cortical circuits, and (ii) the potential malleability and degeneracy of the relation between neural activity and different aspects of movement.
To address the two questions, we monitored via population calcium imaging the activity of pyramidal neurons in L2/3 and L5 of both primary (M1) and premotor (M2) cortex of head-fixed mice during motor learning. Specifically, we trained water-restricted mice daily for up to 50 minutes/day on a lever-press task for approximately 14 days, during which the activity of the same neuronal populations was recorded. We obtained the discrete calcium events and the inferred spike probability from approximately 200 neurons per mouse for the duration of each recording/training session. We analyzed the population activity with respect to (i) changes in the statistical properties of neural activity and network states, and (ii) the relation between motor cortex neural activity and movement parameters, such as lever position, velocity and speed. These analyses revealed two important features of motor cortical activity.
First, population activity rearranged during motor learning. The correlations among pairs of pyramidal neuron activity changed across motor learning sessions. Concurrently, cortical circuits maintained the overall network state, as evaluated with respect to criticality using neuronal avalanche analysis.
Second, the correlation between motor cortex neural activity and lever movement parameters, such as position, velocity, and speed, was significantly heterogeneous across neurons, and changed across learning sessions, (In addition, the number of movement-related neurons increased with learning. Despite the observed heterogeneity, changes, and differences in cortical activity, all tested subjects performed similarly well in learning the lever-press task, as quantified

by the number of obtained rewards.
In conclusion, these results support the hypothesis that neural activity in cortical circuits rearranges during learning within the constraint of a stable network state, yet with a vast number of activity configurations at its disposal that each is consistent with a given behavior. It is tempting to speculate that the observed neural diversity may assist populations of neurons to combine different functions more flexibly to execute motor action.

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Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

Location: SDCC Halls B-H

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Program #/Poster #: 493.03/OO15

Topic: E.04. Voluntary Movements

Support: MEXT/JSPS KAKENHI Grant Number 16K16421

Title: The effect of forced limb training for recovery of motor paralysis in a photochemically induced thrombosis model of cerebral ischemic stroke in rats

Authors: *C. SATO[1], K. AKAHIRA[1], S. KOEDA[1], K. SUMIGAWA[1], M. MIKAMI[1], J. YAMADA[2]
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Abstract: Ischemic stroke often causes hemiplegic motor dysfunction, greatly impairing patient quality of life. Post-stroke rehabilitation can reduce the degree to which physiological and neurological function is impaired. A number of rehabilitation strategies exist. For instance, constraint-induced movement therapy is regarded as an effective treatment for impaired upper limb movement after stroke in humans and animals. Additionally, the forced impaired limb use (FLU) task has been found to improve neural function, while the reaching task component of the motor skills training (MST) program has been found to promote neural plasticity in the central nervous system. Despite the variety of approaches, the optimal method for treating motor dysfunction has not been established. Furthermore, few studies have examined the associated mechanisms of neural change in ischemic stroke models. The aim of this study was to investigate the effects of the FLU using the MST for upper limb function in a rodent model of cerebral ischemic stroke. We positioned deeply anesthetized male SD rats in a stereotaxic device and performed a craniotomy to open a window in the skull. After an intravenous administration of rose bengal through the caudal vein, we conducted photo illumination with a 540-nm green laser directed at the brain area controlling upper limb function. The beam of light was delivered

through the dura mater for a duration of 10 min. The rats were divided into three groups: a non-exercise group (non-Ex. group, n = 9) and two exercise groups. One of the exercise groups was trained using the single-pellet reaching and FLU tasks (FLU+MST group, n = 9), and the other group was trained using only the FLU task (FLU group, n = 9). Rehabilitation took place on days 4-10 after the surgery. We assessed motor function using the wire hang test, forelimb-placing test, beam-walking test, and single-pellet reaching test. All tests were performed before surgery and at day 1, 4, 10, 14 after surgery. The animals in all groups were severely paralyzed on day 1 after surgery. Data from the beam-walking test, which served as an assessment of hindlimb function, indicated no differences among the groups after rehabilitation. The scores on the wire hang and forelimb-placing test were higher in the FLU+MST group compared with the FLU and non-Ex. groups ($P<0.05$). These data indicate that the FLU+MST promotes recovery of upper limb function. Particularly, the MST appears to be effective for treating gross motor dysfunction but not fine motor dysfunction.

Disclosures: C. Sato: None. **K. Akahira:** None. **S. Koeda:** None. **K. Sumigawa:** None. **M. Mikami:** None. **J. Yamada:** None.

Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 493.04/OO16

Topic: E.04. Voluntary Movements

Support: L'Oreal USA For Women in Science

Title: A center-out sequence task for studying multiple multiple forms of motor learning in non-human primates

Authors: *A. L. ORSBORN, B. PESARAN
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Mastering a motor skill involves different forms of learning distributed across the brain. Understanding the brain mechanisms of motor learning therefore depends on analyzing behaviors with multiple co-occurring learning mechanisms in concert with neural recordings spanning large neural networks. We present a task for non-human primates to parse multiple learning mechanisms. Analyzing behavior in such a task can go beyond identifying a single form of learning to differentiate potentially distinct learning mechanisms. Primate behavioral models combined with large-scale neural measurements and manipulations can then facilitate investigation of underlying neural mechanisms. Sequence learning is hypothesized to involve both action selection learning (identifying the order of actions) and execution learning (refining the movements themselves). Existing work suggests these are distinct forms of learning mediated

by different neural circuits. We trained one monkey (macaca mulatta) on a form of the serial reaction time task, which is a center-out variation of the sequence task from Matsuzuka et al. 2007. At the start of each trial, a grey target array (center and 7 peripheral targets spaced in a circle) was presented on a touchscreen. The monkey was trained to make a series of 3 center-out reaches to receive a reward. Sequence elements were cued by color changes. Targets could be acquired prior to cues. Cue timing was used to encourage sequence learning and probe sequence order knowledge. Motor execution of sequence elements were studied using motion tracking of 5-8 retroreflective markers placed on the monkey's arm and hand. Initial training employed a task condition in which peripheral targets were randomly chosen and cued with short delays (150-200 ms). Subsequent training employed a condition with predictable sequences of peripheral targets with interleaved short and long (up to 1500 ms) cue delay trials. Cue colors were changed between conditions. Over 6 daily training sessions, the fraction of targets acquired prior to the cue increased from 22.7% to 60.5%, reflecting explicit sequence learning. Median trial execution times decreased from 5.78 ± 0.14 s to 3.20 ± 0.03 s, which may be due to both sequence knowledge (i.e. not waiting for the cue) and motor execution improvements (increased speed). We will present analyses of movement kinematics (reach speed, accuracy) and task behavior to test whether execution-related improvements are distinct from acquisition of the sequence. Dissociating behavioral measures of learning, in concert with large-scale neural recordings, will provide insights into how neural circuits support distinct forms of learning.

Disclosures: A.L. Orsborn: None. **B. Pesaran:** None.

Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 493.05/OO17

Topic: E.04. Voluntary Movements

Support: DARPA Targeted Neuroplasticity Training

Title: Temporally precise vagus nerve stimulation (VNS) enhances motor learning and performance of a skilled forelimb reach task

Authors: *J. L. HICKMAN, X. PENG, D. DONEGAN, C. G. WELLE
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Abstract: Vagus nerve stimulation (VNS) paired with execution of a motor behavior has been shown to increase cortical plasticity and improve rehabilitation following motor impairment. However, the influence of temporally-paired VNS on motor outcomes in healthy animals has not been fully explored. Here, we implement a novel chronic VNS mouse model to study the effects on motor learning in a healthy animal. Wildtype C57B6 mice were implanted with a flexible

silicon cuff with an internal diameter of 100 µm (Cortec, MicroSling) on the left cervical vagus nerve. Following a two-week recovery, mice were trained to perform a dexterous forelimb reach to obtain a food pellet. VNS (30 Hz, 0.3mA, 100 µs pulse width) was applied immediately following a successful completion of a reach during either the learning process (n = 5) or in an animal already proficient in the task (n=5). To investigate the circuit mechanism responsible for effects of VNS on skilled motor learning, a separate cohort of mice expressing an immediate-early gene-driven(cfos) destabilized GFP (B6.Cg-Tg(Fos-tTA,Fos-EGFP*)1Mmay/J; n = 3) received VNS, and brain and brainstem tissue were collected 1 hour later. In a third experiment, alterations to cortical circuit dynamics during VNS were investigated in mice expressing a calcium indicator in motor cortex neurons (C56BL/6J-Tg(thy1-GCaMP6 GP5) imaged while freely-moving using a miniscope (UCLA Miniscope).
VNS paired with reach success increases performance throughout all phases of learning: early (days 1-4, $p<0.001$), middle (day5-9, $p<0.05$), and late (10-14, $p<.01$). In addition, paired VNS improves the performance of the dexterous reach in previously trained animals by 20% ($p<0.001$). Histological analysis of cfos expression shows neuronal activation in NTS (where vagal afferents terminate), locus coeruleus (a noradrenergic nucleus) and basal forebrain (a cholinergic nucleus), suggesting that VNS may mediate motor learning through activation of ascending cholinergic and/or noradrenergic afferent projections. Analysis of neuronal firing during VNS revealed decorrelated spiking in superficial motor cortex neurons. These results suggest that temporally-paired VNS can influence the learning and performance of a skilled motor task, and this effect may be mediated by neuromodulatory influence on motor cortex circuit dynamics.

Disclosures: J.L. Hickman: None. **X. Peng:** None. **D. Donegan:** None. **C.G. Welle:** None.

Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

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Program #/Poster #: 493.06/OO18

Topic: E.04. Voluntary Movements

Support: SUNY Geneseo Foundation Grant

Title: Sex differences in paw-reaching behavior of mice

Authors: M. A. BRADY[1], J. C. BOYER[2], *D. R. MCPHERSON[4], T. BAZZETT[3]
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Abstract: Reach-to-grasp tasks are commonly used in rodent models to study coordinated motor skills as affected by neurodegenerative disorders and stroke. The present study examined sex

differences in mouse (*Mus musculus*) paw reaching behavior using a novel automated operant chamber. This particular chamber is designed to quantify latency to begin reaching, total reach attempts, successful pellet retrieval, and total number of pellets consumed. Operant measures were collected from male (n=20) and female (n=16) C57BL/6J mice beginning at 18 weeks of age and continuing through adulthood. Tests were conducted as 15-minute sessions, twice per week. Our preliminary results show that males perform significantly better than females in all measures. Similar sex differences in more rudimentary reach-to-grasp tasks have been previously reported, and they suggest that sex-related differences may become amplified when the age at which operant training begins is increased. Sex differences have also been observed in some human neurodegenerative disorders that are marked by impaired motor function. For example, females who inherit the gene allele responsible for Huntington's disease (HD) are typically diagnosed with symptoms at an earlier age than their male counterparts. In contrast, Parkinson's disease (PD) is more prevalent among males than females. Mouse models for such neurodegenerative disorders are frequently used for experiments in which researchers attempt to quantify the motor skill declines resulting from brain lesions, genetic aberrations, and normal aging. The present results suggest that sex differences may be pertinent to the interpretation of those experiments, and particularly when using skilled limb movement analysis such as the reach-to-grasp task. Additional studies are currently underway to assess correlations between paw reaching behavior and grip strength measures in these mice. Future research using these techniques will be designed to evaluate motor decline and sex differences in mouse models of HD and PD.

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Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

Location: SDCC Halls B-H

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Program #/Poster #: 493.07/PP1

Topic: E.04. Voluntary Movements

Support: NINDS-NS093002
PRESTO
JSPS KAKENHI

Title: Genetic and functional dissection of corticospinal circuit for skilled motor behavior

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Abstract: The corticospinal (CS) circuit is an essential neuronal pathway for voluntary and skilled movements. However, its organizational and functional connectivity still remains unknown. Here we map the connectivity between CS neurons and various spinal interneurons in mice, and demonstrate that distinct CS-interneuron circuits control specific aspects of skilled movements. By using a set of neuronal tracers and genetically modified mice, we identify subpopulation of CS neurons which have different cortical locations and connectivity. Especially, the neurons positioned in the medial motor and lateral sensory cortex project axons topographically to the ventral and dorsal areas of the spinal cord, respectively. Each CS fiber subtype has connections with specific types of genetically encoded spinal interneuron. CS neurons in the motor cortex innervate axons onto premotor interneurons including Chx10+ V2a neurons, whereas sensory CS neurons connect with sensory-related neurons including Vglut3+ dorsal interneurons . Ablation or chemogenetic inhibition of neuronal population involved in the motor and sensory CS circuits exhibits different deficits during reaching and grasping behaviors. These findings reveal that CS neurons in the motor and sensory cortex differentially control skilled movements through distinct CS-spinal interneuron circuits. Our results indicate that the CS circuit is a neuronal complex integrating multiple functional modules to conduct fine skilled movement.

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Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 493.08/PP2

Topic: E.04. Voluntary Movements

Title: Cell type specific computations performed in primary motor cortex

Authors: *J. SCHILLER[1], S. LEVY[1], M. LAVZIN[1], O. BARAK[1], H. BENISTY[1], R. TALMON[2], R. MEIR[2], A. HANTMAN[3]
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Abstract: The primary motor cortex (M1) is the final cortical output region important in motor planning and execution of movements. A main challenge is to bridge the gap between formal descriptions in the language of system's motor control theory, and the actual mechanistic biophysical understanding of sensory-motor coding. Towards this end we developed an

integrated unique experimental setup combining a rich behavioral paradigm of head-fixed hand-reach motor tasks, chronic optical calcium imaging measurements of network and dendritic activities in identified neuronal subtypes and opto- and chemogenetic tools. Importantly, we access key cellular network elements according to their projection targets using novel viable functional retrograde viral vectors. We characterized the coding of layer 2-3 and layer 5 pyramidal track (PT) neurons during the hand reach motor task. We find that while the activity of PT neurons was mostly movement related, the activity of layer 2-3 neurons was both movement and sensory parameter related.

Disclosures: J. Schiller: None. **S. Levy:** None. **M. Lavzin:** None. **O. Barak:** None. **H. Benisty:** None. **R. Talmon:** None. **R. Meir:** None. **A. Hantman:** None.

Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 493.09/PP3

Topic: E.04. Voluntary Movements

Support: PP00P3_150683

Title: Circuit investigation of the GABAergic neurons of the zona incerta

Authors: *Z. LI, A. MERLI, K. TAN
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Abstract: The diencephalic Zona Incerta (ZI) is a region where investigations has been largely neglected over the past century. Recent anatomical tracing studies show direct projections from the ZI to the centers of many (dopaminergic, noradrenalinergic, and serotonergic) neuromodulatory systems, highlighting its potential importance in influencing locomotion, motivational behaviors, and arousal. Past investigations suggested that the ZI could promote ingestive and locomotor behaviors. However, these findings are still controversial given the crude nature of the manipulations, the lack of targeting specificity, and the proximity to the hypothalamus and the subthalamic nucleus, which have been extensively shown to influence both behaviors respectively.
One of the main obstacles in investigating the ZI is its highly heterogenous cell populations, which could be overcome by advancements in transgenic lines and viral targeting approaches. Here, we investigate the most populous GABAergic neurons. Using cell type specific reporter lines and molecular assays, we examine the localization of different GABAergic markers across the ZI. By selectively expressing viral tracers labeled with fluorescent proteins in cell type specific transgenic mice lines, specific connectivities of ZI GABAergic neurons can be identified. Lastly, optogenetic manipulations of ZI GABAergic neurons are used to elucidate its

functional role in behavior. Collectively, our systematic approach provide insights on the ZI GABAergic neurons across many levels.

Disclosures: Z. Li: None. **A. Merli:** None. **K. Tan:** None.

Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 493.10/PP4

Topic: E.04. Voluntary Movements

Support: SNSF PP00P3_150683

Title: Genetic and functional characterization of rubral pathways

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Abstract: The Red Nucleus sustains the integration and correct modulation of somatosensory feedback and fine motor coordination. Although two anatomical sub-divisions have been identified (magnocellular and parvocellular segments) and participate in segregated afferent and efferent circuits, a characterization of different cell classes within the Red Nucleus at a genetic and functional level is lacking. Using single molecule mRNA in situ fluorescent hybridization (smFISH) we have identified a rubral cell population that while expressing the calcium binding protein parvalbumin (PV) it largely co-expresses the excitatory Vesicular glutamate transporter (Vglut2). At the anatomical level the boundaries of this cell cluster are markedly delineated by the encircling expression of the inhibitory Vesicular GABA transporter (Vgat). Optogenetic activation of Vglut2 rubral neurons induces robust postural deficits and heavily impairs locomotion, whereas optical ablation of the Red Nucleus severely impairs fine motor coordination leaving locomotion marginally affected. Pathway specific modulation of Vglut2 containing rubral neurons could prove instrumental in ameliorating motor deficits characterized by abnormal muscle tone and dyskinesias in pathological conditions resistant to classical Parkinsonian syndrome treatments.

Disclosures: G. Rizzi: None. **M. Coban:** None. **A. Merli:** None. **M.A. Ocaña:** None. **K. Tan:** None.

Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 493.11/PP5

Topic: E.04. Voluntary Movements

Support: NIH
DARPA
Simons
HHMI

Title: Signatures of proprioception and vision relevant to corrective motor responses in primate

Authors: *T. FISHER[1], E. M. TRAUTMANN[2], X. SUN[1], D. J. O'SHEA[1], S. RYU[3], K. V. SHENOY[4]
[1]Stanford Univ., Stanford, CA; [2]Stanford Neurosciences, San Francisco, CA; [3]Dept Neurosurg, Palo Alto Med. Fndn., Palo Alto, CA; [4]EE, BioE & Neurobio., Howard Hughes Med. Inst. - Stanford Univers, Stanford, CA

Abstract: Visual and proprioceptive feedback are both crucial for motor control. Differences in primary motor cortex (M1) and premotor cortex (PMd) response latencies provide some indication that proprioception and vision have unique roles in guiding corrective movements. However, how these complementary signals may be separately encoded in the motor cortical areas is not well understood.
Here, a rhesus macaque (U) was trained to maintain a cursor within a centrally located visually defined target by manipulating a haptic device. Following either a mechanical perturbation or a cursor jump, corrections were required to complete a successful trial. We recorded neural activity from three 96 channel Utah arrays implanted in M1 and PMd.
We designed this task to leverage the consistent neural response latency difference between these two modalities. Perturbation trials were either combined mechanical and visual, or visual only. Critically, firing rate changes in these motor areas after a mechanical perturbation begin at ~20ms, leading the responses to a visual perturbation which begin at ~150ms. This task design has the following advantage: activity just following a combined perturbation is primarily mechanical, whereas activity just following a visual perturbation is predominantly visual.
We found neural population dimensions that separate activity by perturbation modality using dPCA. In order for our analysis to be agnostic to the fixed latency difference between modalities we aligned activity to the neural response onset following the perturbation. We found that they are very similar. A dPC that explains over 40% of the total variance is modality-independent suggests a common signal shared by both modalities.
However, dPCA also isolates dimensions capturing modality-specific variance which differs

between visual and mechanical perturbation responses. This indicates that visual and mechanical errors are differentially encoded in motor cortical populations beyond simple differences in latency.
More broadly, this work can help to elucidate the mechanisms by which neural circuits can fuse information from diverse sensory modalities to facilitate dextrous feedback control.

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Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

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Program #/Poster #: 493.12/PP6

Topic: E.04. Voluntary Movements

Support: NIH
DARPA
Simons
HHMI
SIGF

Title: Systematic changes of neural population activity during curl force field adaptation

Authors: *X. SUN, D. O'SHEA, T. FISHER, M. GOLUB, S. RYU, K. SHENOY
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Abstract: Motor learning is thought to proceed as networks of neurons change their population activity in order to generate new behaviors. Previous neurophysiological studies of motor learning, using force-field adaptation paradigms, have characterized single neuron tuning properties in PMd and M1 and discovered that individual neurons adapt their responses to compensate for the learned force field[1, 2]. However, these single-neuron response changes are heterogeneous and hard to interpret mechanistically. Here, we explore the changes in neural population dynamics that underlie adaptation to curl force fields as well as the spatial generalization of adapted behaviors. We trained monkeys to adapt to a curl force field, active only during reaches to a single “adaptation” target in a ring of 12 targets. In addition, reaches to adjacent, non-adapted targets using an “error clamp” were interleaved with the curl field adaptation trials. Behaviorally, monkeys showed a Gaussian-like spatial generalization pattern: the level of hand force compensation decayed as a function of target angle away from the adaptation target. We recorded neural activity in PMd and M1 during adaptation and found gradual changes in population activity patterns both before movement initiation and during movement execution. First, within a 2D subspace of the overall neural population activity state

space, where preparatory activity is radially organized according to reach direction, the preparatory state for the adaptation target shifted towards that of the adjacent target opposite the direction of the curl field (as measured before adaptation). The preparatory states for nearby targets showed similar shifts towards their adjacent target states; the shifted amount diminished with a similar spatial profile as the behavioral generalization. Second, during adaptation, preparatory states for all targets shifted in a third dimension away from the baseline states. This result is intriguing because it also occurred for reaching targets far from the adaptation target for which no behavioral adaptation was observed. These findings are a first step towards identifying a mechanism for how neural population activity change systematically to facilitate adaptation to novel arm dynamics. This in turn may elucidate how neural circuits learn to adapt their activity patterns in response to changing task demands. [1] Li et al., 2001, Neuron. [2] Cherian et al., 2013, J. Neurophys.

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Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

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Title: Population dynamics of proprioceptive error signals in motor cortex

Authors: *D. J. O'SHEA[1], E. M. TRAUTMANN[2], S. RYU[3], K. V. SHENOY[4]
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Abstract: An expansive body of behavioral and neurophysiological evidence suggests that primary motor (M1) and dorsal premotor (PMd) cortices serve as key nodes in a brain network

that drives goal-directed feedback control. Mechanical perturbations of the arm evoke cortical responses within 20-50 ms which have been characterized in individual neurons (Evarts and Tanji, 1976; Pruszynski et al. 2014). However, the population structure of motor cortical responses to proprioceptive error remains poorly understood.

To address this question, we recorded simultaneously from 288 channels across 3 Utah arrays implanted in M1 and PMd in a macaque engaged in a center-out reaching task. The reaches were performed while holding the handle of a haptic feedback device. During a random subset of trials, we delivered a step-force mechanical perturbation through the device that pushed the hand along one of eight directions. Perturbations evoked robust responses in M1/PMd neurons (251/288 channels modulated within 100 ms, $p < 0.01$, ANOVA). These responses varied smoothly in magnitude with respect to perturbation direction. Across the population, perturbation-driven deflections in population neural trajectories were radially organized according to the direction of perturbation.

If error-evoked responses in motor cortex are structured so as to counteract applied forces, we would expect these responses to cancel out in opposite directions. Instead, averaged across the 8 perturbation directions, perturbations drove a net increase in most channels' firing rates (mean changes > 10 threshold crossings/sec in 179 / 251 modulated channels). Across the neural population, perturbation direction-independent changes captured > 50% of the variance of the total evoked responses. A single dimension identified with DPCA displayed identical responses across all perturbation directions and captured > 20% of the total variance. This large, perturbation direction-independent response could facilitate generation of a corrective response to perturbation. It may play an analogous role in orchestrating corrective movements as the large reach-direction independent signal reported by Kaufman et al. (2016) may serve in initiating visually guided reaches.

Our results begin to elucidate the input-driven dynamic computations by which motor cortex participates in motor feedback control, beyond its relatively better-explored role in movement initiation and execution. More generally, perturbation experiments can help to dissect the mechanisms by which neural populations process sensory feedback to achieve dextrous behavior.

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Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

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Topic: E.04. Voluntary Movements

Support: NIH
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HHMI

Title: Neural population dynamics of motor preparation following rapid adaptation to modified reach forces

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Abstract: Movements are thought to be prepared prior to execution [1]. Numerous studies have illustrated the relationship between neural preparatory state and subsequent behavior [2-4]. In this study, we test the relationship between neural preparatory state and the muscle forces generated during a reach, following adaptation to modified environmental dynamics.
We trained rhesus monkeys to perform reaches with a robotic haptic device. In alternating blocks of 70-100 trials, we applied a velocity dependent drag force, opposing the direction of motion, requiring the monkey to rapidly update an internal model and generate approximately 2.5 times as much force as in non drag reaches. Following a block switch, we observe behavioral adaptation within 5-8 trials, and find significant behavioral differences on miscued trials delivered during drag and non-drag blocks. Together, these behavioral results indicate the monkey is preparing different reaches after adaptation.
We used demixed principal components analysis (dPCA) to look for dimensions in neural population state space during the preparatory period prior to movement that explain variance associated with the forces generated on a given reach. Surprisingly, this dimension explains only 0.8% of neural variance during preparation, compared with 21.7% variance explained by the dimension that best separates target location. At the level of individual multiunit channels, only 20 of 288 channels (6.9%) have significant but modest differences in delay period activity between reaches with a heavy drag and those without.
Despite a significant behavioral perturbation and rapid adaptation to external loads, we find only very small differences in delay activity prior to movement, suggesting that an updated internal model presumed to be present in the brain is not reflected robustly in PMd and M1 neural activity. These results help to constrain optimal feedback models of motor control, and suggest a less direct connection between neural preparatory state and muscle force than prior models.
[1] Tanji, J., & Evarts, E. V. (1976) [2] Crammond, D. J., & Kalaska, J. F. (2000)[3] Churchland et al. (2010) [4] Churchland, Santhanam & Shenoy (2006)

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Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

Location: SDCC Halls B-H

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Program #/Poster #: 493.15/PP9

Topic: E.04. Voluntary Movements

Support: NIH
HHMI
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Simons

Title: Motor cortical preparatory activity is causally involved in visuomotor learning

Authors: *S. VYAS[1], D. J. O'SHEA[2], E. TRAUTMANN[4], F. WILLETT[3], K. V. SHENOY[5]
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Abstract: Previous studies suggest that delay period activity in premotor cortex (PM) is critically involved in motor preparation. A recent study (Vyas et al., Neuron 2018) found that visuomotor learning is correlated with systematic changes in motor cortical preparatory activity. Despite such findings, the mechanism by which preparatory activity facilitates motor learning, if at all, remains unknown. Here, we causally disrupted delay activity in PM, to assess its role in visuomotor learning. We first hypothesized that additional time during the delay period could correlate with increases in speed of visuomotor learning. Consistent with this hypothesis, we found that monkeys adapted to a 45-degree visuomotor rotation faster if they were given more time to prepare during a delay period spanning 300-500ms before the go-cue ($p < 1e-3$). This benefit was only present if additional time was granted during the delay period, and not at any other point in the trial. Neural population analyses revealed that during learning, the motor system continually optimized the preparatory neural state intra-trial if additional time was given to prepare, in contrast to saturating quickly after target onset ($p < 0.01$). To causally evaluate these effects, we performed block-wise subthreshold intracortical microstimulation (ICMS) of PM delay activity right at the go-cue (333Hz, 60ms duration, bimodal pulses with 150us cathodal followed by 150us anodal pulses separated by 250us). We found that ICMS at the go cue was sufficient to disrupt and slow down learning ($p < 1e-5$). In separate sessions, we randomly interleaved ICMS and non-ICMS trials during learning, and measured per-trial learning progress, defined as the decrease in error on the current trial relative to the previous trial. Surprisingly, we found no difference in learning progress between ICMS and non-ICMS trials, but instead we found that trials which immediately followed ICMS trials showed significantly less learning progress than trials following non-ICMS trials ($p < 1e-3$). This suggests a mechanism where

ICMS of PM delay activity actually disrupts motor learning, rather than indirectly affecting learning by disrupting behavior on individual trials. To test whether any manipulation at all during the delay period is sufficient to disrupt learning, we performed ICMS at 300ms post-target onset followed by 350-600ms of additional delay time pre-go-cue. We found no disruption in learning, suggesting that allowing the network to reset the preparatory state post-ICMS abolishes learning deficits. Our results provide the first ICMS-causal evidence for the role of motor cortical preparatory activity in visuomotor learning.

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Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

Location: SDCC Halls B-H

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Topic: E.04. Voluntary Movements

Support: CDMRP130266

Title: Role of primary motor cortex in saccadic and vergence eye movements

Authors: *C. W. TYLER[1], L. T. LIKOVA[2]
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Abstract: Introduction. The eye movement control pathway is generally considered to be driven by signals from the Frontal Eye Fields (FEF) to the superior colliculus (SC) and thence to other subcortical oculomotor structures, with concomitant involvement of parietal regions such as the lateral intraparietal sulcus (LIPS). Unlike reaching hand movements, no involvement of primary motor cortex (M1) is generally recognized, although trace activation of M1 may be seen in in most functional MRI (fMRI) studies of eye movements. Here we ask whether the M1-specific activation shows differential properties relative to those of the FEF activation as a whole during saccadic and vergence eye movements. Methods. Functional MRI of human observers at 3T in a whole-brain paradigm, when morphed to the MNI 152 brain coordinates, was used to assess the activation in attentionally non-demanding tasks consisting of repetitive left-right saccade and near-far vergence (each involving only two eye muscles per eye). Results. 1) At least two M1 sites located within the overall face region showed differential activation during saccades and vergence. 2) There was no activation, or even suppression, in adjacent somatosensory (S1) sites, excluding any possibility of artifactual sulcal cross-talk from sensory stimulation of facial structures such as the eyelids during the eye movements. 3) While the inferior M1 site was

activated for both saccades and vergence, the superior M1 site was activated for vergence and suppressed for saccades. 4) In a L/R saccadic directional paradigm, the activation in the inferior M1 site was specific to saccade direction, whereas the FEF and the superior M1 site showed no directional specificity. Conclusion. Although the eye muscles represent only a very small proportion of the ~650 muscles of the body as a whole, our fMRI evidence suggests that local regions of the M1 homunculus mapping play an unrecognized, direction-specific role in oculomotor control, a function that is usually assigned to the FEF. The suppression seen during vergence is consistent with the fact that vergence movements are much slower than saccades, implying that the interocular coupling of the oculomotor control system is optimized for saccades to the exclusion of symmetrical vergence movements. Thus, vergence eye movements involve less-optimal brainstem circuitry requiring the saccadic control signals to be bypassed during vergence activation.

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Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

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Title: Emergence of neuron clusters in mouse motor cortex during learning

Authors: *K. LI, J. K. P. IP, M. SUR
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Abstract: The superficial layers of the mouse motor cortex is connected with both sensory areas and motor thalamus. It is essential for mouse motor learning, and both synaptic strength and temporal activity patterns have been found to change in the motor cortex following motor learning. However, it is yet unclear what computation is carried out in the motor cortex to facilitate learning, and what principle underlies the changes in motor cortex connectivity following learning. To examine the neuronal correlates of motor learning, we performed two photon Ca^{+} imaging of gCaMP6s- or jR-GECO-expressing neurons in the forelimb representation in the motor cortex of wildtype mice while training them on a simple lever push task with water restriction (Peters, Chan and Komiyama, 2014). The mice were trained to hold a lever still, then push it forward on an audio signal for water, or get punished with white noise and extra wait time.

During training, the mice first learned to start the push at the signal, then gradually refined the push trajectory to make a smooth “expert” push. When clustering the trials by dynamic time warping linkage of their trajectories, the “expert” push cluster started to appear around day 5 of training, and grew with training to include most trials towards day 14. The other clusters representing different push trajectories, while initially seen in similar numbers of trials as the “expert” push, gradually shrank in number and started to disappear after day 11. Wildtype mice were trained to perform the “expert” push reliably within two weeks, and we could track the same 20-30 layer 2/3 neurons between regular imaging sessions during training. We first examined the functional connectivity among tracked neurons as measured with “noise” correlations while the animal was not moving. The neurons initially increased the strength of both positive and negative noise correlations indiscriminately during training. From day 10 to day 13, the same time-period when the mice transitioned to use the “expert” push, two clusters formed among the recorded neurons, where correlations within clusters grew more positive and noise correlations grew more negative between the clusters. When classifying the neurons by their correlation with the “expert” push at the end of training, almost all neurons belonging to one cluster were push-correlated, while the other cluster had all neurons with negative or no correlation.
These results suggest that the reorganization of the motor cortex during learning involves the formation of neurons clusters with strong interconnections, which are also activated during movement.

Disclosures: K. Li: None. **J.K.P. Ip:** None. **M. Sur:** None.

Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

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Topic: E.04. Voluntary Movements

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NIH EY028219

Title: Patterns of astrocytic microdomain activity in the motor cortex during motor learning

Authors: *J. SHIH[1], C. DELEPINE[2], M. SUR[2]
[1]Brain and Cognitive Sci., MIT/Picower Inst. for Learning and Memory, Cambridge, MA; [2]Brain and Cognitive Sci., MIT/Picower Inst. For Learning and Memory, Cambridge, MA

Abstract: Excitatory neurons of the primary motor cortex (M1) function as part of neuronal ensembles, which are populations of neurons whose activity becomes correlated as an animal learns a stereotyped movement pattern. Astrocytes, the main type of glial cell in the cortex, have

been shown to respond to and influence neuronal activity by transiently increasing their intracellular Ca2+ levels. Astrocytic Ca2+ transients have diverse spatiotemporal characteristics and can spread through the entire astrocyte cell body or be limited to primary branches or fine processes. Emerging evidence suggests that different types of astrocytic Ca2+ activity are associated with different types of neuronal activity and signaling by different neurotransmitter systems. However, definitive correlation between astrocyte Ca2+ activity and defined patterns of neuronal activity has not been established. Here, we focus on Ca2+ microdomain activity in astrocyte fine processes, which are closely associated with synapses and are well-positioned to respond to and influence neuronal activity. We trained mice on an auditory tone-cued lever push task, a behavioral paradigm that incorporates associative learning aspect as well as the acquisition of a stereotyped motor movement. Manipulation of astrocyte mechanisms suggest that altered astrocytic Ca2+ signaling influences neuronal activity during motor learning, leading to decreases in task performance. We hypothesize that a stable pattern of M1 astrocyte Ca2+ activity in microdomains develops during acquisition of a stereotyped motor movement, is correlated with neuronal ensemble formation and motor learning, and is potentially causal for learning. We use chronic two-photon imaging of astrocyte Ca2+ microdomain activity *in vivo* to test this hypothesis and show that distinctive patterns of astrocyte microdomain activity emerge as an animal learns the lever push task. Our results so far suggest that Ca2+ activity in microdomains may encode an astrocyte "signature" that is associated with motor learning, and thus identifies a novel neuron-astrocyte interaction that occurs during motor behavior.

Disclosures: J. Shih: None. **C. Delepine:** None. **M. Sur:** None.

Poster

493. Voluntary Movements: Reaching Control: Motor Learning: Animal

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Topic: E.04. Voluntary Movements

Support: NIH EY007023
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Title: Critical contribution of astrocytes to motor learning *in vivo*

Authors: *C. DELEPINE[1], M. SUR[2]
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Abstract: Astrocytes, long thought to operate only as a support network for neurons, are now emerging as key players in the modulation of brain information processing. Astrocytes influence synaptic transmission via glutamate transporters, and respond to, as well as modulate, neuronal activity with calcium signaling. However, many questions remain in understanding the

contribution of astrocytes in vivo to complex behaviors and cognition. During motor learning, primary motor cortex (M1) is functionally and structurally reorganized. The learning of a new movement is associated with changes in neuronal activity and dendritic spine turnover. We hypothesize that astrocytes are modulators of learning-associated neuronal network reorganization by influencing synaptic strength through glutamate clearance and calcium signaling. Here we investigate the role and plasticity of cortical astrocytes in a motor learning, lever-push task *in vivo*. Using the engineered human muscarinic G protein-coupled receptor DREADD-hM3Dq activated by low doses of clozapine-N-oxide (CNO), we find that modulation of astrocyte calcium activity perturbs performance of the animal in the lever-push task (causing decreased lever push responses to a cue sound). Moreover, we use a transgenic mouse line in which the expression of the glutamate transporter GLT1 can be inhibited locally in M1 and show that decreasing astrocyte glutamate clearance prevents learning of smooth motor trajectory. Using genetically encoded calcium indicators and high-resolution two-photon imaging, we then show that perturbation of astrocyte calcium activity modulates the correlation structure of neuronal population activity. In contrast, GLT1 knockout increases neuronal activity and prevents the formation of correlated neuronal ensembles normally associated with the motor learning. This ongoing project utilizes cutting-edge imaging techniques, and novel technologies for manipulating astrocyte activity, to unravel astrocyte function during a physiologically relevant task involving motor cortex plasticity.

Disclosures: C. Delepine: None. **M. Sur:** None.

Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.01/PP14

Topic: E.06. Posture and Gait

Support: University of New Mexico OVPR Grant
University of New Mexico OFAC Grant

Title: Sustained effects of an exercise program on dynamic balance control

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Abstract: Balance control requires central processing of multi-sensory feedback and motor commands responsible for force production. An exercise program was designed to realign spinal curvature, and its effect on balance control immediately after the intervention was documented. To examine the efficacy of the exercise program on balance control over two weeks post-

intervention, the center of gravity (CoG) sway was measured. Subjects (n = 20) were randomly assigned into one of two groups: exercise on a cylinder-shaped tube (Ex-T group, n = 10), and a control group that rested on a flat surface (n = 10). The exercise program consisted of three preparatory positions and seven small motions, and each session lasted approximately 15 min. Subjects in the Ex-T group performed the exercise program twice a day for one week (Day 1-7), while those in the control group lay supine on a flat surface for 15 min twice a day, followed by one week of no intervention (Day 8-14). On Day 0, all subjects underwent baseline CoG sway measurement. On Day 1, CoG sway was measured immediately after either the intervention (Ex-T) or laying on a flat surface (Control). On Days 7 and 14, follow-up CoG sway measurements were taken. CoG sway was measured while standing on a balance system platform (Biodex Medical Systems, Shirley, NY, USA) under both static and dynamic conditions. During the static condition subjects were asked to stand still and the platform was held stationary (e.g., no tilt). During the dynamic condition the platform was allowed to tilt in response to changes of CoG and subjects were asked to maintain the platform in a horizontal position. Five trials of each test condition, for 20 s each were performed. The hypotheses were: a) the decrease in Ex-T group CoG sway on Day 1, 7, and 14 after the intervention would be significantly greater than in the Control group, and b) the decrease in CoG sway during the dynamic platform test condition would be significantly larger than during the static platform test condition.
Mixed-design ANOVAs were used to examine changes in average CoG sway and group differences. There were no significant changes in average CoG sway for the static platform condition. During the dynamic platform condition, CoG sway significantly decreased from baseline on Day 1, 7, and 14 in the Ex-T group ($p < 0.05$), but not in the Control group. These findings indicate that the 1-week exercise intervention improved dynamic, but not static balance control, and the improvement persisted after a 1-week cessation of the intervention. It is speculated that the exercise program enhances processing of sensory feedback and motor commands for dynamic balance control, which sustains without the intervention for 1 week.

Disclosures: D. Shibata: None.

Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.02/PP15

Topic: E.06. Posture and Gait

Support: NIH Grant P20 COBRE
NASA EPSCoR

Title: Inter-limb coordination patterns during external versus internal asymmetric tasks

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Abstract: Aging and pathology, e.g. strokes, may result in asymmetrical gait in the spatial and/or temporal domains. Asymmetrical walking patterns can be induced through several different tasks including unilateral limb loading and split-belt adaptation. However, these two methods induce asymmetrical walking patterns through different mechanisms. While unilateral limb loading (an external weight added to a limb), is perceived as one limb being heavier than the other (internal perception), the split-belt with the two belts of the treadmill moving at different speeds, is perceived as an external change. Determining how spatial and temporal components of gait are effected due to an internal versus an external coordination task may give important insight into developing rehabilitation programs for those with asymmetric sensorimotor abnormalities. In addition, Virtual reality (VR) affects various domains of gait, but it is unclear how VR affects spatial and temporal symmetry during asymmetrical walking.Thirty-eight young adults participated in this study. Twenty subjects walked on a treadmill while adapting to a unilateral limb load (5% of body weight) strapped to their left ankle. Another 18 subjects adapted to a split-belt treadmill paradigm. Half of all subjects were exposed to VR.To compare interlimb coordination, the symmetry index (SI) was calculated for step length and step time. The SI of any gait variable was defined as a ratio of the difference between the variable for the fast/loaded and slow/unloaded limbs to the sum of the variable for the two limbs. Three-way mixed model ANOVAs showed that limb loading and split-belt adaptation, both altered gait in the spatial and temporal domains (condition effect; $p<0.001$). However, the effect of each task on these domains were different ($p<0.05$). specifically, limb loading and split-belt effects during early and late adaptation were significantly different from each other. Limb loading and split-belt were similarly effected by VR for all comparisons except step time ($p<0.05$). When visual feedback was absent, transitioning from loaded to unloaded condition causes significant temporal effects on gait, however, optic flow through VR allows smoother transitions such that gait patterns are not significantly altered.

Disclosures: M. Mukherjee: None. **L. Bowman:** None. **T. Rand:** None.

Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.03/PP16

Topic: E.06. Posture and Gait

Support: JSPS KAKENHI 15H05359

Title: Quantifying the spatial smoothness of knee movement by a three-dimensional curvature

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Abstract: A novel evaluation method based on spatial smoothness has been proposed to quantify movement irregularities of the affected hand in stroke patients (Osu et al., J Neuroeng Rehabil 2011). In the present study, we investigated how to apply this method to the evaluation of knee motion. Four healthy participants participated in the pilot study. The participants sat on a chair and were asked to raise their knee (hip flexion) as fast as possible and as high as possible. This motion was repeated five times in a row. Three-dimensional (3D) coordinates of hemispherical markers attached to the lateral epicondyle of the femur (knee marker) and the greater trochanter (hip marker) were recorded at 60 Hz sampling rate using KinemaTracer (Kissei Comtec Co. Ltd., Japan). For the absolute coordinate position of the knee marker and the relative coordinate position of the same marker with respect to the hip marker, the 3D curvature at each time point was computed. The median of the -log of curvature (MLC), which indicates the spatial smoothness, was calculated in the flexion and extension phases of the knee, respectively. The differences of the mean MLC across the participants were investigated between the absolute and the relative coordinate positions, and between flexion and extension phases. All the participants showed higher MLC in the absolute coordinates than that in the relative coordinates and showed higher MLC in the extension phase than that in the flexion phase. In the absolute coordinates, MLC might be estimated highly because the change in the position of the knee might be contaminated with the movement of the whole body including the trunk. In the evaluation of the stroke patients, this contamination may be more pronounced because the patients often involve compensating trunk motion. Unlike the previous study which focused on the hand reaching motion in the horizontal plane, the knee motion is in the vertical direction. Therefore, participants can drop the knee simply by releasing force, and the motion might be estimated to be smoother in the hip extension phase, consequently. Since continuous force control is difficult for stroke patients, it is highly possible that they adopt the force release strategy in the extension phase. The evaluation of the hip extension phase may not accurately assess the spatial smoothness of the motion of stroke patients. These results suggest that it is important to focus on the flexion phase in the relative coordinates of the knee with respect to the hip in evaluating the spatial smoothness of the knee motion of stroke patients.

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Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.04/PP17

Topic: E.06. Posture and Gait

Title: Developmental changes in postural movement patterns during bilateral arm flexion in children

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Abstract: We investigated the developmental changes in postural movement patterns during bilateral arm flexion in children. A total of 174 subjects participated in this study from 4 to 12 years old (number of subjects (n): 4 years: n = 30; 5 years: n = 36; 6 years: n = 41; 7-8 years: n = 21; 9-10 years: n = 15; 11-12 years: n = 31). In response to a visual stimulus presented at 2-4 s after a warning signal, the subjects initiated the bilateral arm flexion as quickly as possible and then stopped their arms voluntarily at a horizontal position. After 5 practice trials, 10 test trials were performed. Movement angles of the trunk and leg joints during the arm flexion were analyzed, based on the small reflective markers placed over the following positions: head of the fifth metatarsal, external malleolus, knee, trochanter major, and vertebra prominence. Young children mainly extended the trunk rather than the ankle during the arm movement, while older children leaned the whole body backward. The postural movement patterns were categorized on the basis of the movement angle of the foot-leg and leg-trunk into the following three patterns: hip extension (HE), hip flexion (HF), and backward leaning (BL) types. More than half of children aged 4-6 years were categorized as HE (4 years: 76.7%; 5 years: 77.8%; 5 years: 61.9%). BL gradually increased from aged 7-8 years and older. The percentage distribution of each type at aged 11-12 years differed with younger children. The percentage of HF (41.9%) and BL (45.2%) were significantly larger than HE (12.9%). These results suggested that the postural movement pattern during bilateral arm flexion would change with age.

Age groups	Number		Postural movement pattern		
			HF	BL	HE
4	30	%	6.7	16.7	76.7
		Standardized Residual	-1.9	-0.5	1.9
5	36	%	16.7	5.6	77.8
		Standardized Residual	-0.4	-2.4	2.3
6	41	%	17.1	4.9	61.9
		Standardized Residual	-0.4	-2.8	2.6
7-8	21	%	9.5	28.6	61.9
		Standardized Residual	-1.2	1.0	0.1
9-10	15	%	20.0	40.0	40.0
		Standardized Residual	0.1	2.0	-1.7
11-12	31	%	41.9	45.2	12.9
		Standardized Residual	3.6	3.8	-6.0

Note：HF: Hip Flexion type; BL: Backward Leaning type; HE: Hip Extension type

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Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.05/PP18

Topic: E.06. Posture and Gait

Support: Parkinson Canada Pilot Project Grant #2014-726

Title: Detecting balance deficits in Parkinson's disease using a novel MRI compatible balance simulator

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Abstract: BACKGROUND AND AIM: Postural instability is a debilitating symptom of Parkinson's disease (PD) which is not alleviated by most pharmacological and surgical treatments for PD. Identifying the neural substrates contributing to postural instability in PD is made difficult by the need to be supine, or have the head fixed, for most neuroimaging techniques. Motor imagery offers a solution but has been shown difficult to use in PD patients [1] and may be limited for studying non-volitional sensorimotor tasks such as balance. Therefore, we aimed to develop and validate the use of an MRI compatible balance simulator to study static and dynamic balance control in PD patients and healthy controls.
METHODS: We developed an MRI compatible balance simulator (adapted from [2]) that allows subjects to actively balance an inverted pendulum by activating postural muscles around the ankle joint while supine (average load stiffness was 60% of normal stance). Two studies were performed to compare balance performance between upright stance (US), and simulated stance (SS), in PD patients and healthy controls (HC). Study 1 (14 PD; 20 HC) required subjects to maintain static balance during US and SS for 120 s with eyes open and closed. In study 2 (21 PD; 22 HC), subjects repeated the static balance task (90 s, eyes closed only), and also completed a dynamic balance task which required maintaining balance while experiencing random anterior-posterior (AP) perturbations applied to the trunk/pendulum. Angular displacements of the body/pendulum were recorded using angular velocity sensors (Swaystar, study 1) and Optotrak motion capture (study 2) and used to calculate Root Mean Square (RMS) and Mean Power of Frequency for static trials, and peak and time-to-peak for dynamic trials.
RESULTS: During static balance, PD patients had larger amplitude (RMS) of sway in both US and SS compared to HC, independent of vision (study 1). These group differences were replicated in US and SS in study 2. During dynamic balance, PD patients had larger peak and time-to-peak of SS angular displacements, compared to HC. These results followed previous observations in US [3].
CONCLUSION: Deficits in static and dynamic balance control can be detected in PD patients using a novel MRI compatible balance simulator. This technique will allow for functional neuro-imaging to be combined with balance-relevant tasks, and provide new insights into the neural substrates contributing to postural instability in PD.
REFERENCES: [1] Poliakoff, Journal of Neuropsychology, 2013; [2] Fitzpatrick et al. Journal of Physiology, 1992; [3] Visser et al. Journal of Neurology, 2008
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Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.06/PP19

Topic: E.06. Posture and Gait

Support: JSPS Grant-in-Aid for Young Scientists (Start-up)

Title: How does the conscious of self-attractiveness change walking motion

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Abstract: INTRODUCTION: Based on the Sexual Strategies Theory, attractiveness of biological motion reflects individual's healthy and fertile potential. Walking movement, which is daily physical exercise, could be appealing to people. Runway modeling is a specialized walking style for fashion commercialism, which transmits the information regarding motion attractiveness. In this study, we aimed to investigate the biomechanical features of walking motion generated by the one who are conscious of self-attractiveness and the information transmitted by attractiveness-oriented biological motions. Extracted biomechanical parameters were also analyzed for seeking the meaning of the motion based on Laban movement analysis.
METHODS: Seven female runway models and ten female non-models participated in this study. The participants walked on a treadmill for 7 minutes with a speed of 3.6 km/h under 2 footwear (barefoot/high-heel) × 2 conscious (normal/attractive) conditions. During attractive walking condition, participants tried to walk as attractive as possible. Whole body joint motions data was obtained by using a 3D motion capture system. Joint motion time series were segmented into each gait cycle started from right foot contact, which was calculated by using heel marker position data. Each joint motion profile was then compared between groups × footwear × conditions.
RESULTS: LEG: Models' knee joints were significantly more extended during stance phase compared with non-models. Non-models extended their knees during attractive conditions much more than that during normal condition but not so much as models. Hip adduction was larger for models during stance phase, which reflects "catwalk", and became much larger when the models were conscious of beauty of the movement. TRUNK: For both groups, being conscious of attractiveness led them to bend their back and neck backward and forward, respectively. Such features of the trunk shape was much more significant for models compared with non-models. ARM: Arm swing of models was smaller than non-models and the swing motion of models

moved backward during attractive walking condition.
DISCUSSION: The conscious of self-attractiveness propelled non-models to extend their knees, laterally swing their hips, bend backwards, and pull their chins. Such walking motion could make the whole body shape look "extended", which can be translated as "self-confidence" based on Laban movement analysis. Walking motion of runway models was an exaggeration of such features of non-models during attractive-conscious condition, suggesting that runway walking motion could be based on biologically affective human body movement.

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Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.07/PP20

Topic: E.06. Posture and Gait

Support: JSPS KAKENHI Grant Number #18K10916

Title: Involuntary changes in leg cycling cadence following transcutaneous spinal direct current stimulation

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Abstract: Transcutaneous spinal direct current stimulation (tsDCS) is a one of technique to modulate excitability of central nervous system (CNS). Recently, we reported that the tsDCS preceding motor task could modulate the performance in maximal effort sprint cycling by improving the fatigue in later phase of it. The improvement would be attributed in modulation effects of tsDCS on neural populations generating motor output to their muscles. In contrast, it is known that neural population involved in generation of its locomotive pattern was not fully identical depended on the locomotion speed. Therefore, we investigated whether the tsDCS could modulate rhythmicity of submaximal cycling cadence.tsDCS was applied to 10 subjects by using 2 electrodes (35 cm2) which were located over the vertebral column (Th11 to L1) as stimulation electrode and the other was located on the right shoulder as a reference. Polarity of the stimulus and reference electrodes were cathodal and anodal respectively. The stimulus

intensity was 3 mA and the duration were 15min with 15-s ramp-up and -down periods, while the current was immediately ramped-down after reaching the maximum current in sham stimulus condition. Prior to tsDCS, subjects were asked to perform constant cadence leg cycling at 60 rates per minutes (rpm) for 180s with closed eyes as pre-stimulus task. The load of the cycling task was set at 0.02 kp / kg body weight. During first 60s of the task, subjects were presented auditory click sound with 1Hz to secure correct cycling rhythm. Following the feedback period, the sound was converted into white noise for last 120s. The cycling task was also repetitively performed 4 times every 10min from just after tsDCS as post-stimulus tasks. In cathodal tsDCS, the cadences at no auditory feedback period in all post-stimulus tasks were increased compared to that in pre-stimulus task. In contrast, the changes of cycling cadence at same period did not occurred in sham tsDCS. There were also significant differences of the cycling cadences between cathodal and sham stimulus condition. These results would imply that the tsDCS could modulate the neural population generating motor output at low level of cadence in cycling.

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Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.08/PP21

Topic: E.06. Posture and Gait

Support: Grant-in-Aid for JSPS Research Fellow

Title: Adaptive control of trunk movement for chronic stroke patients to achieve sit-to-stand

Authors: *H. HANAWA[1,2], K. HIRATA[1], M. SONOO[3], T. MIYAZAWA[4], Y. MATSUMOTO[1], K. KUBOTA[1], T. WATANABE[1,5], Y. HAMANO[1], K. AOKI[1], T. KOKUBUN[6], N. KANEMURA[6]
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Abstract: [*INTRODUCTION*] Movement disorders due to cortical damage are one of the main problems after stroke. Movement disorders are directly linked to the impairment of daily activities, such as sit-to-stand. Sit-to-stand often fails due to sit-back at the seat-off, and the support surface cannot be transferred to the foot located in front of the trunk. We examined how

the trunk movements of chronic stroke patients are adaptively controlled; thereby contributing to the basic knowledge that helps predict the adaptive process of the nervous system from the resulting movement. [*METHODS*] Sit-to-stand was performed by four chronic stroke patients, three healthy elderly subjects, and three healthy young subjects. We obtained kinematic data using a three-dimensional motion analysis system and calculated three sagittal plane parameters, as shown in the results. We compared each parameter by performing a t-test (Bonferroni correction) between the groups. The resulting statistical significance level was set at $p < 0.01$. [*RESULTS*] (1) The temporal pattern of the thoracic-distal and pelvic-proximal powers relative to the internal waist extension moment were strongly antiphase in all groups (average of cross correlation coefficients: -0.95). However, in stroke patients, (2) the amplitudes at seat-off were smaller than those of the other two groups. Furthermore, (3) the negative work (time integral of power) from the distal end of the pelvis to the internal hip extension moment decreased to a value below that of the other two groups. [*DISCUSSION*] The anterior tilt of the pelvis that occurs at the beginning of the sit-to-stand reflects the positive power (the delivery of mechanical energy from the lumbar extension muscle to the pelvis). By the anterior tilt of the thorax stopped acceleration from the external force (negative power) is synchronized with the anterior tilt of the pelvis, lumbar extensors achieves isometric contraction. This improves the energy transfer efficiency from the lumbar extensor to the pelvis. In stroke patients, the nervous system is adaptively controlled to achieve seat-off by (1) maintaining this temporal coordination while (2) decreasing the amplitudes. In the lower limbs, the anterior tilt of the pelvis antagonizes the internal hip extension moment (negative work). The hip extensor muscle therefore absorbs the mechanical energy. Stroke patients with (3) a small amount of this absorption may be at a disadvantage during hip extension after seat-off (energy release). Considering that the lower limb muscles may compensate for this energy deficiency, we also present muscle synergies and interpret adaptive control.

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Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.09/PP22

Topic: E.06. Posture and Gait

Title: Kinetic symmetry in landing leg relative to whole body in stroke locomotion: Split-belt treadmill adaptation behavior

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Abstract: [Introduction] Post stroke survivors have an asymmetric gait, which is caused by certain impairments that may increase dependence on the nonparetic limb. Despite the presence of these impairments, it is necessary to ask why patients who usually walk asymmetrically are capable of walking symmetrically. In most studies on the split-belt walking paradigm, in which two belts are driven independently of each other, the adaptability of human bipedal locomotion was demonstrated using models and shown to induce adaptation in stroke patient. The purpose of this study was to investigate the commonality of kinetic symmetry between stroke patient and healthy subject during adaptation in split-belt locomotion.[Methods] Eight chronic stroke patients with hemiparesis (age = 71.5 ± 5.2) and eight healthy young adults walked on a split-belt treadmill under symmetric and asymmetric conditions. We investigated the changes in stance time, step length, and vertical angle between the line from center of pressure (CoP) to center of mass (CoM) and vertical line from CoM (CoM-CoP angle) at heel strike using motion capture system. All parameters were corrected for three periods, which were in belt velocity symmetry condition (tied-belt period), immediately after belt velocity asymmetry condition (split-belt period), and 5 min after asymmetry condition (adaptation period). The ratios from the three periods were analyzed using ANOVA with repeated measurements. Post hocanalyses were performed using Tukey's honest significant difference test when ANOVA yielded significant results ($p < .05$).[Results] Both the stroke patient and the healthy groups showed stance times with significant differences between the tied-belt and the other periods ($p < .05$). Both groups showed a step length that was not significantly different between the tied-beltand adaptation periods ($p = 0.05, 0.34$). The CoM-CoP angles for stroke patients were also dissimilar but not significantly different between the same periods ($p = 0.19$).[Discussion] By continuing split-belt locomotion, stroke patients re-established baseline step length asymmetry. Similarly, they also re-established the relative positions of CoP and CoM in the adaptation period. Despite the step length asymmetry of the patients, the position of the leading leg relative to CoM was almost symmetrical at heel strike. These phenomena were in common with the healthy subjects. In other words, the asymmetry of spatial parameters for the stroke patients is only an apparent asymmetry. The landed leading leg of stroke patient relative to whole body maintains symmetry equivalent to that of a healthy subject and possibly contributes to locomotor adaptation.

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Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

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Topic: E.06. Posture and Gait

Support: Academy of Pediatrics Research Grant, V Marchese PI

Title: Exploring lower extremity force modulation while jumping in childhood cancer survivors

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Abstract: Background: Children with acute lymphoblastic leukemia (ALL) receive extensive medical treatments consisting of neurotoxic chemotherapy agents such as vincristine and methotrexate. Vincristine causes peripheral neuropathy and muscle weakness in distal extremities while methotrexate causes central nervous system neurotoxicity leading to motor processing and developmental delays. Musculoskeletal effects include decreased strength and limited ankle ROM, while neuromuscular effects may be expressed as motor delays, coordination deficits and poor balance.
Purpose: The inability to quickly generate muscle force in ankle plantarflexors and knee extensors while jumping has been identified in children as a predictor of strength and functional mobility limitations. The purpose of this pilot study was to explore countermovement jump performance in ALL childhood cancer survivors (CSS) to identify force modulation and timing deficiencies.
Methods: 12 children (6 males, 7-16 years), 6 ALL CCS and 6 age/gender matched controls, performed three countermovement jumps. Measures included full body kinematics and ground reaction forces. Subjects were compared by: 1) maximum center of mass (COM) jump height; 2) ankle, knee, and hip torques determined by inverse dynamics; 3) synchronization of peak ankle, knee and hip torques. Effect sizes were determined using Cohen's d. Statistical comparisons were performed by unpaired t tests on mean values. Standard deviations were compared using F tests (alpha=0.05).
Results: ALL CCS average jump height was significantly less than controls (0.711 (±0.034) vs 0.761 (±0.031), normalized to height). There were no significant group differences for normalized hip, knee, or ankle torque. Time durations to reach peak COM acceleration and joint torques were not significantly different between the two groups, although the time to reach peak COM acceleration effect size was large, d=0.815 (ALL=0.399 (±0.055) seconds vs controls=0.447 (±0.063) seconds). There were no significant between-group differences for peak

joint torque synchronization.
Conclusions: Differences in COM jump height reflect lower-body force modulation deficits in ALL CCS, but the lack of significance in peak joint torque comparisons indicates the deficiency does not correlate to a specific joint. Intersegmental timing for jumping is not deficient in ALL CCS as indicated by: 1) similar times to achieve peak joint torques; and 2) similar peak joint-torque synchronization for hip, knee and ankle joints. Neural deficits manifest as force modulation rather than motor delays, coordination deficits or poor balance for countermovement jumping in ALL CCS.

Disclosures: R.A. Creath: None. **V. Gray:** None. **T. York:** None. **V. Marchese:** None.

Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.11/QQ2

Topic: E.06. Posture and Gait

Title: Sports exercise effect on changes in motor evoked potentials of the first dorsal interosseous muscles while maintaining neck flexion position

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Abstract: The present study applied transcranial magnetic stimulation (TMS) to the motor area of the first dorsal interosseous (FDI), and investigated sports exercise effect on changes in motor evoked potentials (MEP) of the FDI while maintaining neck flexion position. Subjects were classified into two groups: sports experience group that has belonged to sports club for 4 years or more (SE group, n = 10) and sports inexperience group that has never belonged to any sports club (SI group, n = 15). The experimental protocols were approved by our institutional ethics committee. All subjects provided written informed consent after receiving an explanation of the experimental protocols. The motor area of the FDI was determined as the site at which MEP was elicited by TMS. MEP was measured with the chin resting on a stand (chin-on condition) and with voluntary maintenance of neck flexion (chin-off condition) at 80% maximal neck flexion angle. Significant difference between these postural conditions was examined in the latency and amplitude of MEP, by using a one-sample t-test. The alpha level for statistical significance was set at $p < 0.05$. In SE group, MEP latency shortened 0.27 ± 0.35 ms ($t_9 = 2.32$, $p < 0.05$) and MEP amplitude increased 60.9 ± 43.0% ($t_9 = 4.12$, $p < 0.01$) in the chin-off, compared with the chin-on condition. On the other hand, in SI group, no significant difference in latency and

amplitude of MEP was found between these postural conditions. These results suggested that the brain activation with maintaining the neck flexion position enhanced the excitability in the motor area of the FDI, and furthermore, that sports experience will be effective in the brain activation to the motor area of the FDI.

Disclosures: K. Kunita: None. **K. Fujiwara:** None. **T. Kiyota:** None. **K. Anan:** None.

Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.12/QQ3

Topic: E.06. Posture and Gait

Support: JSPS KAKENHI Grant Number 17K01479

Title: Effect of static stretch of the calf muscles on the postural orientation and equilibrium during human quiet standing

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Abstract: Neural control of human posture has two principal behavioral goals, such as postural orientation and postural equilibrium. The purpose of this study was to investigate the effect of static stretch of the calf muscles on the postural orientation and equilibrium during quiet standing, especially focusing on its time-dependent characteristics.Six healthy women (20-21 yrs.) participated in the study. In pre-stretch condition, participants maintained 60-s quiet standing (QS) on a flat, firm surface with eyes closed for 5 times. After the pre-stretch condition, participants first stood for 3-min on a stretch board that imposes a 25 deg of dorsiflexion stretch of the left and right calf muscles simultaneously. Immediately after the stretching, they maintained 5-min QS on the flat surface with eyes closed. The participants repeated these stretching and QS tasks for 5 times with no interval between them (the post-stretch condition). During QS, ground reaction forces were measured with a force platform. From ground reaction forces, we calculated the anterior-posterior position of the center of pressure (CoP) and the anterior-posterior acceleration of the center of mass (CoM_{acc}) as measures of postural orientation and equilibrium, respectively. To examine the time-dependent characteristics of the effect of static stretch, we divided a single 5-min QS trial in the post-stretch condition into 15 time periods (20-s long each) and evaluated the time course of the above-mentioned two variables, i.e., CoP and CoM_{acc}. We found a significant anterior shift of the mean CoP position (0.95±0.15 cm, mean ± standard error) during the 1^{st} period of the post-stretch QS when compared to the

pre-stretch condition. At the same time, the participants exhibited increased CoM_{acc} during the 1st period of post-stretch QS (1.69±0.20 cm/s^2 as the root mean square value) as compared to the pre-stretch condition (1.28±0.10 cm/s^2). Interestingly, these two variables showed different time course after the 2nd period of the post-stretch QS. That is, the mean CoP position kept showing posterior shift until the 15th period of the post-stretch QS and it did not return to a value observed in the pre-stretch condition even in the end of 5-min trial. On the other hand, the CoM_{acc} immediately fell to the level found in the pre-stretch condition during the 2nd period of the post-stretch QS and was almost unchanged until the 15th period. Our results suggest that the effect of static stretch on the postural orientation and equilibrium have different time-dependent characteristics. To reveal the neural basis responsible for such difference, further investigation with electro-physiological techniques is needed.

Disclosures: S. Sasagawa: None. **K. Yaeshima:** None. **H. Sekiguchi:** None.

Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.13/QQ4

Topic: E.06. Posture and Gait

Support: Greater Milwaukee Foundation 74915

Title: Dynamic balance training in persons with multiple sclerosis

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Abstract: Impaired balance control interferes with walking and increases fall risk in persons with multiple sclerosis (MS). Rehabilitation interventions to improve standing balance emphasize the use of sensory strategies to challenge the balance system to adapt to environmental tasks. However, gait therapies often provide aids, such as handrails or assistive devices, reducing the need for the person to control their balance. Therefore, the purpose of this pilot study was to evaluate the effects of a gait-training paradigm aimed at challenging balance while walking on dynamic balance and walking outcomes in persons with MS. In this preliminary study, we evaluated nine persons with MS who participated in the training protocol. For the training protocol, participants walked at their self-selected pace on our treadmill system 30 minutes per day, 3 days per week, over 4 consecutive weeks. Using a motion base system, we controlled the motion of the entire treadmill to move in an unpredictable manner in the medio-lateral (ML) direction to challenge balance while walking. To test if integrating balance

challenges while walking improves balance and walking, we quantified dynamic balance and walking function prior to and following completion of the training. We performed clinical measures of dynamic balance (functional gait assessment, FGA), over ground walking speed (10 Meter Walk Test), and balance confidence (Activities-specific Balance Confidence (ABC) Scale). We also performed kinematic measures of dynamic balance and walking function while participants walked on a stable (non-moving) treadmill. We quantified the ML margin of stability (ML-MoS), step width, step length, and step frequency. Prior to training, persons with MS walked with a cautious gait pattern, by taking shorter, wider and quicker steps to limit center of mass movement (i.e. higher ML-MoS). Following training, persons with MS walked with decreased step width (2.8% decrease), increased step length (14.3% increase), decreased step frequency (3.0% decrease) and lower ML-MoS (15.8% decrease). From the clinical assessments, we observed increased FGA scores (+2.3 points), faster over ground walking speeds (+0.1 m/s for self-selected and fast-as-possible walking speeds), and increased ABC scores (+5%). These preliminary findings suggest that challenging balance while walking can improve dynamic balance, increase walking speed and increase balance confidence in persons with MS.

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Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.14/QQ5

Topic: E.06. Posture and Gait

Support: Brain Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Science, ICT & Future Planning (2016M3C7A1904984)

Title: Potential parameters for wrist-worn single accelerometer and gyrosensor in functional evaluation of upper extremity in hemiplegic stroke

Authors: *H. NAM[1], W. LEE[1], H. SEO[2], M. W. SMUCK[3], S. KIM[1]
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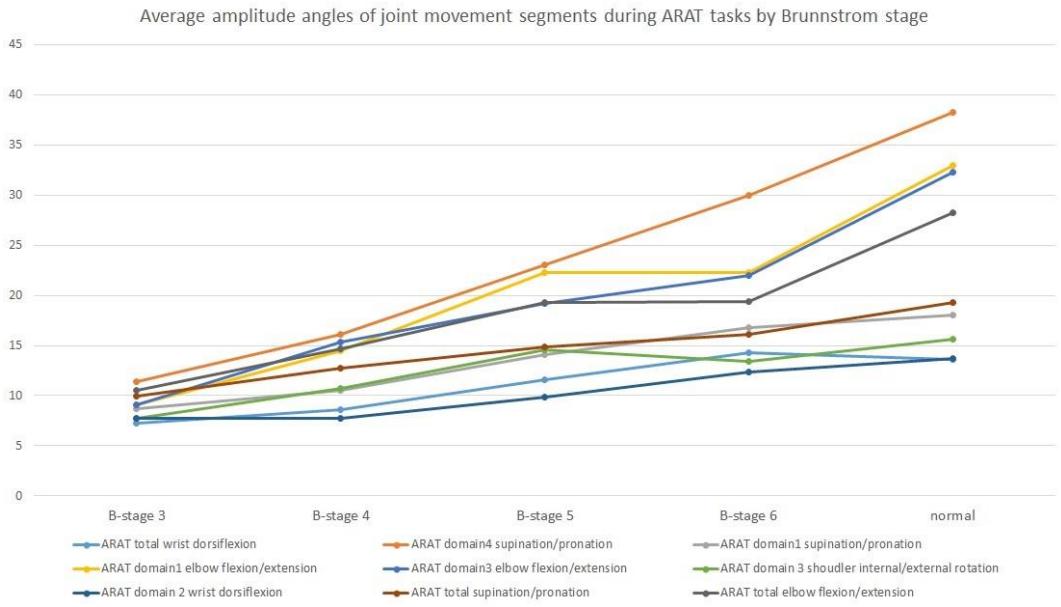
Abstract: Previously many studies on accelerometers and gyrosensors were performed for upper extremity movements in stroke, yet there exist no standardized methods with significant clinical relevance. We aimed to determine parameters and appropriate tasks that may serve as potential clinical outcome measures, which can be measured with a single sensor on the wrist. Ten healthy volunteers and nine patients with hemiplegic stroke were recruited to perform Action Research

Arm Test (ARAT) and selected activities of daily living (ADL), with wearable multiple IMU sensor based motion capture system. Acceleration of the wrist and hand sensors in three global orthogonal directions and Euler angles of sensors in each segment of the upper limb with reference to their proximal segment were measured. ARAT score and Brunnstrom stage were evaluated for all patients. Average amplitude and maximum amplitude of the movement segments, logsum and logsum per time was extracted and analyzed. Logsum was defined as integration of all displacements or changes for corresponding measurements. Of the parameters that showed significant differences between healthy subjects and patients and also significant correlation with clinical measures, average amplitude of forearm supination/pronation angle during ARAT domain 4 tasks demonstrated significant decline of the value in severely impaired patients compared to normal subjects (29.83%) and profound difference between severely and mildly impaired patients (48.46%). During ADL tasks, logsum per time for supination/pronation showed significant difference between severity levels (38.33%). Average amplitude of acceleration in x-axis (left-right) and z-axis (up-down) of hand and wrist sensors during ARAT tasks demonstrated a range of 45 to 62% value compared to healthy subjects, with 21.6 to 35.1% difference along the severity spectrum. Although accurate measurement with single wrist sensor may not be possible, specific parameters may play a significant role in simple or serial functional evaluation as an important predictor of clinical outcome measures.



Disclosures: H. Nam: None. **W. Lee:** None. **H. Seo:** None. **M.W. Smuck:** None. **S. Kim:** None.

Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.15/QQ6

Topic: E.06. Posture and Gait

Title: Quantitative stretch reflex measurement using motor system for the elbow joint

Authors: *T. ARAKI, H. MURAMATSU, Y. ITAGUCHI, S. KATSURA
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Abstract: Abstract
Introduction: The spasticity is one of aftereffects of a cerebrovascular disease. Symptom of the spasticity is occurrence of abnormal resistant torque at a specific angle through joint movement. The spasticity makes a daily living activity difficult because it becomes hard to move a limb as desired. Accordingly, an evaluation method of the spasticity is necessary to rehabilitate the patients properly. Therapists have evaluated the degree of the spasticity qualitatively by examining a torque response of a patient limb during passive movement. However, the qualitative evaluation is insufficient for the proper rehabilitation because of individual different recognitions. The purpose of this study is to measure the degree of spasticity quantitatively with a measurement system. In this study, the stretch reflex properties of healthy subjects were quantitatively examined because the spasticity is caused by sthenia of the stretch reflex. The elbow-joint-measurement system composed of a direct drive motor, which does not contain extra mechanical elements such as gears, enables high-accuracy angle and torque measurements.
Methods: Resistant torques of three healthy subjects were measured with elbow extension motion in a sitting posture. The exercise commands were set to 1.0, 2.0, 3.0, 4.0, 5.0, 6.0 rad/s constant velocity movements to imitate the real measurement because the evaluation of the spasticity is performed by moving a patient target part at constant velocity. The range of motion was 80 degrees. Before the measurements, the subjects were directed to make the arm relaxed.
Results: According to the experimental results, the resistant torque occurred in the countering direction and the stretch reflexes occurred twice in each experiment. Mean latent periods of the stretch reflexes were 62 ms (SD=5) and 143 ms (SD=25) after the extension motion started. Mean torque responses of the first reflex and the second reflex were -2.37 Nm (SD=0.43) and -1.59 Nm (SD=0.75) for all conditions. Each mean torque response of the second reflex was -0.58 Nm (SD=0.18), -0.76Nm (SD=0.19), -1.63 Nm (SD=0.48), -2.25 Nm (SD=0.37), -2.18 Nm (SD=0.30), and -2.09 Nm (SD=0.31) at 1.0, 2.0, 3.0, 4.0, 5.0, and 6.0 rad/s, respectively.
Discussion: We found the three stretch reflex properties quantitatively. (1) The latent periods of the two stretch reflexes occurred at 62 ms (SD=5) and 143 ms (SD=25). (2) Since the standard deviation was small as SD=0.43, the torque responses of the first stretch reflex were

approximately constant torque -2.37 Nm regardless of the movement velocity. (3) The torque of the second reflex varied at the movement-velocity threshold between 2.0 and 3.0 rad/s.

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Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.16/QQ7

Topic: E.06. Posture and Gait

Support: Elsass foundation

Title: Age-dependent differences in neuroplastic response to daily home-based treadmill training in children and adults with cerebral palsy

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Abstract: Improved toe-lift and heel strike in children with Cerebral palsy (CP) following daily home-based treadmill training is accompanied by increased beta and gamma band coherence between populations of dorsiflexor motor units. This indicates that plastic changes in the central drive to dorsiflexors may be responsible for improved gait in the children. In the present study we investigated whether these plastic changes are age-dependent by comparing changes in gait function and coherence following daily treadmill training in 35 children and adults with CP covering an age span from 3 to 65 years of age. Coherence was estimated from two separate EMG recordings over the Tibialis anterior muscle in the swing phase of gait. Toe lift and heel strike were estimated from 3-D kinematic video analysis. For children below the age of 12 years we observed a significant training-related increase in beta and gamma band coherence, which was closely correlated to improved lift of the toes in late swing. For children and adults above the age of 12 years no change in coherence and only limited change in toe lift was observed. These findings suggest that plastic changes in the central drive to dorsiflexor motor neurons are easier to induce through training in children below the age of 12 years than later in life. This may be related to the normal maturation of gait function in children.

Disclosures: J.B. Nielsen: None. **J. Lorentzen:** None. **M. Willerslev-Olsen:** None.

Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.17/QQ8

Topic: E.06. Posture and Gait

Support: Japan Science and Technology Agency CREST (#JPMJCR14E4)
Japan Society for the Promotion of Science (JSPS) KAKENHI (#15J09583)

Title: Enhanced unidirectional motor cortex to muscle connectivity in beta and gamma bands during voluntary gait task in humans

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Abstract: INTRODUCTION: Modification of ongoing walking movement requires accurate voluntary control, which is dependent on the environmental situation. In cat studies, it has been established that the motor cortex has crucial roles for precisely adjusting muscle activity during gait modification. In humans, however, it is unclear whether and how the motor cortex contributes to adjustments of locomotor muscle activity during gait modification. In this study, we examined effective connectivity between the motor cortex and leg muscles during voluntary gait modification and compared the connectivity with that during steady state walking.
METHODS: Twelve males participated in this study. The participants performed two different walking tasks on a treadmill: 1) normal walking and 2) precision stepping that forced the participants to step on pre-specified positions on the treadmill. In the precision stepping, the stepping position was projected on the treadmill by a projector and was randomly presented based on 5 and 3 predetermined positions in the anteroposterior and mediolateral directions, respectively. We measured electromyographic (EMG) activity from the tibialis anterior (TA) and the soleus (SOL) muscles and electroencephalographic (EEG) signals from 63 electrodes over the scalp. Effective connectivity (i.e., directional information flow) between the motor cortex and leg muscles was examined by estimating full-frequency Directed Transfer Function (ffDTF), which is a frequency-domain estimator of causal interaction utilizing a multivariate autoregressive model, between an EEG signal from Cz electrode and the EMG signals.
RESULTS: In both muscles and both walking tasks, significant effective connectivity was observed from the motor cortex to the leg muscles, while not from the muscles to the motor cortex. For the TA, the cortex to muscle connectivity increased in the gamma band (30-40 Hz) in the swing phase during precision stepping compared to that during normal walking. For the SOL,

the connectivity increased in the high-beta band (26-30 Hz) and decreased in the alpha band (8-12 Hz) in the stance phase during precision stepping than normal walking.
DISCUSSION: The present results strongly suggest that the motor cortex is effectively involved in modification of locomotor muscle activity. It has been suggested that corticomuscular connectivity in the alpha band contributes automatic movements and that in the beta and gamma bands is involved in movements that require high attentional demand. These functional differences among the frequency bands would be related to the changes of the effective connectivity during precision stepping.

Disclosures: H. Yokoyama: None. **N. Kaneko:** None. **Y. Masugi:** None. **T. Ogawa:** None. **K. Watanabe:** None. **K. Nakazawa:** None.

Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.18/QQ9

Topic: E.06. Posture and Gait

Title: Asymmetry in neuromuscular control for damping behavior during object transport in healthy young individuals

Authors: *S. A. WINGES[1], A. SONG[2], M. J. MACLELLAN[2]
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Abstract: Anticipatory control of grip force and coordinated movement of upper limb movements counterbalance inertial forces while walking and transporting objects. In addition to maintenance of a secure grasp through anticipatory adjustment of grip force on the transported object, the vertical displacement of the object relative to trunk displacement is limited. However, it is still unknown how the muscles function to produce the damping behavior during object transport. The purpose of this study was to identify the neuromuscular control of the upper limb used to transport an object and to determine if any asymmetry is present between the patterns of muscle activation in the dominant (DO) and non-dominant (NDO) arms. Whole body kinematics were recorded, along with bilateral activations of eight upper limb muscles in seven healthy young right-handed adults. A damping ratio was computed as the peak-to-peak vertical displacement of C7 and the object when the object was transported with the right or left hand. The average damping ratio across participants did not differ between the DO and NDO object transport conditions ($p = .311$). However, only one participant had damping ratios that were very similar between dominant and non-dominant hands. Three participants had NDO damping ratios that were 30-89% larger than DO, while three other participants exhibited 13-34% less damping

in the NDO compared to DO condition. Muscle synergies derived using non-negative matrix factorization revealed two temporal patterns during which proximal arm muscles peaked just prior to heel contact while forearm and hand muscles reached peak activation approximately at heel contact of the contralateral leg. These preliminary results suggest that the shoulder and elbow joints were stabilized first by the recruitment of the upper arm muscles prior to heel contact, followed by the wrist and finger muscles, to maintain the stability of the object against the perturbation caused by the impact of heel contact. However, examination of individual muscles patterns and peaks reveal subtle asymmetries across limbs that may explain the differences in damping behavior.

Disclosures: S.A. Winges: None. **A. Song:** None. **M.J. MacLellan:** None.

Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.19/QQ10

Topic: E.06. Posture and Gait

Support: Shurl & Kay Curci Foundation

Title: Mice learn to modulate intra- and inter-limb paw kinematics with training on a novel locomotor behavioral paradigm

Authors: *K. P. NGUYEN[1], A. SHARMA[2], S. M. CHASE[2], A. H. GITTIS[3]
[1]Biomed. Engin., [2]Ctr. for the Neural Basis of Cognition, [3]Biol. Sci., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: A critical feature of the motor system is its ability to adapt movements to constantly changing environments. This is especially true for locomotor control. Historically, the majority of focus on locomotor control has been on understanding how central pattern generators within the spinal cord regulate coordinated movements. Recent studies, however, have demonstrated that the subcortical circuits of the basal ganglia and cerebellum are necessary for locomotor learning. Despite the importance of locomotion in our daily lives, the roles that these subcortical circuits play in mediating the acquisition and expression of skilled locomotor behavior remain unclear. This is in large part due to the lack of behavioral paradigms which assess complex motor tasks with sub-second precision during rapid perturbation of genetically-defined neurons. Thus, we have established a novel hardware and software infrastructure that provide the groundwork for disentangling how targeted neural circuits give rise to distinct locomotor features. More specifically, we designed and constructed a two-wheel running paradigm for rodents in which body and paw kinematics can be tracked at up to 500 frames per second,

providing a high degree of spatial and temporal behavioral readout during skill learning. Here, we demonstrate that mice learn to perform on our custom running wheel over a period of several days. Improved performance correlates with a forward shift in body center position on the wheel when both wheels are driven at a fixed speed. To run at a particular speed, stride length and step frequency must be constrained to a coupled set of values we term the optimal solution space. Over the course of training, we note that mice change their strategy within this optimal solution space by taking quicker and shorter steps. Moreover, we observe an increase in stance-phase stride length and stride frequency as the wheel moves faster, similar to gait patterns previously characterized on a flat terrain in quadrupeds. Finally, wheel training is also correlated with the development of regular interlimb coordination patterns. These data suggest that mice learn to modulate intra- and inter-limb paw kinematic strategies to mediate successful wheel running with training. In summary, the data collected from our custom running wheel system provides a unique and powerful approach to extracting the piecewise gait components for studying how distinct neural mechanisms and loci enable locomotor skill acquisition.

Disclosures: K.P. Nguyen: None. **A. Sharma:** None. **S.M. Chase:** None. **A.H. Gittis:** None.

Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.20/QQ11

Topic: E.06. Posture and Gait

Title: Visual perturbations between immersive virtual reality modalities on healthy and multiple sclerosis participants' balance control

Authors: *L. I. RIEM[1,2], T. ONUSHKO[2], S. RAAB[2], S. A. BEARDSLEY[3], B. D. SCHMIT[4]
[1]Marquette, Milwaukee, WI; [2]Biomed. Engin., [3]Dept. of Biomed. Engin., Marquette Univ., Milwaukee, WI; [4]Dept. of Biomed. Engin., Marquette Univ. Dept. of Biomed. Engin., Milwaukee, WI

Abstract: In this study we examined the impact of disrupted visual feedback within a virtual reality (VR) environment on balance compensation in persons with multiple sclerosis (MS). Balance impairment is the second most common symptom in MS, however, the sources of disruptions in postural control and the influence of visual inputs are not well understood. The objective was to characterize the impact of applying medial-lateral (ML) shifts in the VR visual scene on balance in subjects with MS. Disruptions were examined during embodied (EB) and out of body (OB) perception in two types of fully immersive VR environments using ML visual perturbations applied at different frequencies. Subjects participated in three VR test conditions (counterbalanced across subjects): (1) a 270degree Christie Cave system with active stereoscopic

glasses (EB), (2) the same cave system, but with blinders attached to the glasses to restrict visual feedback to out of body perception, and (3) the HTC Vive headset (OB). During each test condition, subjects underwent two 5-minute trials. Within each trial, 20 second intervals of quiet standing were followed by 10 cycles of a sinusoidal 1m ML visual displacement at frequencies varying from .3-.95 Hz. The participant's center of pressure (COP) over time was obtained using time-frequency analysis and compared to their position relative to the visual stimulus. Temporal fluctuations in subjects' COP increased from rest (0.12 Hz), and became phase-locked with displacement frequencies up to 0.7 Hz. For sinusoidal visual displacements presented at 0.7 Hz, mean ML sway in the COP, velocity, area, and excursion all showed significant increases relative to quite standing ($t(12)$, $p<0.05$). Analysis of the change in COP showed that MS subjects experienced an increased reaction to visual displacements applied in the Vive VR environment. In conjunction with phase locking and increased postural sway, significant increases were observed in COP mean ML sway, velocity, area, and excersion ($t(12)$, $p<0.05$) during visual perturbations for both EB and OB perceptions. Tests with healthy young adults revealed similar responses, albeit with more continuous changes in postural control. The increase of peripheral visual flow provided in out of body conditions elicited stronger postural mechanisms. These results demonstrate that in persons with MS, there is an increased reaction and predisposition to a more immersive virtual environment. MS subjects matched their sway to the displacement of the visual scene and at a higher frequency compared to healthy participants. This increased reliance on visual feedback could enable rehabilitation via a low-cost head mounted VR system.

Disclosures: L.I. Riem: None. **T. Onushko:** None. **S. Raab:** None. **S.A. Beardsley:** None. **B.D. Schmit:** None.

Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.21/QQ12

Topic: E.06. Posture and Gait

Support: NSERC DG RGPIN-2017-06790

Title: Lower- and upper-body control during standing balance for individuals with incomplete spinal cord injury

Authors: *J. W. LEE[1,2], J. YOO[1,2], K. CHAN[2,3], J. UNGER[2,3], K. MUSSELMAN[2,3,4], K. MASANI[1,2]
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Abstract: Individuals with incomplete spinal cord injuries (iSCI) often have an impaired ability to maintain balance during standing. For able-bodied (AB) individuals, it is known that the ankle joint control as well as the lower- and upper-body coordination play important roles in stabilizing the whole body. We hypothesized that individuals with iSCI do not sustain this coordination, causing difficulties in maintaining their standing balance. In this study, we investigated the coordination of the lower- and upper-body during standing for individuals with iSCI. Eleven young AB individuals (ABy) (5 female and 6 male; 25.1±5.3 years old), eleven individuals with iSCI (7 female and 4 male; 58.6±11.5 years old) and twelve age- and sex-matched AB individuals (ABm) (9 female and 3 male; 60.1±9.7 years old) participated. The participants were instructed to perform quiet standing for 150 seconds with their eyes open. Using a motion capture and a force platform system, we measured kinematic and kinetic data. We calculated the center-of-mass (COM) of the lower-, upper- and whole-body, as well as the corresponding segment angles. The root-mean square of the linear and angular acceleration data was used to quantify body fluctuations. We also evaluated the coordination between the two segments using the coordination index, based on our previous study. The analysis of variance (ANOVA) with Tukey's test, as the post-hoc analysis, was used to compare the measures among the three groups. The whole-body COM linear accelerations were significantly different among the three groups (ANOVA: $p=0.007$). The post-hoc analysis revealed that the whole body COM acceleration in participants with iSCI was significantly larger than the other two groups (ABy vs iSCI: $p=0.0126$ and ABm vs iSCI: $p=0.0180$), indicating that participants with iSCI have compromised balancing abilities. We also found that the lower body angular acceleration was larger for individuals with iSCI than for AB participants (ANOVA: $p=0.01$; ABy vs iSCI: $p=0.0088$ and ABm vs iSCI: $p = 0.0293$). On the contrary, the upper body fluctuation was larger in iSCI compared to only ABy (ANOVA: $p=0.042$; ABy vs iSCI: $p=0.0455$ and ABm vs iSCI: $p=0.121$). The coordination index was not different among the three groups (ANOVA: $p=0.984$). We demonstrated that individuals with iSCI sway more during standing, indicating that they have compromised ability to maintain balance. Despite this instability, the lower- and upper-body coordination was statistically equivalent to AB participants. Therefore, the instability in individuals with iSCI must be related to the reduced control in their ankle joint control.

Disclosures: J.W. Lee: None. **J. Yoo:** None. **K. Chan:** None. **J. Unger:** None. **K. Musselman:** None. **K. Masani:** None.

Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.22/QQ13

Topic: E.06. Posture and Gait

Support: NIH Grant R01 AR-050520
NIH Grant R01 AR-052345
DoD Grant MR150091
USC Provost Fellowship

Title: Using genetic algorithm to control tendon-driven systems with unknown structure

Authors: *A. MARJANINEJAD[1,2], R. ANNIGERI[2], F. J. VALERO-CUEVAS[1,3]
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Abstract: Understanding the neural control of movement in detail requires that we confront the same mechanical problem the brain faces: controlling multiple tendons. This problem has two simultaneous features: it is redundant when it comes to the control of tendon forces, but over-determined when controlling the lengths and velocities of muscles pulling on those tendons. Here we address the latter problem by using a genetic algorithm to solve the over-determined problem of finding the time-history of muscle lengths to produce smooth and accurate movements in a simulated human arm.
Methods: We use a Genetic Algorithm to find a series of muscle excursion values to move the limb in a desired trajectory accurately. Our proposed method works without prior knowledge of the structure of the system, and does not require linearity. The method was tested on a 3 tendon 2 DOF system with posture-dependent moment arm values.
Results: We were able to accurately track the predefined goal trajectory (a circle at the endpoint of the limb) without prior knowledge about the structure of a nonlinear tendon-driven system. We believe that this, and similar approached will enable us in controlling tendon-driven systems with unknown parameters with high accuracy. However, smoothness requires a much more refined control. The average execution time to find the desired excursion values was long (seconds) which precludes its real-time application. Therefore, adding biomechanical constraints as well as trying other Machine Learning algorithms can help extend this approach into a real-time controller for this problem. This highlight the fact the moving smoothly and accurately is neither simple nor a forgiving task for tendon-driven systems with afferented muscles.[1,2]
References:
1. Valero-Cuevas, F. J. Fundamentals of neuromechanics. 8, (Springer, 2015).
2. Hagen, D. A. & Valero-Cuevas, F. J. Similar movements are associated with drastically different muscle contraction velocities. J. Biomech. 59, 90-100 (2017).

Disclosures: A. Marjaninejad: None. **R. Annigeri:** None. **F.J. Valero-Cuevas:** None.

Poster

494. Posture and Gait: Kinematics, Muscle Activity, Exercise and Fatigue, and Biomechanics II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 494.23/QQ14

Topic: E.06. Posture and Gait

Support: SDSU Summer Undergraduate Research Program
SDSU Undergraduate Research Program Faculty Mini-Grant

Title: The effects of two types of variable assistance on motor learning of a novel swing phase trajectory

Authors: *A. DOMINGO[1], E. RAMIREZ[2]
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Abstract: Robot-assisted therapies have been developed to improve gait function in patients with motor disorders. It is not clear how best to use these robotic devices to maximize motor learning and functional outcomes. The Ekso is a commercially available wearable robotic exoskeleton used for gait rehabilitation after neurological injury. It contains motors at the hips and knees that provide assistance at these joints in the sagittal plane during ambulation. The Ekso is able to provide variable assistance, meaning that when the user follows an assigned swing phase trajectory, the device's software reduces the motor assistance, with the goal of increasing engagement and effort of the user. It has two variable assistance modes, Adaptive (where the movement is continuous and users are given feedback on the percentage of motor assistance) and Fixed (where the movement is interrupted if the user is not contributing a minimal level of their own power to the movement). The purpose of this study was to compare if either mode is better for motor learning of a novel swing phase trajectory in able-bodied subjects. We hypothesized that subjects that trained in the Fixed mode would learn the trajectory faster during training, because it would provide more opportunities for error detection and correction. 20 able-bodied subjects were randomly assigned to either the Adaptive or Fixed mode while walking in a linear path (18 m in length) 10 times followed by a second day (24-48 hours later) to assess retention of learning. Learning was measured by the assistance required from the motors to maintain the assigned swing phase trajectory. Preliminary results show that there no differences between groups in the assistance given by the robot at baseline (P=877). Both groups were able to learn the novel swing phase trajectory and significantly lowered assistance from the device from the beginning to the end of training(P<.001), but there were no differences between groups (P=.271), and no interactions (P=.182). There were also no differences in retention of learning between groups (P=.513). For able-bodied subjects, either type of feedback was helpful for learning a

novel swing phase trajectory. For those with compromised motor and/or sensory function, one type of variable assistance mode may be superior.

Disclosures: A. Domingo: None. **E. Ramirez:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.01/QQ15

Topic: E.06. Posture and Gait

Support: NSERC Discovery Grant to C. Paquette.
Canadian Foundation for Innovation Grant to C. Paquette.

Title: The neural correlates of continuous gait adaptation to the split-belt treadmill are influenced by gait pattern characteristics: An ^{18}F-FDG PET Study

Authors: *D. HINTON[1,3], A. THIEL[2,4], L. J. BOUYER[5], C. PAQUETTE[1,3]
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Abstract: Gait alterations on a split-belt treadmill (SBT), where each leg is driven at a different speed, highlight the nervous system's ability to quickly adapt the locomotor plan to its environment. However, specific contributions from the brain to this motor adaptation remain unknown. The fact that participants with cortical strokes, hemispherectomy, and even infants prior to independent stepping, have the ability to make changes to their gait cycle within 5 steps of walking on a SBT suggest that a distributed network may be involved. Here we establish if cerebral and cerebellar brain regions change activation during continuous gait adaptation to the SBT compared to typical treadmill walking in healthy adults and how the gait pattern influences these changes. Methods: Directly following bolus injection of ^{18}F- fluorodeoxyglucose tracer, 10 healthy adults walked on a treadmill for 30 minutes. In the tied-belt (TB) condition, both belts were maintained at a comfortable speed. On a separate occasion, the continuous adaptation (CA) condition changed the speed ratio between treadmill belts every 15 seconds. Positron emission tomography (PET) images of cerebral glucose metabolism of each condition were compared to assess for clusters with significant changes in metabolism when continuous, unexpected gait pattern changes are required. A multiple linear regression predicted participants' peak activation change within each significant cluster based on their cadence, number of steps taken and step length variability. Results: A significant increase in metabolism during CA was only found in 4 main clusters: the left supplementary motor area (SMA), the right posterior parietal cortex

(PPC), the anterior cingulate cortex (ACC) and the left anterior cerebellum ($p<0.05$). Of these four clusters, participants' peak Z values in the PPC and the Cerebellum could be predicted from gait characteristics. The change in cadence, a temporal measure of gait, was the only predictor of peak activation within the PPC ($R^2=0.725, p<0.01$), whereas step length variability, a spatial measure of gait, was the only predictor of peak cerebellar activation ($R^2=0.528, p<0.05$). Conclusion: Our results suggest that complex control of temporal and spatial aspects of the gait cycle increase metabolism in anatomically separate areas of the brain and imply a parieto-cerebellar network could be required for continuous locomotor adaptation. A lack of change in metabolism of the PFC indicates that executive function may not play a substantial role while activation of the ACC independent of gait characteristics signals the need to sustain increased task directed attention in this complex walking task.

Disclosures: D. Hinton: None. **A. Thiel:** None. **L.J. Bouyer:** None. **C. Paquette:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.02/QQ16

Topic: E.06. Posture and Gait

Title: The effects of transcranial direct current stimulation on age and race implicit association tests during complex motor tasks

Authors: E. P. KELLER[1], *C. J. KETCHAM[2]
[1]Biol., [2]Exercise Sci., Elon Univ., Elon, NC

Abstract: Humans exhibit attitudes towards groups of people different than themselves, some they may be aware of and some not so aware of. This group identity leads to stereotyping others and creating unconscious assumptions, which control human behavior (Greenwald & Krieger, 2006). However, inhibitory control in the prefrontal cortex is critical to controlling activation of these biases (Sellaro *et al.,* 2015). It is unknown if implicit biases are amplified when engaged in a high motor load task, or if it can be mitigated by an external stimulation treatment. Engagement in a dual motor task may draw attention away from the usage of the prefrontal cortex to modulate bias (Schmader, Johns & Forbes, 2008). This project investigated if the use of noninvasive brain stimulation via transcranial direct current stimulation (tDCS) in conjunction with evidence based excerpts of the effects of implicit bias, will positively influence bias, specifically racial bias. Twenty-one participants (age = 19.8 ± .98), who self-identified as white college students, completed four Implicit Association Tests (IAT), which is a computer based reaction task where participants responded to images of stimuli for age and race that were paired with words of good verses bad. Participants were randomly assigned to either tDCS stimulation (1mA.40 min) or sham (1mA.30 sec) conditions at the dorsolateral prefrontal cortex. The IAT software produced

an IAT score. The first IAT participants took was a baseline followed by another IAT while balancing on a Biodex Balance System. The participants then completed training with tDCS stimulation while reading and writing reflections on a series of excerpts from literature based books while balancing on a stability ball. The written reflections were compiled as a qualitative result of how participants describe and understand their explicit biases. This was followed by a post training IAT and a one-week post training IAT. Results of the IAT showed that a high motor load has no effect on implicit racial or age bias ($p<0.05$). Further research should continue to consider motor load as a mediating factor that could influence bias.

Disclosures: E.P. Keller: None. **C.J. Ketcham:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.03/QQ17

Topic: E.06. Posture and Gait

Title: Neural correlates of human dual-task gait: Effect of secondary task difficulty

Authors: *H.-T. GOH, S. EWING, D. MARCHUK, A. NEWTON, I. NYANGANI
Physical Therapy, Texas Woman's Univ., Dallas, TX

Abstract: Dual-tasking has a detrimental impact on human gait and is an important index for fall risk. Both Dorsolateral Prefrontal Cortex (DLPFC) and Supplementary Motor Area (SMA) have been shown to be involved in dual-task gait. Our previous work showed that 5Hz repetitive transcranial magnetic stimulation (rTMS) applied to SMA, but not DLPFC, improved dual-task gait speed in young healthy adults, supporting the role of SMA in dual-task gait. One possible explanation was that the level of difficulty imposed by the secondary task mediated the differences between SMA and DLPFC. Subsequently, the purpose of the current study was to determine whether the secondary task difficulty modulates the neural correlates of dual-task gait. Eighteen young healthy adults (7 males, mean age = 27.6 ± 6.3 years) participated in the study and were equally divided into 2 groups (Easy or Difficult secondary task group). Gait speed was assessed under single- (walk only) and dual-task (walk and count backward) conditions. The Easy group counted backward by 3 from a given number (ranged from 40-100) while the Difficulty group counted backward by 7. Both groups put priority on the counting task during dual-task walking. Each participant received a 5Hz-rTMS protocol (90% resting motor threshold, 1200 stimulations) applied to left DLPFC, SMA or primary motor cortex (M1) at 3 different sessions (~ 1 week apart) in a pseudo-randomized order. Gait and counting performance was assessed before and after rTMS application. Counting backward by 7 was significantly more difficult than counting backward by 3 as evidenced by more correct counting responses were observed in the Easy group than the Difficult group (p =. 00). rTMS applied to SMA led to a

significant increase in dual-task gait speed (p = .01) regardless of secondary task difficulty (p= .70). rTMS applied to DLPFC and M1 did not lead to reliable changes in dual-task gait speed. Gait speed under the single-task condition was not altered by either rTMS application. In conclusion, SMA plays an important role in mediating dual-task walking in humans and its role appears to be independent from the secondary task difficulty. Future work will investigate the effect of rTMS to SMA and DLPFC on dual-task gait in individuals with brain damage.

Disclosures: S. Ewing: None. **D. Marchuk:** None. **A. Newton:** None. **I. Nyangani:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.04/QQ18

Topic: E.06. Posture and Gait

Title: Is it possible to perform independent rhythmic movements with the upper and lower limbs?

Authors: *W. QI[1], K. KATO[2], M. SAKAMOTO[3], T. NAKAJIMA[4], K. KANOSUE[2]
[1]Sport Sci., Waseda Univ., Saitama, Japan; [2]Fuculty of Sport Sciences, Waseda Univ., Saitama, Japan; [3]Kumamoto Univ., Kumamoto, Japan; [4]Kyorin Unversity Sch. of Med., Mitaka City/Tokyo, Japan

Abstract: The rhythmic movements of daily life, such as tapping and walking, appear in many forms. Complex movements may involve the performance of two or more rhythms simultaneously. The present study focused on whether two rhythmic movements could be produced independently. Eleven subjects performed rhythmic finger tapping concurrently with four different lower limb movements; 1) self-paced walking (SW), 2) walking at a given pace (GW), 3) alternative bipedal heel tapping while sitting (BT), and 4) unipedal heel tapping while sitting (UT). Subjects first performed the foot movement more than 60 times (self paced in the SW task and with a 600 ms interval in the other tasks). Then metronome sounds (375 ms interval) were given to the subjects to synchronize finger tapping with the sounds and keep pace with the foot movements. After another 60 foot movements, the metronome for finger tapping was stopped, and the subjects were required to continue the two rhythmic movements without external stimuli during the period in which the subjects did foot movements at least 60 times. Performance was evaluated by the distribution of the relative phase of finger tapping and foot movement. The task was considered successful if the relative phase was evenly distributed. In the SW and GW tasks, the number of relative phase distributions was not beyond the chance level, indicating independency of the walking
and tapping rhythms. On the other hand, for the BT and UT tasks, relative phase distribution was significantly above the chance level around 0° (360°) and 180°, and was significantly below the

chance level around 90° and 270°. This indicates that the relative phase of finger and foot movements dropped to a 2:1 rhythm (the subject failed to perform independent movements of the finger and feet). We attribute successful performance of the SW and GW tasks to the existence of two control mechanisms, one in the supra-spinal brain (for finger tapping) and the other in the locomotion-related neural circuits of the spinal cord (for walking). We attribute failure of the BT task and UT tasks to be due to the control of both finger and leg movements by supra-spinal mechanisms which conflict with each other. We conclude that two separate rhythmic movements can be independently performed only if they were controlled by discrete neuronal mechanisms.

Disclosures: W. Qi: None. **K. Kato:** None. **M. Sakamoto:** None. **T. Nakajima:** None. **K. Kanosue:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.05/QQ19

Topic: E.06. Posture and Gait

Support: Barrow Neurological Foundation

Title: Motor cortex activity during locomotion and postural corrections in the mouse

Authors: *I. N. BELOOZEROVA[1], E. F. CABRALES[2], Z. MIRZADEH[2]
[1]Neurobio., [2]Neurosurg., Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Neuronal activity in the motor cortex is modulated with the rhythm of strides in diverse species including humans, non-human primates, cats, rabbits, and rats. It was shown that in humans, cats, and rabbits, it is also modulated by postural corrections after a perturbation. In mice, however, where genetic tools have facilitated the neurophysiological study of various behaviors, the role of the motor cortex in locomotion and postural corrections was not investigated. In this study, we recorded the activity of single neurons in the motor cortex of head-fixed male and female C57BL/6J mice that were standing, walking, and balancing on a floating ball. We found that the activity of neurons in cortical layer 5 was profoundly modulated by both locomotion and balancing movements. Specifically, the activity of most individual neurons was higher during one phase of the stride and postural correction and lower during another phase. Different neurons are active during different phases of the behavior. The entire population was slightly more active during the swing phase of the stride and the limb extension phase of the postural correction. Our findings suggest that the motor cortex of the mouse, similar to that of higher mammals, is involved in control of locomotion and posture.

Disclosures: I.N. Beloozerova: None. **E.F. Cabrales:** None. **Z. Mirzadeh:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

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Program #/Poster #: 495.06/QQ20

Topic: E.06. Posture and Gait

Support: NASA Nebraska Space Fellowship
NIH Grant P20G109090

Title: Flexibly switching postural responses between structured visual stimuli depends on the temporal determinism of the stimuli

Authors: *Z. MOTZ[1,2], T. SADO[2], W. DENTON[2], M. MUKHERJEE[2]
[1]Univ. of Nebraska At Omaha, Omaha, NE; [2]Biomechanics, Univ. of Nebraska at Omaha, Omaha, NE

Abstract: Healthy postural sway is characterized by the ability to respond to changes in the environment, and adapting to these changes allows us to maintain balance while performing different tasks (e.g. on a ship at sea or in space). However, when such environmental conditions quickly change among several different conditions, whether we can flexibly adjust our postural responses, is not clear. Studying such flexibility patterns could provide insight into alleviating abnormal sensorimotor recalibrations and enhancing adaptation to ever-changing stimuli in dynamic environments. The purpose of this study was to test the ability of flexibly switching postural entrainment from one stimulus structure to another. Seven healthy participants were recruited to voluntarily shift medial-laterally and attempt to match their sway to a moving visual stimulus. Both deterministic (periodic and chaotic) and non-deterministic (random) stimuli were tested individually (baseline) and in combination. The combination trials comprised of either 20 second sections of the random stimulus followed by 20 seconds of the periodic stimulus, repeating for three minutes or the same structure with the chaotic stimulus instead of the periodic. The degree of center-of-mass (COM) – target stimulus coupling was quantified using cross-recurrence quantification analysis (cRQA) which represents duration of coordination and cross-sample entropy (cSE) which represents the repeatability between the two signals. Mixed-factor ANOVA statistical design was used to determine main effects of section, condition and interaction. Results show significant section, condition and interaction effects ($p<0.001$) for both baseline and combination trials. Postural entrainment to the random stimulus was significantly different from periodic and chaotic stimulus across early to late trials. Across baseline and combined signals, the unpredictable stimulus showed an increase in repeatability and coupling duration across trials; and as a group had lower repeatability and coupling duration than the deterministic stimuli. Coupling to deterministic stimuli at a frequency similar to normal postural sway (0.24 Hz), shows strong entrainment with a reduced learning effect. The study showed the

ability to flexibly switch between characteristically different patterns of visual stimuli depends on their temporal determinism. Future directions should test higher velocities to tease out adaptive flexibility across different deterministic stimuli and explore the transition points to determine uncoupling-coupling characteristics.

Disclosures: Z. Motz: None. **T. Sado:** None. **W. Denton:** None. **M. Mukherjee:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

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Program #/Poster #: 495.07/QQ21

Topic: E.06. Posture and Gait

Support: NIH Grant S10RR028114-01
NIH Grant 5T32HD007490
Foundation for Physical Therapy PODS I Award

Title: Pain during learning reduces retention of a strategic locomotor learning task

Authors: *J. E. GALGIANI, S. M. MORTON
Physical Therapy, Univ. of Delaware, Newark, DE

Abstract: Certain forms of motor learning and retention can be influenced by non-motor elements, including attention, cognition and other factors. Pain is one potential factor that may affect motor learning, but to date, this has not been systematically studied. Of note, several cortical brain regions involved in pain processing overlap with those responsible for motor learning and consolidation, indicating that the two processes have the potential to interact. We compared the learning and retention of a strategy-based locomotor learning task between two groups of young healthy individuals, randomly assigned to either a ‘no pain’ or a ‘pain’ group. Individuals in the pain group received a painful stimulus induced by the combination of capsaicin and heat applied to the skin. All participants learned to alter their step lengths differently on each leg by watching a screen showing real-time feedback of their steps, displayed as a dynamic bar graph. For each step, a target step length was displayed, based on the average step length. During learning on Day 1, the feedback display was gradually distorted over 10 minutes, encouraging participants to take increasingly longer steps with one leg and increasingly shorter steps with the other, resulting in a newly learned asymmetric gait pattern. The pain group had the experimental pain delivered to one of the lower legs during the Day 1 learning period only. Twenty-four hours later, we tested retention of learning by assessing step lengths during the first few trials of walking with the same distorted feedback as at the end of Day 1. We found that while there was no difference in learning on Day 1, individuals in the pain group showed reduced retention of learning, demonstrated by initially less asymmetric stepping on Day 2. Our

results suggest that pain during strategic learning may interfere with the consolidation process of learning, resulting in poor retention. This work is significant because it provides novel insight into brain mechanisms of consolidation and retention and because it has important implications for application of rehabilitation interventions utilizing motor learning strategies in patients who have pain.

Disclosures: J.E. Galgiani: None. **S.M. Morton:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.08/QQ22

Topic: E.06. Posture and Gait

Support: University of Idaho Seed Grant
CLASS Key Fund

Title: The performance cost of postural biofeedback

Authors: *J. L. BAER[1], R. G. COHEN[2]
[2]Dept. of Psychology & Communication Sci., [1]Univ. of Idaho, Moscow, ID

Abstract: Background: Maintaining an upright sitting posture in the workplace may help reduce or prevent neck pain. The recent development of biofeedback interventions, which draw attention to postural feedback cues, raises the question of a possible trade-off between attention to posture and attention to task performance, such that maintaining upright posture may negatively affect task performance.
Approach: To investigate this possible trade-off, we assessed upright posture (based on neck length) and score on a 10-minute computer game, played with and without biofeedback in counterbalanced order.
Results: When participants used biofeedback, their postural alignment was significantly improved and their game performance was significantly worse than when they played without biofeedback, demonstrating a dual task cost. The magnitude of the dual-task cost was positively correlated with neck shortening while using biofeedback, indicating that participants who were worse at maintaining upright posture (and thus would have greatest need for biofeedback) had greater task performance decrements when using biofeedback.
Conclusion: Developers of biofeedback systems would be well-advised to consider individual differences and possible dual-task costs when designing training protocols.

Disclosures: J.L. Baer: None. **R.G. Cohen:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

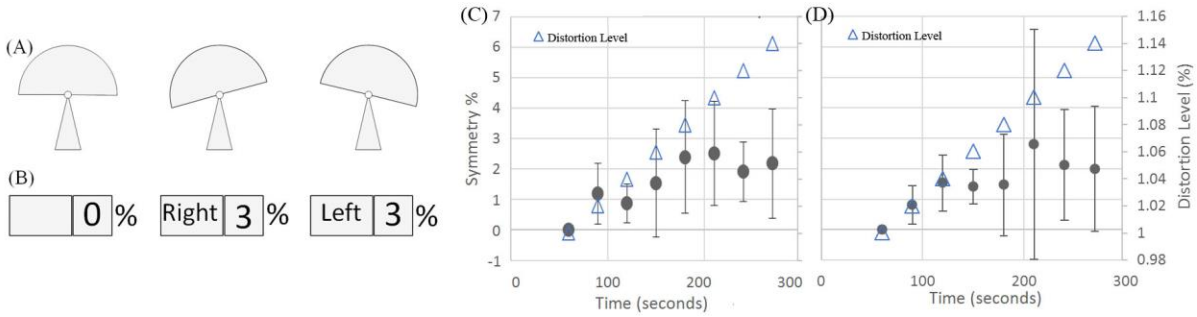
Program #/Poster #: 495.09/QQ23

Topic: E.06. Posture and Gait

Title: Effects of feedback distortion on visuomotor adaptation with gait

Authors: *S.-J. KIM[1], E. MARTINEZ[2]
[1]Mechanical & Bioengineering, [2]California Baptist Univ., Riverside, CA

Abstract: We have proposed a novel task design (*visual feedback distortion)*, in which the both step lengths are measured during treadmill walking and displayed as two vertical bars, and the length of only one bar is distorted. Our previous work demonstrated that subjects spontaneously modulated gait symmetry in response to the distortion. Thus, the use of the visual feedback distortion may involve *sensory prediction error-based learning*, in which the motor system cannot tolerate differences between a prediction of motor commands and the execution perceived through visual feedback, thereby leading to gait adaptation.
We further investigated how gait adaptation may be compromised in two different modalities of feedback distortion; 1) visual graph feedback and 2) digit feedback. For the first trial, the visual graph feedback represented the step length with a semi-circle (Fig. A). As the right step length is longer than the left step length, the semi-circle moves left and vice versa. For the second trial, the digit feedback displayed a number percentage off from step symmetry with information of which side of the leg is longer (Fig. B). Our pilot trials consisted of 5 minutes treadmill walking. The distortion level increased 2% on the right side for every 30 seconds up to 14% after the first one minute. All participants were aware of the distortion and instructed to walk normally while looking at the visual feedback. Subjects made spontaneous modulations away from actual symmetry in response to the feedback distortion, no matter the modality (Fig. C & D). Despite the simple graph or digital feedback distortion of gait symmetry, it appears to still cause adaptation possibly through sensory prediction error-based learning, which does not necessarily rely on visually-guided feedback of movements.
Figure. Illustrate of visual graph feedback (A) and digit feedback (B), and gait symmetry change in response to the graph feedback distortion (C) and the digit feedback distortion (D). The symmetry ratio (%) was measured by 2*(R-L)/(R+L) and the symmetry change was referenced to the base line (the first one minute).



Disclosures: S. Kim: None. **E. Martinez:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

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Program #/Poster #: 495.10/QQ24

Topic: E.06. Posture and Gait

Support: Intramural funding, Okinawa Institute of Science and Technology
Fellowship for Overseas Researchers from the Japan Society for Promotion of Science (JSPS)
Kakenhi Grant-in-Aid for JSPS Fellows

Title: Application of real-time marker-based motion capture for the kinematic analysis of freely behaving mice

Authors: *A. KUCK, B. M. IGNATOWSKA-JANKOWSKA, M. Y. UUSISAARI
Neural Rhythms in Movement Unit, Okinawa Inst. of Sci. and Technol., Onna, Japan

Abstract: Movement analysis in freely moving rodents is of high importance in systems neuroscience as well as research of motor behavior and disorders. However, since most of the current state-of-the-art tools for movement analysis in freely moving rodents employ marker-less motion tracking techniques, they require cumbersome off-line analysis and are limited in their precision of kinematic tracking. To overcome these limitations and to allow for high-resolution recording of limb positions simultaneously with neural recording and stimulation, we employed a marker-based motion capture system to track limb and body kinematics of freely moving mice in real time. The system consists of seven high-precision motion capture cameras (Oqus 7, Qualisys AB, Göteborg, Sweden), tracking the position of several permanently attached, custom-made retroreflective motion capture markers. Markers were positioned on both hind- and forelimbs as well as hip and back of the animal, enabling tracking of limb kinematics, body orientation and posture in 3D with sub-millimeter precision at a sampling rate of up to 1kHz. To demonstrate the capabilities of the system, we showcase the kinematics of mice locomoting

freely on open field, vertical climbing wall and on a horizontal rope. We extract a rich set of kinematic variables, to describe the animals' behavior during gait, reaching, climbing, grooming and exploration. The data allows detecting subtle differences in movement and behavior, as a response to pharmaceutical, environmental, optogenetic or other types of interventions. We show that the employment of such a marker-based kinematic system in freely moving, unrestrained rodents is possible and suggest its great potential to a range of neuroscience fields. The high-precision kinematic analysis of rodents' behavior as well as the possibility of movement-driven, real-time, closed loop experimental protocols opens new paths to dissecting the neural circuitry underlying motor behavior and dysfunction.

Disclosures: A. Kuck: None. **B.M. Ignatowska-Jankowska:** None. **M.Y. Uusisaari:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.11/QQ25

Topic: E.06. Posture and Gait

Title: Timings of attentional switching to perturbation and postural preparation during transient forward or backward floor translation

Authors: *K. FUJIWARA[1], C. YAGUCHI[2], N. KIYOTA[1], M. MAEKAWA[3], M. IREI[4]
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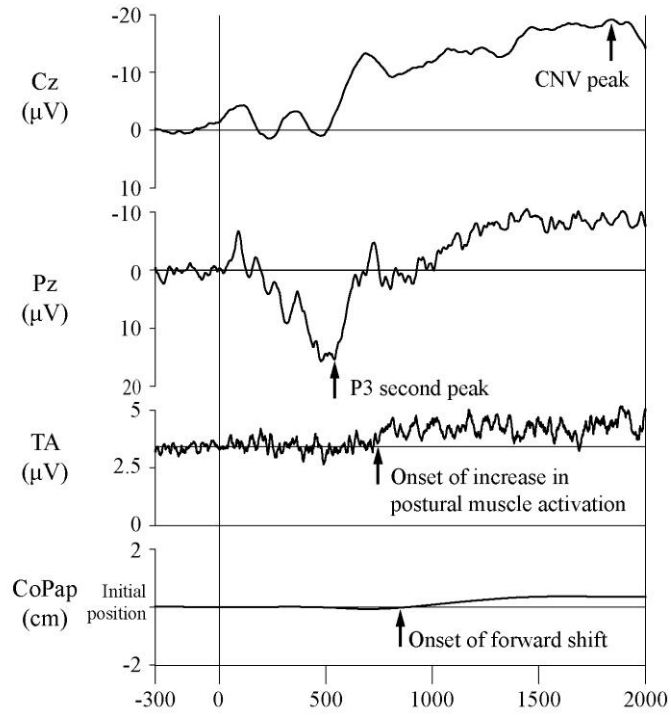
Abstract: Rapid attentional switching from sensory information and/or an ongoing task to a postural disturbance is an important function for postural control. However, few studies have used neurophysiological methods. In this study, relationships between the timings of attentional switching and postural preparation were investigated using a choice-reaction paradigm with transient floor translation (S2), with the direction indicated by a warning auditory signal (S1). Thirteen healthy young adults participated in this study. S2 started 2 s after S1 onset while standing on the platform. The platform moved forward when S1 was a high tone, and backward when S1 was a low tone. In the S1-S2 period, attentional switching was evaluated by P3 component of event-related potentials. A shift in the center of pressure in the anteroposterior direction (CoPap) or a continuous increase in postural muscle activation toward S2 was recognized as postural preparation. Changes in postural muscle activation were found just before the CoPap shift. P3 was observed about 250-650 ms after S1. Onset of postural preparation was significantly later (about 200 ms) than latency of P3 ($p < 0.001$) (Figure 1) and correlated strongly with P3 latency (forward: $r = 0.81$, backward: $r = 0.74$, $p < 0.01$). Postural preparation for S2 was demonstrated to start after attentional switching from S1 to S2.



Disclosures: K. Fujiwara: None. **C. Yaguchi:** None. **N. Kiyota:** None. **M. Maekawa:** None. **M. Irei:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.12/QQ26

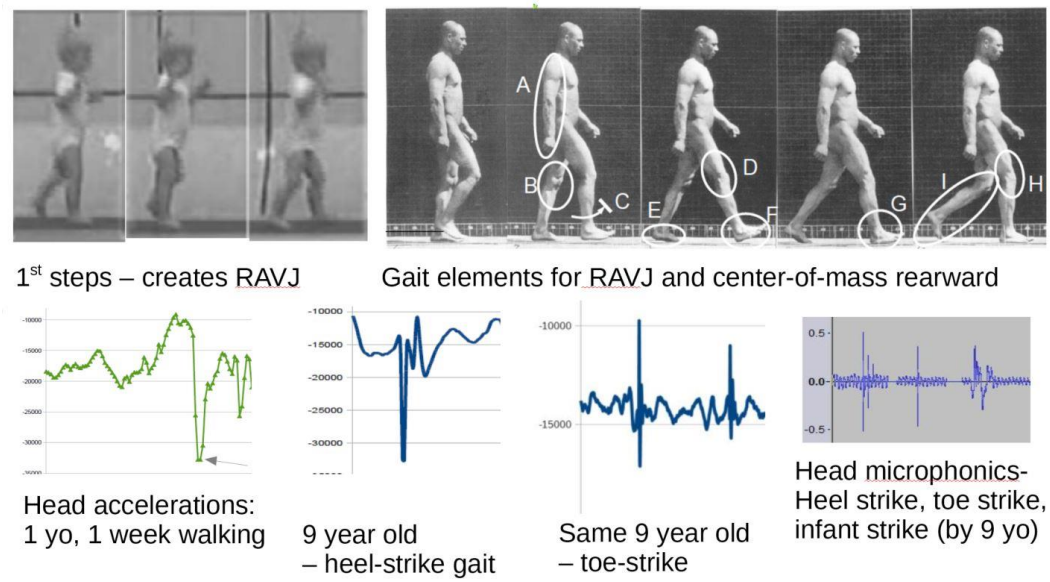
Topic: E.06. Posture and Gait

Title: A simple neural mutation that generates reward from rhythmic audible vestibular jolts fully explains all aspects of human bipedal gait development, including cerebral palsy gaits

Authors: *M. RIGGLE
Causal Aspects, Charlottesvle, VA

Abstract: The human bipedal gait starts with toddlers walking by clubbing the floor with their feet, then years of development until the adult heel-strike gait. Our gait has often been assumed to require unique structures in the motor control neural areas -- presumably placed there by evolution. However, a simple alternative to needing motor control changes is a neural change that produces an internal reward from the sensation of rhythmic audible vestibular jolts (RAVJ). If RAVJ is rewarding, we can show that all human gaits from the initial toddler gait to the adult gait, and even the cerebral palsy toe strike gaits, arise as learned via operant conditioning.

Normal human gaits generate RAVJ because of foot impacts to the floor which create a shockwave that travels to the head via the skeleton. That shockwave at the head produces a strong vestibular jolt and it is audible. As the gait matures, the gait must produce RAVJ but is also modified to reduce slips, trips, and collisions because they can be painful (learned modifications). We show the gait modifications from toddler to the adult allows more time for recovery from a trip or for avoiding obstacles but still generates strong RAVJ. As a rewarded behavior, walking is well practiced and thus becomes automatic.
Additionally, during the first week of walking, toddlers have learned to avoid slip falls by using muscles to stop the forward motion of the swing leg prior to floor contact (which requires a reflex development). With cerebral palsy, stopping the swing leg accurately by muscle is not reliable and they must instead use a foot strike that produces RAVJ but also reliably stops the foot to prevent a slip fall. That foot strike is often a skeleton damaging toe-strike and this theory suggests possible solutions.
There is additional evidence supporting that RAVJ is rewarding in humans but is not rewarding in non-human primates; this includes rhythmic headbanging and infant movement responses to rhythmic music.
We review published data from many areas to support this theory.



Disclosures: M. Riggle: None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.13/RR1

Topic: E.06. Posture and Gait

Support: MIT Lincoln Laboratory Internal R&D

Title: Human-exoskeleton adaptation: Predicting individualized adaptability from sensorimotor & cognitive factors

Authors: *A. GUPTA[1], R. J. MCKINDLES[3], L. A. STIRLING[2]
[1]Hlth. Sci. & Technol., [2]Dept. of Aeronautics & Astronautics, MIT, Cambridge, MA;
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Abstract: Individualized adaptation timelines and natural adeptness of exoskeleton operators may be predicted by their underlying perceptual, cognitive, and motor abilities. Until recently, the research and development being carried out by academic and industry groups focused on exoskeleton mechanical and material design or control methods with the goal of improving neurorehabilitation, enhancing human performance, and preventing injury. These researchers noted high variability in human adaptation and technology adoption with no current explanation. Our overarching study begins to quantify these individualized user differences that will inform (1) identification of adept exoskeleton operators, (2) creation of training methodologies, and (3) exoskeleton control architectures. Here we investigated which perceptual, cognitive, and motor capabilities best predict short term exoskeleton adaptation. We hypothesize that the rate of adaptation of a naïve exoskeleton user will be correlated to sensorimotor and cognitive function. This pilot study focuses on the development and validation of two novel tasks. The first focused on a known executive function task (i.e. Simon Task) typically performed as a visual, upper extremity response task and translating it to a tactile, lower extremity response task. The experiment included visual and lower extremity tactile stimuli that were either congruent or incongruent. Subjects (n=20) were asked to respond as quickly as possible by either a button press or foot tap. Though response times were on average slower for foot taps ($p<0.05$) and tactile stimuli ($p<0.05$), the results confirmed our hypothesis that the Simon task could be translated to lower extremity studies. For the second task, we developed and tested a self-paced, treadmill walking paradigm that examined user adaptation to a goal-directed walking task. Subjects (n=4) were asked to reach and maintain target speeds of 0.5, 1.0, and 1.5 m/s for 60 second trials on a self-paced treadmill (Motekforce Link). Results showed that there were varied responses to using the self-paced treadmill, characterized as speed overshoot (range 0-1.01 m/s) and time to steady state (range 1.1-18.6 seconds). In the next phase of this study, we will examine how these tests and other metrics of perception, cognition, and motor skills may help predict human-exoskeleton adaptation. DISTRIBUTION STATEMENT A. Approved for public release. Distribution is unlimited.

Disclosures: R.J. McKindles: None. **L.A. Stirling:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.14/RR2

Topic: E.06. Posture and Gait

Support: Newcastle University Institutional Support

Title: Prefrontal cortical activity in Parkinson's disease decreases during dual tasks and is not associated with cognitive effort

Authors: *A. PANTALL[1], L. KAPA[2], R. VITORIO[4], S. STUART[5], L. ALCOCK[3], L. ROCHESTER[3]
[1]Neurosci., Newcastle Univ., Newcastle Upon Tyne, United Kingdom; [2]Psychology, [3]Neurosci., Newcastle Univ., Newcastle, United Kingdom; [4]São Paulo State Univ., São Paulo, Brazil; [5]Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Background: Cholinergic networks, from the pedunculopontine nucleus in the brainstem and the subcortical nucleus basalis of Meynert, influence postural control, gait and cognition [1]. Most activities involve dual tasks (DTs), such as walking and talking. Optimal DT performance requires both networks to be functional. However, in Parkinson's disease (PD), postural control, gait and cognition, specifically executive function, are often impaired. Executive function includes attention and allocation of cognitive reserve and is associated with the prefrontal cortex (PFC) [2]. Analysis of PFC activity and cognitive task (CT) errors during DTs may provide insight into mechanisms underlying cognitive cost of DTs in PD.
Aims: (1) to evaluate the effect of PD on PFC activity when performing DTs compared to a single task; (2) to investigate the relationship of PFC activity with CT performance.
Methods: 60 participants were recruited – 30 with PD (68.5±14.0 years), 15 healthy older adults (OA) (74.1±6.9 years) and 15 healthy younger adults (YA) (23.5±2.9 years). PFC activity was recorded using a wireless functional near infra-red spectroscopy device (Oxymon, Artinis Medical Systems). Participants performed two tasks for 300s: a) alternating 30s bouts of standing still (SS) and standing whilst performing a CT (SSCT); b) alternating 30s of usual walking (UW) with walking plus the CT (DTW). The CT involved recalling how many odd or even numbers were spoken during 30s. The averaged normalised fNIRS differences between SS and SSCT and between UW and DTW were calculated. Statistical analyses used linear mixed models and Pearson's correlation test with significance set at $p<0.05$.
Results: PFC activity decreased for DTW task compared to UW ($p=.009$) for PD whereas no change was found for OA and YA. No change was observed in PFC activity from SS to SSCT whereas OA and YA increased activity. CT performance differed significantly between groups ($p<.001$) with lowest performance recorded for the PD group. The task effect was significant

only for the PD group (p=0.002) with better CT performance during DTW compared to SSCT. No significant correlation was observed between PFC activity and task performance in PD (p=0.085).
Conclusions: People with PD display different neural activation patterns during DTs compared to healthy adults. PFC activity decreased in DTW although this change was not related to lower CT performance. Decreased PFC activity during DTW may explain why people with PD experience difficulty performing dual task activities.
References:
[1] Rochester at el., 2012. *Brain*, 135(9), 2779–2788.
[2] Maidan et al., 2016. *Neurorehab.Neural Repair*, 30(10), 963-971.

Disclosures: A. Pantall: None. **L. Kapa:** None. **R. Vitorio:** None. **S. Stuart:** None. **L. Alcock:** None. **L. Rochester:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.15/RR3

Topic: E.06. Posture and Gait

Support: DFG Research Fellowship RE 3780/1-1

Title: A phase-independent balance shift is generated by phase-dependent muscle activation in response to galvanic vestibular stimulation during walking

Authors: *H. REIMANN[1], T. D. FETTROW[2], E. D. THOMPSON[4], D. GRENET[2], J. J. JEKA[3]
[1]Dept. of Kinesiology and Applied Physiol., [3]Kinesiology, [2]Univ. of Delaware, Newark, DE; [4]Temple Univ., Newtown Square, PA

Abstract: To maintain upright posture of the body during locomotion in the frontal plane, the central nervous system has to activate muscles to push against the ground to stabilize the position of the center of mass and the orientation of the body. Several studies have reported balance responses in the lower body that strongly depend upon the phase of the gait cycle, whereas responses in the upper body are usually only weakly phase-dependent. We hypothesize that there might be an underlying control mechanism for balance which is phase-independent. To test this hypothesis, we perturb the balance system during locomotion and observe the responses of the motor system. Subjects walked on a self-paced, split-belt instrumented treadmill, surrounded by a virtual reality environment projected onto a domed screen. Balance was perturbed by bipolar, binaural Galvanic vestibular stimulation for 600ms with an amplitude of 0.5mA every 6-9 strides. Stimulation was triggered by heelstrike of the right foot, and started after a randomized phase delay of 0, 150 or 450ms. Results show that in response to the stimulus, the center of

pressure shifts in the direction of the perceived fall relative to the center of mass. The onset of this CoP shift occurs approximately 250-350ms after the stimulus onset, independent of the phase delay. In the 450ms delay condition, the CoP response cannot be realized by the current stance foot as it shifts to swing. Instead, the CoP shift transfers to the opposite foot as it enters stance, preserving the balance response. EMG results show that in the first post-stimulus step, the stance leg peroneus longus EMG is increased for a perceived fall away from the stance leg in the 0 and 150ms delay conditions. In the 450ms condition, a similar peroneus longus EMG modulation occurs during the second step in the contralateral leg, which is then in stance. These results indicate that there is a functional balance response to the GVS in the form of a CoP shift, driven by modulation of the stance foot peroneal muscles. Although the activation of the underlying musculature is phase-dependent, the functional response of the CoP is phase-independent with respect to the gait cycle.

Disclosures: T.D. Fettrow: None. **E.D. Thompson:** None. **D. Grenet:** None. **J.J. Jeka:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.16/RR4

Topic: E.06. Posture and Gait

Title: Greater visual attentional demands during saccadic eye movements do not improve postural sway

Authors: M. A. YEOMANS, A. V. MICHEL, K. MOORE, T. DIAZ, J. JOHNSON, J. SCHIPPER, S. YAN, *J. M. HONDZINSKI
Kinesiology, Sch. of Kinesiology; Louisiana State Univ., Baton Rouge, LA

Abstract: The purpose of this study was to better understand the effects of saccadic eye movements on postural control. By performing visually guided saccades during quiet stance, people can attenuate standing postural sway compared to fixating on a stationary target. Although such postural control may stabilize the visual system, it may increase attentional demands for whole body control or provide external cues for such control. We questioned whether self-paced saccades to imagined targets in a dark environment would attenuate sway relative to fixation. Performing self-paced saccades eliminated external cueing of a metronome and additional attentional cues. We also questioned whether increased attention on targets during visually guided fixation or saccades would attenuate sway relative to visually guided fixation or saccades on targets requiring less attention. Young adults were asked to stand still on a force plate and either stare at a fixation point (FP) target or to perform saccadic eye movements (SAC) to targets. An imagined target was used in a DARK environment, while a real target, either a 2 cm diameter DOT or a randomly presented 2 cm number/letter (NL), was presented on a

computer screen for non-DARK trials. Target presentation for SAC was at an 11 degree visual angle. Increased attentional demands were achieved by having participants name each number or letter orally (NLoral) or to themselves (NL). They performed 6 trials (3 FP and 3 SAC) in each condition while standing on a force platform (AMTI, Watertown, MA). Gaze position was tracked with a mobile Eye Tracker (SMI, Teltow, Germany). Analyses performed on several sway measures for the center of pressure revealed the following. In visually guided conditions (i.e., DOT, NLoral, and NL), SAC frequently attenuated sway relative to FP. Visually guided conditions also produced less sway compared to DARK, especially when considering SAC trials. NLoral and NL conditions did not differ from sway measures for the DOT condition. Results of the present study match previous work, which showed saccades can attenuate standing sway when visual guidance is provided. Decreasing visual attentional demands with no external cueing can increase sway compared to provision of external visual cues. Providing additional visual attentional demands, associated with reporting a number/letter during fixation and saccades like those performed in this study, does not improve postural sway. Thus, external cueing alone cannot explain attenuated sway associated with saccades. Data support that the external cueing associated with visually guided saccades improves postural control and gaze accuracy needed to stabilize the visual system.

Disclosures: M.A. Yeomans: None. **A.V. Michel:** None. **K. Moore:** None. **T. Diaz:** None. **J. Johnson:** None. **J. Schipper:** None. **S. Yan:** None. **J.M. Hondzinski:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.17/RR5

Topic: E.06. Posture and Gait

Title: Motor-cognitive interference in older adults walking with a visual verbal Stroop task

Authors: *B. WOLLESEN[1], C. VOELCKER-REHAGE[2]
[1]Univ. of Hamburg Fac. of Educ. Psychol, Hamburg, Germany; [2]Inst. of Human Movement Sci. and Hlth., Technische Univ. Chemnitz, Chemnitz, Germany

Abstract: Gait performance depends on sensorimotor and cognitive function. To identify people's susceptibility to adopt impaired gait patterns, often resulting in an increased risk of falling, the cognitive processing of locomotion in dual- or multi-tasking situations, (e.g. crossing the street while observing traffic flow, Faulkner et al., 2007); is important. In order to better understand the multiple requirements of motor skills and cognition, the Dual-task paradigm (DT) has become prominent to analyze cognitive-motor interference (CMI) in old age. Different models try to explain the contradictory results for the DTC (Wollesen et al., 2016). The aim of this observational study was to compare the differences of demographics, comorbidities and

physical functioning of older adults with positive and negative DTC while walking with a visual-verbal Stroop task. **Methods** A total of 241 participants (72.3 ± 5.4 years) performed a ST and a DT condition (visual-verbal Stroop task) while walking on a treadmill in randomized order. Gait parameters (step length, step width, gait line) were measured at 100 Hz. DTC were calculated by the formula (ST-DT/ST *100). Demographics, comorbidities and physical functioning were assessed (SF-12, FES-1, hand grip force, MMST, SPPB). An ANOVA was used to reveal subgroup differences of the baseline characteristics by using SPSS 24. **Results** We found DTC for step with and step length from 1% (step length) und to 2% (step width) with a SD between 8-15% for the 241 participants. Three subgroups with n=57 with positive (DTC-1) and n= 66persons with negative DTC (DTC-2) and n=118 persons with DTC for step length or step width (DTC-3) were distinguished. The baseline characteristics between the subgroups showed significant differences in age (DTC-1 73.7 ± 5.9; DTC-2 70.7 ± 5.2 and DTC-3: 72.6 ± 5; $F_{(2,233)}$=5.092, p=0.007) and concerns of falling (DTC-1: 20.4 ± 4.4; DTC-2 22± 5.4; DTC-3: 20 ± 3.4;$F_{(2,233)}$=3.732,p= .026). No differences were found for hand grip force, SPPB, MMST, SF-12. **Conclusions** The results showed that a huge number of participants cannot be clearly specified into a group with positive or negative DTC. A trend from differences in baseline characteristics (SF-12, FES-I, hand grip force, MMST, SPPB) between negative and positive DTC performer was observed. Interestingly, the main differences cannot be explained by older age. The persons with neg. DTC showed more motor and cognitive deficits in comparison to the participants with positive DTC. These results should be further analyzed to gain recommendations for interpreting dual-task assessments or training studies.

Disclosures: B. Wollesen: None. **C. Voelcker-Rehage:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.18/RR6

Topic: E.06. Posture and Gait

Support: NIH Grant 5T90DA032466
NIH Grant 1P50NS098685
NSF Grant 1137229
Georgia Tech Neural Engineering Center
Residential Care Facilities for the Elderly Authority of Fulton County

Title: Dissociation of muscle and cortical response scaling to balance perturbation acceleration

Authors: *A. PAYNE[1,2], G. HAJCAK[3], L. H. TING[2]
[1]Georgia Tech., Atlanta, GA; [2]Biomed. Engin., Emory Univ., Atlanta, GA; [3]Psychology and Biomed. Sci., Florida State Univ., Tallahassee, FL

Abstract: Reactive balance recovery engages sensorimotor control centers throughout the nervous system, but the role cortical activity in online control of balance is unclear. Cortical EEG activity during reactive balance recovery reveals a robust negative peak of activity (N1) over the supplementary motor area at ~150ms latency, but its relationship to concurrent and subsequent balance-correcting automatic postural responses (APR) in muscle is not understood. Prior work on averaged responses suggest that muscle and cortical responses share modulation by somatosensory inputs (Dietz 1984b, 1985a/b; Berger 1987; Staines 2001). We hypothesized the balance N1 shares somatosensory inputs with the initial burst (IB) of the muscle APR in order to monitor the simultaneous brainstem-initiated balance response and to influence later balance-correcting muscle activity. Because perturbation acceleration modulates the amplitude of the initial burst of the muscle APR (Lockhart 2007), we predicted that the balance N1 amplitude would also scale with perturbation acceleration and correlate to the muscle APRs on a trial-by-trial basis. We recorded EEGs during perturbations to standing balance that were unpredictable in timing, direction, and acceleration magnitude. Across subjects, we found much weaker acceleration-dependence of cortical responses (R^2=0.022) compared to muscle responses (R^2=0.323). Only half of individuals showed acceleration-dependent cortical responses despite acceleration-dependent muscle responses in all individuals. Variation of balance N1 amplitudes between subjects (R^2=0.528) was much greater than variation within subjects, with larger amplitudes in shorter subjects (R^2=0.412). Z-transformed balance N1 and muscle APRs were weakly correlated (R^2=0.075), in part due to differences in acceleration-dependence, but also due to a greater reduction in amplitude across trials of the balance N1 (R^2=0.047) compared to muscle APRs (R^2=0.015). Importantly, balance N1 was larger on trials in which subjects took a step to recover balance (two-way T-test, $p<0.0001$), and was correlated with longer-latency muscle activity (R^2=0.039). We conclude that the balance N1 receives the sensory inputs driving the muscle APR IB, but its amplitude depends more on the individual and recent experience, which may relate to known influences of attention and perceived threat. Our data further highlight a possible relationship between the balance N1 and stepping behavior, suggesting a potential influence of the cortex on longer latency muscle activation related to changes in strategy.

Disclosures: A. Payne: None. **G. Hajcak:** None. **L.H. Ting:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.19/RR7

Topic: E.06. Posture and Gait

Support: NIH R01NS104772

Title: Human cortical response to sensorimotor perturbations measured with high-density electroencephalography

Authors: S. M. PETERSON[1], *D. P. FERRIS[2]
[1]Biomed. Engin., Univ. of Michigan, Ann Arbor, MI; [2]Biomed. Engin., Univ. of Florida, Gainesville, FL

Abstract: Human balance requires precisely-timed coordination between sensory information and motor control. Studies have shown that improving cognitive function improves the ability to maintain balance, suggesting that cortical activity may be an informative biomarker of balance performance (Bherer 2015). We studied the responses of 30 healthy young adults (15 female/15 male; age 22.5±4.8 years, mean±SD) to sensorimotor perturbations that challenged their balance. Subjects performed four 10 minute conditions total of tandem stance and tandem gait while either being mediolaterally pulled or viewing brief 20 degree field of view rotations in virtual reality. We recorded 136-channel high-density, source-localized electroencephalography (EEG) clustered across all subjects. Based on previous research (Varghese et al. 2014; Wagner et al. 2016), we hypothesized that both the physical pull and visual rotation perturbations would elicit time-frequency fluctuations in theta (4-8 Hz) and beta (13-30 Hz) bands, with increased occipito-parietal activity during the visual rotations compared with the physical pull perturbations. Our results confirmed this hypothesis. For both visual and pull perturbations, we found early theta band synchronization and late alpha-beta (8-30 Hz) band desynchronization following perturbation onset (Figure 1). This pattern was strongest in occipito-parietal areas during visual perturbations and strongest in sensorimotor and anterior cingulate areas during pull perturbations. These results indicate that electrocortical patterns when humans respond to sensorimotor conflict are similar for both visual and physical perturbations.. Local field potential recordings in the subthalamic nucleus show similar time-frequency activity during visual conflict (Zavala et al. 2016). This common electrocortical pattern may have important implications for assessing balance control in both healthy adults and individuals with motor disabilities.

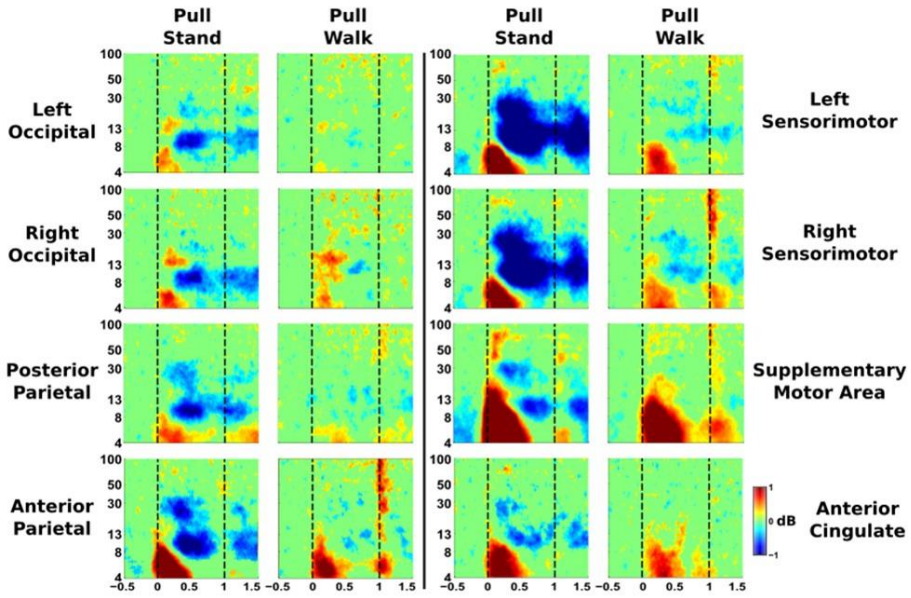

Figure 1. Time-frequency EEG activity in response to the physical pull perturbation (onset at 0 sec) during tandem standing (columns 1 and 3) and tandem walking (columns 2 and 4).

Disclosures: S.M. Peterson: None. **D.P. Ferris:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.20/RR8

Topic: E.06. Posture and Gait

Support: NSF SL-CN SMA-1640909
NIH R21/R33 MH096967

Title: A quantitative, objective, and synchronized dual movement/cognitive task; pilot study in autism spectrum disorder

Authors: T. L. SIMMONS[1], L. CHUKOSKIE[2], J. TOWNSEND[3], *J. SNIDER[4]
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Abstract: It is common to isolate a single cognitive or motor task in laboratory studies, but the reality of our everyday experience is that we engage in multiple tasks simultaneously, e.g. walking while talking (or texting) on our phones. We designed a task to simultaneously quantify balance, fine motor skill, and cognitive ability with objective outcome measures. The system's

temporal precision and modular design also allow for the incorporation of other sensors as needed, like EEG or heart rate variability. We tested the task on a pilot cohort of children with autism spectral disorder (ASD) and matched controls. The system consists of a glove programmed to accurately record finger tapping, a forceplate, and a microphone. The glove has conductive pads on the fingertips that act as switches as participants pinch their fingers and thumb together. The forceplate records center of pressure data at 100Hz. The microphone allows the participant to interact with the task verbally, since their hands may be occupied with tapping. We use custom plugins to the WorldViz Vizard VR development platform to coordinate presenting the task and simultaneously recording multiple data streams.In our pilot study, participants performed a vocally-triggered N-back task, while simultaneously executing combinations of standing and finger tapping. Participants demonstrated their balance control by attempting to remain erect while standing still. We also recorded a measurement of speeded finger tapping. Our pilot study compared the performance of young adult males with autism spectrum disorder (ASD) with normal to high IQ (WASI II) to the performance of typically-developing young adult males with similar IQs. We hypothesized that the additional demands of the balance and speeded finger-tapping task would further degrade motor performance in the simultaneous conditions, but not impact N-Back performance. Movement data was evaluated by comparing the change of each group across 3 levels of cognitive load (0-, 1-, and 2-back). N-Back performance was similar across both experimental and control groups. However, ASD participants were shown to have increased amounts of sway, as well as a slower ability to correct their movements back to center relative to the control group. Similarly, finger tapping speed also decreased more substantially for ASD participants. These results indicate that our task taps into a neural resource shared between cognitively demanding tasks and basic movement tasks.

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Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.21/RR9

Topic: E.06. Posture and Gait

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Future Labs Reloaded 2013, University of Technology Graz, Austria
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Title: Error-related brain dynamics predict step adaptation in a challenging gait task

Authors: *J. WAGNER[1], R. MARTINEZ-CANCINO[1], G. R. MUELLER-PUTZ[2], S. MAKEIG[1]
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Abstract: Gait is not merely automated motor activity but requires attention and other executive function (EF). Relationships between age- and disease-associated declines in cognitive function and mobility are of increasing interest. A growing body of evidence using dual-task walking paradigms indicates a pivotal role of EF in gait control and fall prevention in the elderly and Parkinson's subjects (Mirelman, 2012). EF may compensate for age-associated decline in motor function, however evidence suggests that EF itself is involved in challenging gait tasks (Potocanac, 2014). In a recent gait study using EEG imaging (Wagner, 2016), we provided direct proof of involvement of EF and prefrontal control in gait adaptation. To further pinpoint the roles of cognitive control processes in gait adjustments we examined the source-resolved EEG dynamics of participants attempting to step in time to an auditory tone sequence. Participants had to adapt their step length and rate to shifts in tempo of the pacing stimulus (e.g., following unpredictable shifts to a faster or slower pacing tempo). Analysis revealed a negative potential in the source-resolved EEG, localized to dorsomedial prefrontal cortex (DMPFC) 200-300 ms after onset of the tempo-shift marking stimulus (Figure 1). Multiple regression analysis shows that single-trial amplitude of this negative deflection predicts the size of the subsequent step adaptation for tempo re-adjustment ($R^2 = 0.2$) beginning 500 ms after the shift-marking cue. Negative scalp event-related potential peaks over DMPFC ~250 ms after incorrect button presses, described as error-related potentials, have been associated to control functions including error correction (Holroyd & Coles, 2002). Our results suggest that error-correction processes are directly involved in gait adaptation allowing flexible adaptation of steps to changing external requirements. Future research will investigate age- and disease-associated impairments of these control processes in gait disorders to develop biomarkers for fall risk prediction, e.g. in early-stage Parkinson's.

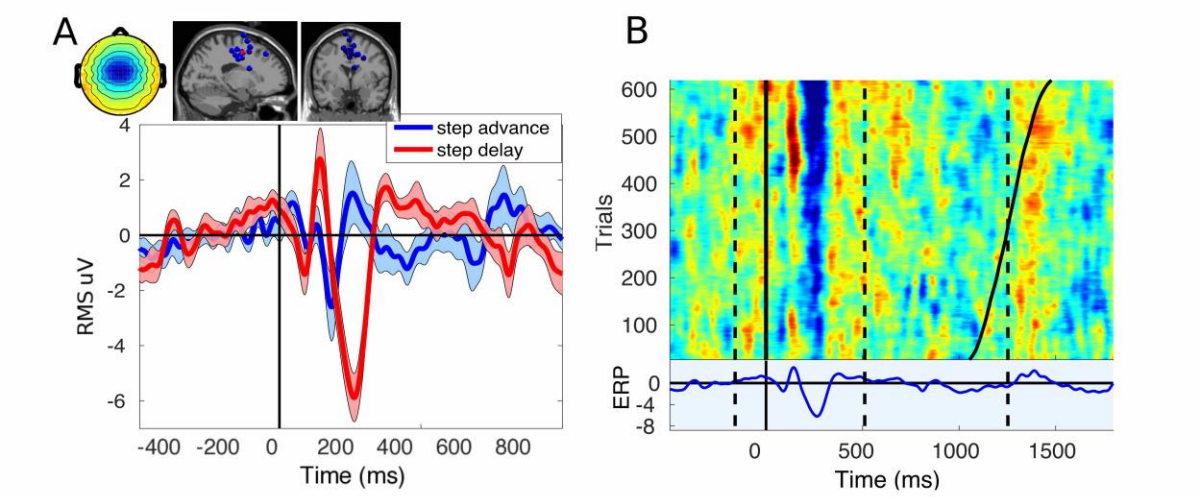

Figure 1: A) Cluster mean scalp projection and cluster single equivalent current dipoles and average ERPs relative to the tone cueing step advance and step delay perturbation. B) Single trials of all 14 subjects for step delay perturbations sorted by the normalized size of the adptation step. The solid vertical line at zero represents the beep indicating the tempo shift; dashed vertical lines are median step latencies. The curved line around 1200ms indicates the relative length of the adaptation step. A larger negative amplitude in the EEG potential predicts a larger adaptation step producing a better adptation to the new tempo (adptation step is defined as inter-step interval (ISI) between 2nd and 3rd steps following the tempo shift expressed as percentage change in pre-shift ISI)

Disclosures: J. Wagner: None. **R. Martinez-Cancino:** None. **G.R. Mueller-Putz:** None. **S. Makeig:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

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Program #/Poster #: 495.22/RR10

Topic: E.06. Posture and Gait

Support: NSERC RGPIN-2016- 04471
FRQS Salary Award (A.L.)
CRIR Scholarship (M.A.B.)

Title: Avoiding pedestrians while walking in physical and virtual environments

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Abstract: Virtual reality provides a unique opportunity to safely assess and train people with disabilities under ecological conditions. While appealing to research and clinical practice, its usefulness is limited by the extent to which it can elicit natural behaviours. To date, this assumption has little supporting evidence, especially when considering complex locomotor tasks such as the avoidance of pedestrians. Objectives were to compare circumvention strategies in response to static and moving pedestrians in a virtual (VE) vs. a physical environment (PE). Twelve participants were assessed while walking towards a target and avoiding a collision with interferers in a PE vs. VE (random order). The VE, viewed in VR goggles, simulated the PE which was the gait laboratory. In the static obstacle condition, participants avoided one interferer that remained static at 3 or 3.5 m from the participants' starting position. In the dynamic obstacle condition, one interferer randomly approached from the left, middle or right (± 40°, 0°), towards a theoretical point of collision located 3.5 m ahead of the starting position. Compared to the PE, circumventing static and moving pedestrians in the VE was characterized by slower walking speeds ($\Delta = 0.14 \pm 0.04$ m/s (mean ± 2SE); $p < .0001$), larger obstacle clearances ($\Delta = 0.10 \pm 0.04$ m; $p < .0001$) and larger mediolateral path deviations ($\Delta = 0.10 \pm 0.04$ m; $p = 0.0002$). No significant differences were observed between environments for the preferred side of circumvention ($p = 0.33$) and onset distance of trajectory deviation ($p = 0.44$). The larger clearances around the interferers and slower walking speeds in the VE suggest the use of "safer" avoidance strategies.The similarities in circumvention strategies between the two environments, however, suggest that virtual reality is a valuable tool to study complex locomotor tasks and shows potential as a rehabilitation tool.

Disclosures: M.A. Bühler: None. **A. Lamontagne:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.23/RR11

Topic: E.06. Posture and Gait

Support: CIHR

Title: Motor impairment in mice with a gain-of-function mutation in retinoic acid receptor beta

Authors: *J. L. MICHAUD, N. LEMMETTI, C. NASSIF
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Abstract: Retinoic acid (RA) signalling is required for the development of several organs, including the eye and the brain. In target cells, RA binds to heterodimeric receptor complexes that function as ligand-activated transcription factors. We previously described several patients with microphthalmia, cognitive impairment and dystonia who carried *de novo* mutations in the

retinoic acid receptor beta gene (*RARB*). We found that these mutations enhance RA-induced transcriptional activity 2- to 3-fold over the wild-type receptor in an in vitro assay, suggesting a gain-of-function (GOF) mechanism.
Dystonia is typically caused by dysfunction of the striatum. RA signaling plays an important role in the generation of striatal neuronal types. Loss of *Rarb* leads to a reduction of striatonigral neurons due to premature differentiation of their progenitors and motor abnormalities in mice. Thus, loss of *Rarb* function may cause motor deficits by disrupting early development of striatal circuits. *We hypothesize that the motor impairment of patients and mice with RARB GOF mutations is caused by increased RARB signaling in the striatum, possibly disrupting homeostatic control of the same pathways as those affected by decreased Rarb signaling*.
In order to investigate this hypothesis, we used CRISPR-Cas9 to introduce p.R394C, the equivalent of the recurrent p.R387C GOF mutation found in some patients, at the *Rarb* genomic locus in mice. We generated 2 independent lines of $Rarb^{R394C/+}$ mice. Behavioral assessment at 2 months of age showed a specific motor phenotype characterized by a short stride, normal strength in the hanging test, increased activity in the open field test, and dramatically reduced motor coordination in the rotarod paradigm. This motor phenotype is reminiscent of that of mouse models of dystonia. We are currently determining when these motor abnormalities first appear and whether they worsen with age. $Rarb^{R394C/R394C}$ mice are born at the expected mendelian ratio but they show a waddling gait, their growth is compromised and they die between birth and 3 weeks of life. In order to understand the cellular basis of the motor impairment associated with p.R394C, we are currently characterizing the striatum of $Rarb^{R394C/+}$ and $Rarb^{R394C/R394C}$ mice using molecular markers.

Disclosures: J.L. Michaud: None. **N. Lemmetti:** None. **C. Nassif:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 495.24/RR12

Topic: E.06. Posture and Gait

Title: Investigating sensorimotor integration in the trunk motor cortex in adult rats

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Abstract: While there exists extensive information about sensorimotor integration in the forelimb, hindlimb and barrel cortex, little is known about details of trunk cortex. Since volitional control of trunk musculature is essential for postural stability and weight supported locomotion, understanding sensorimotor integration in the trunk cortex is useful for studies of

neurological injury or disease where the somatotopic organization of cortex changes. The trunk is especially important for the impact of mid-thoracic spinal cord injury where reorganization of the trunk motor cortex is necessary for the recovery of function. To understand sensorimotor integration in the trunk cortex, we first assessed the extent of trunk motor representation using intracortical microstimulation (ICMS). Then, we examined somatosensory representation in the trunk motor cortex by recording evoked responses to peripheral electric stimulation of forelimb, hindlimb and trunk. **Methods:** Naïve Sprague Dawley rats were anesthetized and a craniotomy over the medial post Bregma area (MPBA) and the caudal forelimb area (CFA) exposed most of the motor cortex. EMG electrodes were implanted in the trunk muscles at different levels of the vertebral column along with hind limb and forelimb muscles. Low impedance Tungsten electrode was slowly lowered to layer 5 of the cortex, in predefined locations. Movement representations were evaluated at the minimum current required to elicit movement/EMG response. Neuronexus probes were then inserted into fixed locations spanning the motor cortex. Evoked responses to peripheral electric stimulation of limbs and trunk were measured. **Results:** Activation of trunk muscles in response to ICMS at threshold current extended from +0.75 to -2.25mm rostrocaudally and from 1.0 to 2.25mm medial from Bregma. However, exclusive activation of trunk musculature is small and medial, and the locations were not consistent across animals. More likely, the trunk motor representation contained 3 distinct coactivation zones: 'synergistic trunk', characterized by unilateral synchronous activation of the forelimb & the hindlimb; 'hindlimb trunk', characterized by co-activation of the hindlimb & trunk musculature and 'forelimb trunk', characterized by co-activation of forelimb and trunk muscles. Evoked responses to both forelimbs hind limbs and trunk were found in the trunk motor cortex, suggesting there is extensive sensorimotor integration within the trunk motor cortex. **Conclusion:** This knowledge from normal animals can be used for greater insight into the reorganization of the trunk motor cortex after spinal cord injury.

Disclosures: B. Nandakumar: None. **G.H. Blumenthal:** None. **K.A. Moxon:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

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Program #/Poster #: 495.25/RR13

Topic: E.06. Posture and Gait

Support: NSF 1535036

Title: Do performance errors and environmental switches regulate generalization of learned locomotor features across contexts?

Authors: *D. DE KAM, W. STARING, G. TORRES-OVIEDO
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Abstract: Movement patterns learned in one context partly generalize to untrained contexts. This generalization is limited by contextual cues, such as large performance errors, that promote linking of motor patterns to the context in which they were learned. We investigated if different strategies to reduce error size promote generalization of locomotor learning to a similar extent. Human locomotor learning was induced by a split-belt treadmill eliciting initial asymmetry in step lengths and subsequent adaptation towards symmetric gait. The control group experienced large performance errors through a semi-abrupt split-belt perturbation (40 strides ramp). Performance errors were reduced in two other groups through distinct learning strategies: 1) by explicitly reducing performance errors (step length asymmetry) using visual feedback, or 2) by implicitly (subconsciously) reducing errors through a gradual split-belt perturbation (600 strides ramp). Generalization was quantified by step length asymmetry after-effects upon removal of the perturbation during overground walking. Smaller errors during adaptation resulted in reduced overground after-effects (gradual, $p=0.025$, feedback $p=0.024$). This was surprising given previous work showing a negative association between error size and generalization (Torres-Oviedo 2012). We reasoned that there were two possible reasons for these contrasting results: 1) a non-linear effect of error size during adaptation and generalization (less generalization if errors during adaptation are too large or too small) or 2) errors experienced upon removal of the perturbation (catch trial) induce less generalization because they facilitate switching between split and regular walking patterns. Thus, we contrasted the generalization of our control group to: 1) an abrupt group experiencing a sudden introduction of the split perturbation, inducing performance errors larger than controls and 2) a catch group that experienced the same perturbation profile as controls but also a catch. Overground after-effects were substantially reduced compared to controls in the catch group only ($p<0.01$). Our results indicate that error size plays an important role in generalization of motor learning from trained to untrained contexts. However, errors experienced when the perturbation is introduced (positive errors) or removed (negative errors) have opposite effects on generalization. Positive errors facilitate generalization possibly because they induce more learning, whereas negative errors mitigate generalization because they enable subjects to recall the appropriate motor pattern according to the context at hand.

Disclosures: D. De Kam: None. **W. Staring:** None. **G. Torres-Oviedo:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

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Program #/Poster #: 495.26/RR14

Topic: E.06. Posture and Gait

Support: NSF-GRFP Grant No.1247842
Pittsburgh Claude Pepper Older Americas Independence Center (P03 AG024827)

Title: Split-belt walking similarly changes active step length perception at different speeds and step lengths

Authors: *C. J. SOMBRIC, M. GONZALEZ-RUBIO, G. TORRES-OVIEDO
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Abstract: Stroke induces motor deficits (e.g., asymmetrical stepping) that limit patients' mobility. Some stroke subjects do not recover symmetric stepping due to additional perceptual deficits, or impaired awareness of their own asymmetrical stepping (Wutzke et al., 2015). Thus, there is a clinical interest to understand if the perception of step lengths can be altered. It is already known that split-belt treadmills, which drive the feet at different speeds, induce shifts in belt speed perception (Vazquez et al., 2015). Therefore, we hypothesized that split-belt walking induces step length perceptual shifts that will vary with walking speed, and thus step length, similarly to motor after-effects (Vasuvaden et al., 2009). We used a virtual reality headset (Oculus Rift) to block visual cues while subjects walked on a treadmill and received feedback about the target step length and their actual step lengths. With this feedback, subjects learned to take three distinct step lengths (short, comfortable, and long). Subject's step length accuracy when feedback unexpectedly only showed 35% of their step length error was used as a proxy for active step length perception. Each subject's perception was measured on the treadmill with both belts moving the same speed before and after two treadmill walking trials: tied- (both belts 1m/s) and split-belt (fast leg 1.5 m/s, slow leg 0.5 m/s). Three groups (n=7 each, 24.4±5 y.o.) differed only in the perception task in order to distinguish the effect of speed and step length on active perception: (1) comfortable (1m/s) walking with short steps, (2) comfortable (1m/s) walking with long steps, and (3) slow walking (0.5m/s) with short steps. Subjects had perceptual shifts such that they overshot all targets with their fast leg and undershot all targets with their slow leg following split, but not tied, walking ($p<0.01$). All groups had similar perceptual shifts ($p=0.99$) indicating that perception doesn't contextualize based on speed or step length, perhaps implying that peripheral sensors or circuits mediate perceptual shifts. Importantly when performance was assessed without visual feedback after training and after split-belt after-effect extinction, all subjects maintained the learned step lengths ($p=0.28$). Unlike perception, motor after-effects (measured step length difference across legs during a short tied-belt trial during adaptation) are larger at slow walking speeds ($p=0.02$; Vasuvaden et al., 2009) even though all groups adapted similarly ($p=0.35$). These results are promising because they imply that split-belt protocols can be tuned for motor outcomes while maintaining perceptual shifts to robustly improve patient's mobility.

Disclosures: C.J. Sombric: None. **M. Gonzalez-Rubio:** None. **G. Torres-Oviedo:** None.

Poster

495. Posture and Gait: Higher Order Control, Multi-Task Integration, and Theory

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Program #/Poster #: 495.27/SS1

Topic: E.06. Posture and Gait

Support: NIH 5K01NS092785

Title: Unifying model of savings, interference, and generalization of motor learning in locomotion

Authors: *G. TORRES-OVIEDO, A. SALATIELLO, D. M. MARISCAL
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Abstract: Split-belt walking, in which legs move at different speeds, can improve patients' mobility by correcting their gait asymmetry (e.g. Reisman et al 2013). For this strategy to be effective it is necessary to maximize the retention of motor memories acquired on the treadmill and their generalization to over ground walking. It has been shown that errors drive the sensorimotor adaptation process, but also the recall of past motor memories (Herzfeld et al. 2014; Ingram et al. 2017). Here we ask if errors could also serve as contextual cues to develop distinct motor memories within the same environment. To address this question we developed a computational model in which the error experienced when a split perturbation was introduced (i.e., positive error) or removed (i.e., negative error) created distinct motor memories. We found that our model was able to reproduce empirical observations of savings, interference, and generalization in the context of locomotor adaptation. More specifically, it reproduced 1) the faster adaptation rate upon experiencing multiple repetitions of the same perturbation (a.k.a., Savings), 2) the slower adaptation rate when two repetitions of the same perturbation were separated by an opposite perturbation in between (a.k.a., Interference) and 3) the reduced adaptation effects when walking over ground (i.e., untrained context) compared to those walking on the treadmill (i.e., training context). In sum, our results indicate that errors are relevant for the development of motor memories, but also their recall when switching between walking environments.

Disclosures: G. Torres-Oviedo: None. **A. Salatiello:** None. **D.M. Mariscal:** None.

Poster

496. Rhythmic Motor Pattern Generation: Speed and Phasing

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 496.01/SS2

Topic: E.07. Rhythmic Motor Pattern Generation

Support: JSPS KAKENHI Grant No. 16K16482
JSPS KAKENHI Grant No. 15KT0015
JSPS KAKENHI Grant No. 26120006

Title: Computational modeling investigation of phase-dependent responses of spinal motoneurons to afferent stimulation during fictive locomotion

Authors: *S. FUJIKI[1], S. AOI[2], K. TSUCHIYA[2], S. M. DANNER[3], I. A. RYBAK[4], D. YANAGIHARA[1]
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Abstract: Animals walk adaptively in diverse environments by appropriately modulating locomotor behavior based on the sensory information. Locomotion involves the reciprocal activation of flexor and extensor muscles and physiological studies have suggested that these activities are produced by the central pattern generator (CPG) in the spinal cord. Stimulation of peripheral nerves in the legs during fictive locomotion can alter motoneuron burst durations and induce a transition between extensor and flexor motoneuron activities. The difference between these responses mainly depends on the timing of the stimulation (phase dependency). The aim of this study was to elucidate the mechanism of the phase dependency during fictive locomotion in terms of dynamic system theory. We used a previously developed computational model of the CPG consisting of networks of neurons modeled in the Hodgkin-Huxley style to simulate fictive locomotion in the cat. We showed that the model can reproduce the phase-dependent response to the applied stimulation as observed in the physiological experiments. The model was used to investigate and mathematically analyze the mechanism that determines the phase-dependent response through the dynamical structure of the governing equations, such as the changes in the nullclines, the positions of the fixed points, and the eigenvalues around the fixed points.

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Poster

496. Rhythmic Motor Pattern Generation: Speed and Phasing

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Topic: E.07. Rhythmic Motor Pattern Generation

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NIH Grant R01 NS095366
JSPS KAKENHI Grant JP15KT0015
JSPS KAKENHI Grant JP26120006

Title: Interactions between spinal circuits and afferent feedback to control locomotion at different speeds: Insights from computational modeling

Authors: *S. M. DANNER[1], S. AOI[2], S. FUJIKI[3], D. YANAGIHARA[3], I. A. RYBAK[1]
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Abstract: To survive in a complex, fast-changing environment, legged animals, including mammals, need to be able to quickly change locomotor speed and gait to express required behavior and adapt it to the environment. Recent optogenetic studies in mice have shown that slow locomotion observed during exploration behavior and fast locomotion observed during escape are differently controlled by supraspinal and spinal neural circuits. Yet, differences in control of slow vs. fast locomotion, including interactions between spinal circuits, afferent feedback, and biomechanical properties of the musculoskeletal system, remain poorly understood. We have developed a neuromechanical computational model of hindlimb locomotion in mouse and used it to study the mechanisms of sensorimotor integration and the role of different afferent pathways in the stabilization of locomotion at different speeds and in different environmental conditions. The model includes a neural network model of the spinal circuits controlling and coordinating limb movements, coupled with a 2D musculoskeletal model of the mouse hindlimbs (3 joints and 7 muscles per limb). Each limb is controlled by a two-level central pattern generator (CPG) consisting of a rhythm generator (RG), and pattern formation (PF) network, as well as circuits, mediating basic reflexes and motoneurons actuating hindlimb muscles. In our model, the RGs control the basic locomotor oscillations, commissural interneurons (CINs) mediate left-right interactions between the CPGs, and PF circuits form motor synergies and generate muscle-specific activation patterns. The velocity- (Ia), force- (Ib) and length-dependent (II) feedback from each muscle as well as cutaneous feedback modulate the operation of each CPG, their interactions via CINs, motor synergies formed at the PF level,

and motoneuronal activities. CMA-ES (covariance matrix adaptation evolution strategy) was used to find a pattern of afferent feedback connections to the spinal circuits that provide stable locomotion at different speeds during level and slope walking. The proposed connectome of spinal circuits and the organization of afferent feedback allowed the model to closely reproduce characteristics of mouse locomotion with slow (exploratory) and fast (escape) speeds and to adapt locomotion to unpredictable changes in the environment. Analysis of locomotor disturbances and failures in the model following selective removal of individual intraspinal, commissural or feedback pathways allowed us to suggest the specific role of these pathways in different forms of locomotor behavior and in providing stable locomotion under different conditions.

Disclosures: S.M. Danner: None. **S. Aoi:** None. **S. Fujiki:** None. **D. Yanagihara:** None. **I.A. Rybak:** None.

Poster

496. Rhythmic Motor Pattern Generation: Speed and Phasing

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Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH grant R01NS090919
NIH grant R01NS095366
NIH grant R01NS100928

Title: Computational modeling of brainstem circuits controlling locomotor speed and gait selection

Authors: *N. A. SHEVTSOVA[1], V. CAGGIANO[2], J. AUSBORN[1], S. M. DANNER[1], I. A. RYBAK[1]
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Abstract: Locomotion is an essential motor activity allowing animals to explore and to survive in complex environments. Depending on the environmental context and current needs quadruped animals including mice can switch locomotor behavior from slow left-right alternating gaits, such as walk and trot (typical for exploration), to higher-speed synchronous gaits, i.e. gallop and bound (specific for escape behavior). Recent studies have shown that the above distinct types of gaits and locomotor behaviors are differently controlled by two brainstem nuclei: the cuneiform nucleus (CnF) and the pedunculopontine nucleus (PPN) (Caggiano et al. 2018). Glutamatergic (Glu) neurons within both of these nuclei contribute to the control of slow, alternating-gait movements, whereas only stimulation of CnF is able to elicit high-speed, synchronous-gait

locomotion. Neurons from both of these regions project to and activate spinal locomotor circuits via descending reticulospinal tracts including the lateral paragigantocellular nucleus (LPGi) (Capelli et al. 2017).
To model and computationally investigate the brainstem control of locomotion, we built upon our previous model of spinal circuits, consisting of four rhythm generators (RGs, each controlling one limb) interacting via networks of local cervical and lumbar commissural interneurons (CINs) and long propriospinal neurons (LPNs) connecting cervical and lumbar compartments (Danner et al. 2017). This model was able to reproduce the experimentally observed speed-dependent gait transitions, but did not include the supraspinal control provided by brainstem circuits. We extended the model to incorporate the bilaterally interacting CnF and PPN circuits and their LPGi-mediated descending pathways to the spinal cord. The suggested organization of synaptic inputs from these pathways to the spinal RGs, CINs and LPNs allowed the model to reproduce the experimentally observed effects of stimulation of excitatory (Glu) and inhibitory neurons within CnF, PPN, and LPGi. Using the model we investigate (a) the involvement of CnF and PPN in the control of low-speed alternating-gait locomotion, (b) the specific role of CnF in the control of high-speed synchronous-gait locomotion, and (c) the roles of inhibitory neurons from the above areas in slowing down and/or stopping. Specifically, the model shows that the suppression of PPN during the CnF stimulation-evoked locomotion leads to the experimentally observed shift of the speed-dependent transition between trot and gallop/bound to lower locomotor speeds.
The model provides important insights into the brainstem-spinal cord interactions and supraspinal control of locomotion.

Disclosures: N.A. Shevtsova: None. **V. Caggiano:** None. **J. Ausborn:** None. **S.M. Danner:** None. **I.A. Rybak:** None.

Poster

496. Rhythmic Motor Pattern Generation: Speed and Phasing

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Program #/Poster #: 496.04/SS5

Topic: E.07. Rhythmic Motor Pattern Generation

Support: DFG SM206/3-1
DFG RTG 1960

Title: Intermitted in-phase activity of the crustacean locomotion circuit

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Abstract: Coordination of central pattern generators (CPG) is an important feature accomplished by the nervous system and is responsible for many forms of effective locomotion. Crayfish and other long-tailed crustaceans swim by rhythmically moving limbs called swimmerets. Movements of adjacent swimmerets maintain an approximate quarter-period phase difference, independent of frequency, with the more posterior limbs leading the cycle. The crayfish swimmeret system is one of the very few, if not the only, locomotor systems in which the structure and properties of both the CPG and its coordinating circuit have been clearly identified at the neuron *and* synaptic level, and therefore it provides an excellent model system to investigate the coordination of distributed neural oscillators.
The four pairs of crayfish swimmerets are innervated by a chain of four abdominal ganglia. In each segment (a hemiganglion), a half center oscillator (HCO), consisting of two interneurons with mutual inhibition, controls motor neurons to activate the limbs in alternating cycles of power-stroke and return-stroke. The intersegmental network comprises in each segment three types of neurons: two spiking Coordinating Neurons (ASC_E and DSC) and one Commissural Neuron (ComInt1); together they synchronize the activities of the HCO chain such that neighboring HCOs maintain a quarter-period phase difference.
Recently, we found that the application of 4-Aminopyridine (4-AP), a K^+-channel blocker, on a well-coordinated isolated nerve cord disrupted the normal quarter-period phase-locked coordination pattern and produced intermittent in-phase activity, i.e., the activity switched between periods of tonic activity and periods of in-phase activity of the motor neurons in all segments. Two major changes in the coordinating circuit were observed and analyzed in this condition: first, there was no longer activity in the DSC (the descending coordinating neuron that projects posteriorly), while the activity of ASC_E (the ascending coordinating neuron that projects anteriorly) was intact with the correct timing; second, there was no longer a gradient of synaptic strength from different segmental ASC_E's to ComInt1. Using a mathematical model with added noise, we found that each of the two changes led to a significant decrease in the phase-lag between neighboring segments, and together they replicated the observed in-phase coordination pattern.
The above result suggests that the blocking of K^+ channels in the crayfish swimmeret neural circuit could lead to a complete shift in its coordinating pattern from the natural quarter-period phase-locking to an intermittent in-phase synchronization.

Disclosures: C.R. Smarandache-Wellmann: None. **L. Schlaeger:** None. **C. Zhang:** None.

Poster

496. Rhythmic Motor Pattern Generation: Speed and Phasing

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 496.05/DP09/SS6

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIDCD Grant DC015827
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Title: Principles underlying the feedforward control of multi-jointed limbs

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Abstract: The precise control of multi-jointed limbs is central to our ability to perform a vast array of behaviors. Multi-jointed limbs allow an animal to tune its motor output finely, but controlling the many degrees of freedom resulting from multi-jointed limbs is a well-recognized challenge. A central question in motor control is how the nervous system transforms larger behavioral goals into the complex computations necessary for the moment-by-moment control of multi-jointed limbs. Here we employ genetics, *in-vivo* electrophysiology, and quantitative analysis of leg kinematics to determine the respective contribution of circuits in the brain, circuits in thoracic ganglia, and sensory feedback to the generation of limb movements. By manipulating central control and sensory feedback under diverse preparations, we come to four conclusions regarding the control of leg movements in *Drosophila*. First, without sensory feedback from the environment, inter-leg coordination is almost completely disrupted. Second, in contrast to inter-leg coordination, many aspects of intra-leg coordination remain intact. In particular, retraction-protraction (RP) and extension-flexion (EF) are flexibly coordinated by central circuits such that a vast majority of movement epochs can be classified into a small number of discrete movement-types. Third, maintaining this structured movement requires descending inputs from the brain. Fourth, feedback from the environment seems critical for eliciting levation-depression movements which in turn structures movement into alternating stance and swing phases. We use this framework to underpin the role of descending neurons (DNs) from two different parts of the brain in shaping motor output by recording from them while measuring leg kinematics. We find that one class of DNs mediate sensorimotor transformation: they respond to sensory stimuli and mediate movement in a subset of legs. A second class of DNs do not perform specific sensorimotor transformations: they do not respond to any sensory stimuli, and their activity is not dependent on the identity of the leg that is moving. Rather, they respond only when a particular type of movement is executed. In sum, there is a division of labor between feedforward and feedback which represents an elegant solution to the “degrees of freedom” problem.

Disclosures: V. Bhandawat: None. **C.T. Hsu:** None.

Poster

496. Rhythmic Motor Pattern Generation: Speed and Phasing

Location: SDCC Halls B-H

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Topic: E.08. Respiratory Regulation

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Title: Activation timing and order in the sequence during rhythmic burst is dependent on cell type of inspiratory neurons in the pre-Bötzinger complex of the mice medulla slice

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Abstract: The pre-Bötzinger complex (preBötC) is an important medullary region, which generates spontaneous respiratory rhythm. In the preBötC of rodent medullary transverse slices, rhythmic burst activities can be recorded as local field potential (LFP) as well as using calcium imaging. Interestingly, the activation-order of inspiratory neurons changes stochastically cycle-by-cycle but with loose regularity where a subset of inspiratory neurons appear to cover the initial part of the activation sequence. To analyze the timing of activation and to understand the observed loose regularities, we tested how the neuron type influences its position in the activation sequence using double-transgenic mice expressing EGFP in glycine transporter 2 (GlyT2)-positive neurons and tdTomato in glutamic acid decarboxylase 65 (GAD65)-positive neurons. Based on the maximum cross-correlation (maxCC coefficient) between the neuronal calcium signal of each cell (7 x 7 pixels ROI) and the LFP, we identified 5 groups of inspiratory neurons, that showed, in principle, a different time of activation. We found two groups of respiratory neurons, which showed a large calcium signal with clear waveform (regular type neurons). (1) GlyT2-/GAD65- neurons : regular type excitatory neuron (R-Ex) and (2) GlyT2+/GAD65-: regular type glycinergic neuron (R-Gly). Additionally, there were three groups of neurons showed a small maxCC coefficient and small and short waveform during the rhythmic burst (irregular type neuron): (3) GlyT2-/GAD65-: irregular type excitatory neuron (Irr-Ex) (4) GlyT2+/GAD65-: irregular type glycinergic neuron (Irr-Gly) (5) GlyT2+/GAD65+: irregular type cotransmitting neuron (Irr-Cotrans). Activation of Irr-Ex and Irr-Gly tended to

occur much earlier (e.g. before the peak of LFP) than those of R-Ex and R-Gly. Activation occurrences of Irr-Cotrans spread widely throughout the rhythmic burst and were detected often late. When investigating the order of activation, Irr-Ex was the major cell type activated during the initial phase of the sequence, when many of Irr-Gly were also activated. Activation of R-Ex and R-Gly were rarely observed in this initial phase, while Irr-Cotrans neurons were also activated late in the sequence. We conclude that the stochastic activation-sequence of preBötC-inspiratory neurons depends on the neuron types.

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Poster

496. Rhythmic Motor Pattern Generation: Speed and Phasing

Location: SDCC Halls B-H

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Program #/Poster #: 496.07/SS8

Topic: E.07. Rhythmic Motor Pattern Generation

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Title: Modulation of spike timing of specific interneurons critical for phase termination by multiple neuropeptides in a small network

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Abstract: Neuropeptides are often present in projection interneurons that modulate the excitability of pattern generating (CPG) interneurons which are responsible for terminating specific phases of multiphasic motor programs. Thus, they can alter the nature of the motor output. However, in complex networks, more than one CPG interneuron can be responsible for phase termination. How neuropeptides may target these different CPG interneurons and alter spike timing is not well understood. We address these issues in the feeding circuit of Aplysia. Feeding behavior is biphasic, each cycle consists of radula protraction-retraction phases. Previous work has identified two CPG interneurons, B64 and CBI-5/6, both of which normally fire during retraction, and when activated, terminate protraction. In addition, several neuropeptides, such as FCAP and ALKs, increase B64 excitability to shorten protraction.

However, it is unknown whether and how CBI-5/6 is modulated by neuropeptides. We sought to study apSPTR-GF-DP2, which has recently been shown to shorten protraction, not by acting on B64, but by increasing the excitability of B20. However, B20 is active during protraction and its effects are indirectly mediated. Here, we show that apSPTR-GF-DP2 exerts a direct action by enhancing CBI-5/6 excitability, and by advancing the spike timing of CBI-5/6 during CBI-2-elicited programs. Moreover, when either CBI-12, which contains apSPTR-GF-DP2, or B20 is stimulated together with CBI-2, protraction becomes shorter and CBI-5/6 activity is phase advanced. Both CBI-12 and B20 also increase the excitability of CBI-5/6. Thus, CBI-12 and its peptide (apSPTR-GF-DP2) act both directly (on CBI-5/6) and indirectly (on B20) to shorten protraction, providing an example of a feedforward loop of peptidergic actions. In contrast, neither FCAP nor ALKs enhance the excitability of CBI-5/6. On the other hand, we demonstrate that ALKs advances spike timing of B64 during CBI-2-elicited programs. We conclude that different neuropeptides target distinct interneurons to alter their excitability and change their spike timing, and ultimately, the motor parameters of feeding programs. These findings highlight critical roles of peptidergic modulation of both excitability and spike timing of CPG interneurons in generating diverse motor outputs.

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Poster

496. Rhythmic Motor Pattern Generation: Speed and Phasing

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 496.08/SS9

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Novo Nordisk
NINDS

Title: Recruitment of Dbx-1-positive spinal neurons encode speed-dependent behavioral states

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Abstract: Dbx-1 positive commissural interneurons (INs) are divided in two subpopulations, the $V0_D$ and the $V0_V$ INs, that are required for left-right alternation at slow speeds of locomotion corresponding to walk or higher speed locomotion corresponding to trot (Talpalar et al. Nature 2013; Bellardita and Kiehn 2015). However, how exactly $V0_D$ and $V0_V$ INs encode left/right alternation during locomotion remains unknown.
To address this issue we have applied combined techniques that allow examination of the

relationship between spatially and temporally coordinated neuronal activity of these interneuron populations during rhythmic locomotor activity. First, we used intersectional mouse genetics and clarity for revealing the anatomical location of the $V0_V$ and $V0_D$ INs in the lumbar spinal cord in E17.5 mice. $V0_V$ INs appeared to have a ventro-lateral position in the ventral horn while the $V0_D$ INs were located dorso-medially. Thereafter, we used calcium imaging and optogenetics in the isolated preparations of the lumbar spinal cord to visualize V0 INs activity and to drive them at different frequencies of fictive locomotion. The calcium dynamics and the optogenetic activation of V0 INs revealed a speed-dependent mode of operation of the spinal circuitries involved in alternation. The majority of the $V0_D$ were activated at low speeds of locomotion followed by the activation of the $V0_V$ at higher speeds of locomotion. Optogenetic activation of V0 neurons strongly modulates rhythm-generation at low speed and this effect tends to decrease as the speed of locomotion increases.
In conclusion, the speed-dependent alternation of limbs necessary for alternating gaits in mice is supported by the speed-dependent recruitment of the V0 INs. A sequential recruitment of the $V0_D$ and $V0_V$ INs support a modular organization of the left-right alternating circuits. The decreased ability of modulating locomotor output by V0 neurons as speed increases support a role of these cells directly modulating the core rhythm-generating circuits.

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Poster

496. Rhythmic Motor Pattern Generation: Speed and Phasing

Location: SDCC Halls B-H

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Program #/Poster #: 496.09/SS10

Topic: E.07. Rhythmic Motor Pattern Generation

Support: Swedish Research Council

Title: Diversity of glycinergic V0d interneurons and their function in the zebrafish locomotor circuit

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Abstract: An intrinsic feature of locomotion is the ability to transition between different speeds while maintaining appropriate alternation of limb and axial muscles. While key circuit mechanisms for speed control have been revealed in adult zebrafish, those controlling reciprocal alternation remain unclear. A study in mice has suggested that inhibitory commissural interneurons (V0d) control limb alternation at slow speeds, whilst excitatory commissural interneurons (V0v) take over at faster speeds. In adult zebrafish, most V0v interneurons are recruited only during fast swimming, yet little is known about the adult V0d population. Here,

we characterise the glycinergic V0d population in zebrafish. There were ~10 V0d interneurons per spinal hemi-segment, significantly fewer than other interneurons in the swim network. Targeted patch-clamp recordings in larvae revealed a majority of V0d interneurons to be recruited only during fast swimming. By contrast, in adult zebrafish, our analysis revealed three main V0d classes - fast, intermediate, and slow - which are recruited at their respective swim speeds and displayed partially overlapping electrophysiological profiles. However, we found an overall predominance of slow-type V0d interneurons, in contrast to the larva. Furthermore, the axon projections and dendritic trees of adult V0d interneurons were heterogeneous, even within classes, suggesting both functional and anatomical changes during development. To test the overall function of the adult V0d population we performed 2-photon ablations of 20-40 V0d interneurons across 5 spinal segments and recorded contralateral, back-labelled motoneurons (MNs). Preliminary evidence showed that midcycle inhibition was sustained only briefly during a swim episode, before reducing in amplitude such that MN firing became tonic and a coordinated swim pattern collapsed. Finally, our analysis identified two distinct, apparently specialised, V0d subtypes in the adult. Each occupies a specific position in the outermost (dorso-medial and ventro-lateral) locations of the spinal cord, and displayed a stereotyped morphology, electrophysiological profile, and activity pattern that all indicate that they may be specialised for escape. Overall, we show that the zebrafish V0d interneuron population undergoes considerable developmental changes in function and morphology, from a relatively homogenous population contributing to fast swimming, to a more heterogeneous population largely involved in slow swimming but supplemented by specialised subtypes. In the adult, the V0d population appears to be critical for the appropriate maintenance of locomotion.

Disclosures: L.D. Picton: None. **R. Björnfors:** None. **A. El Manira:** None.

Poster

496. Rhythmic Motor Pattern Generation: Speed and Phasing

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Topic: E.07. Rhythmic Motor Pattern Generation

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China MOST 2013ZX0950910
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NNSFC 91432114
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Title: Coordinated control of locomotor speed, arousal, and hippocampal theta rhythms by the nucleus incertus

Authors: *L. LU, Y. REN, T. YU, Z. LIU, L. TAN, J. ZENG, Q. FENG, R. LIN, R. WANG, Y. LIU, Q. GUO, M. LUO
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Abstract: When navigating at fast speed through a complex environment, an animal not only needs to execute locomotor programs but also requires higher arousal to attend to rapidly changing environmental cues and retrieves spatial associations from memory that is often associated with hippocampal theta oscillations. However, it remains unclear how these important behavioral and physiological processes are coordinately controlled. Here we show that the neuromedin B (NMB) neurons in the nucleus incertus (NI) of the dorsal pons coordinately control locomotor speed, pupil-linked arousal levels, and hippocampal theta rhythm. Cell type-specific fiber photometry revealed that the activity of NI NMB neurons is tightly correlated with mouse locomotor speed, pupil size, and hippocampal theta power. These processes were reversibly suppressed by optogenetic inhibition and rapidly promoted by optogenetic activation of NI NMB neurons. Finally, anatomical and physiological dissections revealed that the NI NMB neurons provide mainly GABAergic output and form reciprocal connections with several subcortical areas associated with arousal, motivation, and premotor processing. Our experiments thus suggest that the NI—an evolutionarily conserved brainstem nucleus—is strategically located within the neural circuit for navigation control according to particular brains states.

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Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.01/SS12

Topic: E.09. Motor Neurons and Muscle

Title: Assessment of parkinson`s disease through clinical and demographic data

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Abstract: Parkinson disease (PD) is a progressive neurologic condition that causes motor and non-motor manifestations. Treatment provides symptomatic benefit but no current treatment has been proven to slow disease progression. Research studies of PD require a means of rating the

severity of disease by measurement of motor manifestations, assessment of ability to perform daily functional activities, and symptomatic response to medication. The work presented in this paper emphasize on some of the clinical and demographic data's collected from 16 subjects out of which 8nos were PD subjects and 8nos were control subjects. Different rating scales like Mini mental State Examination, Webster Scale, Geriatric Depression Scale, and Unified Parkinson's Disease Rating Scale were used for the clinical assessment of the subjects. Some of the demographic data's were also collected. They were: age, gender, occupation, and exposure to environmental factors like well water drinking, dietary habit, smoking, intake of alcohol, insecticides, pesticides etc, and family history of PD. It was found that above mentioned scales are very much useful with combination of demographic data to detect Parkinson's disease in the early stages and that can lead to benefit for modern diagnostic tool.

Disclosures: A. Saikia: None. **V.K. Pandey:** None. **S. Paul:** None. **M. Hussain:** None. **A.R. Barua:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.02/SS13

Topic: E.09. Motor Neurons and Muscle

Support: KAKENHI 16K01468

Title: Streptozotocin-induced diabetes causes crucial morphological changes in abdominal motoneurons and muscles of rats

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Abstract: Diabetic neuropathy (DN) is a major complication of diabetes. Although it is well-established that DN targets sensory and autonomic nerves, little is known about its influence on motor disorders. This study investigated morphological alterations in abdominal (Abd) motoneurons and muscles of experimental type I diabetic rats. Alterations in the number and size of Abd motoneurons were studied using retrograde labeling techniques in diabetic rats 6 or 14 weeks after injection of streptozotocin (diabetic group). Age-matched control animals were labeled at 6 or 14 weeks after saline injection (control group). Further, the thicknesses of the external oblique, internal oblique, transversus abdominis (TA), and rectus abdominis (RA) muscles were similarly examined and the cross-sectional area of the TA myocytes was measured. The mean number and the mean soma diameter of labeled Abd motoneuorns tended to decrease

in diabetic group. The mean number in L1 and mean size of cell bodies in T13 and L1 significantly decreased in the diabetic group compared with the control group ($P < 0.05$). In the diabetic group, there was a clear decrease in muscle thickness except for RA muscle and in the cross-sectional area of the TA myocytes ($P < 0.05$). The main component of these alterations might be loss of the cell bodies of larger motoneurons, or shrinkage of the cell bodies of larger motoneurons and loss of smaller motoneurons. We suggest that the hyperglycemia could induce the reduction of number and size of Abd motoneurons and caused an atrophy of Abd muscles. Therefore, it could be expected that disorders will start at 6 weeks of diabetes and be related to a wide range of disorders such as those involved with expiratory, defecation function, and trunk movement.

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Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

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Program #/Poster #: 497.03/SS14

Topic: E.09. Motor Neurons and Muscle

Title: miR-138 controls motor behavior and neuronal spine morphology *in vivo*

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Abstract: Dendritic spines are small protrusions from the neuronal dendritic shaft that receives inputs from excitatory axons. Neuronal spines are dynamic, heterogeneous in morphology and play a role in synaptic plasticity. Understanding how spine morphology is regulated is crucial for determining how neurons integrate and generate information. miR-138 is highly expressed in the mouse central nervous system, yet the *in vivo* role of miR-138 has not been investigated. In this work we describe the generation and characterization of miR-138-1/miR-138-2 double knock out (DKO) mice. DKO mice exhibited a number of phenotypes and importantly, performed less well compared to WT controls in a set of motor behavioral tests. To further characterize these defects, we analyzed tissues at the whole mount and histological level. DKO brains weighed significantly less than age-matched controls and sectioning of the DKO brains revealed a thinner width of the motor cortex. Although we detected no differences in number of cells in the motor cortex, the number of stubby spines was significantly greater in DKO mice, and the total number of thin spines decreased. RNA sequencing of motor cortex from WT and DKO mice revealed differences in RNA levels, laying a solid foundation for exploration of molecular mechanism. We hypothesize that the observed motor deficiencies might be due to alterations in spine

morphology in the brain, particularly in the motor cortex. Spine alteration is an important substrate in the pathogenesis of motor disorders as well as neurological disorders such as amyotrophic lateral sclerosis, schizophrenia and Alzheimer's disease. New findings on spine morphology regulation may provide insight into etiologies and therapy. Overall, these data demonstrate an important and as-yet undefined role for miR-138 in the mammalian brain and raise important questions about noncoding RNA roles in human disease.

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Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.04/TT1

Topic: E.09. Motor Neurons and Muscle

Title: Gender and age peculiarities of electromyographic indices in qualified rowing athletes

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Abstract: Introduction. At the present time the problem of educating locomotory skills draws researchers attention due to the large amount of novel facts of brain motor cortex and spinal cord structures plasticity. Electromyographic (EMG) study allows to assess peculiar pattern of inhibition and excitation processes in intrasegmental systems and also to determine the kind of descending influences from motor cortex to segmental spinal motoneuronal pool. It was reported that there were certain specificities of the EMG indices shown by athletes performing different sports. At the same time, influence of gender and age factors on neuromuscular apparatus state remains insufficiently studied. **Purpose.** The objective of the research was to assess gender and age-related peculiarities of EMG indices in qualified rowing athletes. **Materials and methods.** Fifty two athletes-rowers (27 men and 25 women, 17-33 years of age, M_{age}=21.4, SD=3.9) took part in this EMG-study. The method of H (Hoffmann) reflex of soleus muscle and the median nerve conduction velocity (NCV) method were performed at both body sides using neurodiagnostic complex Nicolet Biomedical Viking Select (Viasys Healthcare, USA). Three-factor analysis of variance considering two between-subjects factors (sex and age) and one within-subjects factor (body side) was carried out in the SPSS 17.0. **Results and discussion.** It was found that the sex factor had significant effect on values of the H- and M-responses thresholds (F=5.736, P=0.021; F=7.632, P=0.008 respectively), which were higher in women than in men. This might be due to thicker subcutaneous fat tissue in female body. The sex factor also had effect on values of the H- and M-responses magnitudes (F=5.336, P=0.026; F=7.317,

P=0.010), which were smaller in women than in men. This might be the evidence of less muscle weight and muscle fiber volume in women comparing with men. In young athletes the gender difference of the M-responses magnitude was greater than in adults (the interaction of sex and age factors F=4.071, P=0.050). Although all three factors had no significant effect on median motor NCV, median motor proximal and distal amplitudes were higher at the right side of the body (F=4.950, p=0.032; F=11.247, p=0.002 respectively). Such differences might be due to adaptative neuromuscular system reactions under the influence of longterm physical activity. **Conclusion.** Obtained data demonstrate plasticity of neuromuscular system structures, associated with genetical determination and adaptative reactions to a physical exercise. It is assumed that gender and age should be considered during the electromyographic investigation of human neuromuscular system.

Disclosures: E.V. Kolosova: None. **A.V. Gorkovenko:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

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Program #/Poster #: 497.05/TT2

Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant 1R01DC014679-01A1

Title: Sensory innervation of the human soft palate

Authors: *J. CHEN[1], L. MU[2], J. LI[2], T. NYIRENDA[2], S. SOBOTKA[2,3]
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Abstract: The human soft palate plays an important role in respiration, swallowing, and speech. These motor activities depend on reflexes mediated by sensory nerve endings. To date, the details of human sensory innervation to the soft palate have not been demonstrated. In this study, eight adult human whole-mount (soft palate-tongue-pharynx-larynx-upper esophagus) specimens were obtained from autopsy. Each specimen was bisected in the midline, forming two equal and symmetrical halves. Eight hemi-specimens were processed with Sihler's stain, a whole-mount nerve staining technique. The remaining eight hemi-soft palates were used for immunohistochemical study. The soft palatal mucosa was dissected from the oral and nasal sides and prepared for neurofilament staining. Our results showed that the sensory nerve fibers formed a dense nerve plexus in the lamina propria of the soft palatal mucosa. There was a significant difference in the innervation density between both sides. Specifically, the oral side had higher density of sensory nerve fibers than the nasal side of the soft palate. The mean number and

percent area of the sensory nerve fibers in the mucosa of the nasal side was 78% and 72% of those in the mucosa of the oral side, respectively (P <0.0001). The data presented here could be helpful for further investigating the morphological and quantitative alterations in the sensory nerves in certain upper airway disorders involving the soft palate such as obstructive sleep apnea (OSA) and for designing effective therapeutic strategies to treat OSA.

Disclosures: J. Chen: None. **L. Mu:** None. **J. Li:** None. **T. Nyirenda:** None. **S. Sobotka:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.06/TT3

Topic: E.09. Motor Neurons and Muscle

Title: Modulation of post-contraction potentiation in the central nervous system

Authors: *T. ISHII[1], S. SASADA[2], S. SUZUKI[3], T. KOMIYAMA[1]
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Abstract: Surface electromyogram (EMG) activities of the biceps brachii (BB) during a weak elbow flexion are reported to increase immediately after a strong (25 or 50% maximum voluntary contraction [MVC]) elbow flexion is exerted. This phenomenon is called “post-contraction potentiation (PCP)” and has been thought to be driven by an acute modulation in the central nervous system. However, the underlying mechanisms have not been determined. To address this issue, we investigated the PCP phenomenon using transcranial direct current stimulation (tDCS). A total of 44 healthy volunteers, aged 21–30 years and with no history of neurological diseases, were enrolled in this study. In Experiment 1 (Exp 1), the participants were asked to consecutively perform 2 % (test contraction, TEST 1), then 25, 50 or 100 % (conditioning contraction [CC]), and again 2 % (TEST 2) MVC contraction with a visual feedback of force. EMG was recorded from the right biceps brachii (BB). In experiment 2 (Exp 2), the CC was performed only at a 50 % MVC, but the sequence of contractions was the same as that in Exp 1; before the task, tDCS was applied to the BB area of the motor cortex (2 mA) for 15 min with 3 different polarities (anodal, cathodal, and sham). In experiment 3 (Exp 3), the sequence of contractions was the same as that in Exp 2, but the participants were asked to perform 2 % EMG (TEST 1 and 2) with a visual feedback of the BB EMG. In Exp 1, in three different CC conditions, the EMG activity was significantly increased during TEST 2 compared with during TEST 1. However, there was no significant difference in the EMG activity for TEST

2. In Exp 2, the EMG activity during TEST 2 was decreased after anodal tDCS but increased after cathodal tDCS, compared with after sham tDCS. In Exp 3, when the visual feedback of the BB EMG was administered during the task, the force was significantly decreased during TEST 2 compared with during TEST 1. Frequency power spectrum analysis showed that the power of 10 Hz and 20 Hz band was significantly increased during TEST 2 compared with during TEST 1. The present findings suggest that the motor cortex plays a role, at least partially, in generating PCP and that the change in the excitability in the central nervous system may modify the firing rate of the motor unit.

Disclosures: T. Ishii: None. **S. Sasada:** None. **S. Suzuki:** None. **T. Komiyama:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.07/TT4

Topic: E.09. Motor Neurons and Muscle

Support: Maratona da Saúde
CAPES-FCT
CNPq

Title: The ergogenic effects of caffeine depend on neuronal $A_{2A}R$

Authors: *A. S. AGUIAR, JR[1], A. E. SPECK[2], P. M. CANAS[3], R. A. CUNHA[4]
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Abstract: Ergogenic aid is a substance or method used for enhancing exercise and sports performance. The efficacy of many of these techniques is controversial. Caffeine is the most used ergogenic aid for amateur and professional athletes; the ergogenic effects of caffeine are clear and very well documented. However, the mechanisms of action have not yet been clarified, currently limited to three hypotheses. The increased (1) intracellular Ca^{+2} mobilization and (2) cAMP activity were only demonstrated at toxic mM concentrations. At non-toxic concentrations (uM), caffeine acts as an antagonist of adenosine receptors. First, we evaluated the ergogenic and thermogenic effect of caffeine (a non-selective antagonist of $A_{2A}R$) and SCH-58261 (a selective antagonist of $A_{2A}R$) on WT mice. Then we confirm the role of $A_{2A}R$ in forebrain knockout mice. Thirty-four adult male mice (23±0.4 g body weight, 10-12 weeks old) from a forebrain $A_{2A}R$ knockout colony were used. The animals underwent a period of familiarization on the treadmill (3 days x 10 min, 15 cm/s, 5°, saline i.p) for ergospirometry (running power and respiratory

gases - O_2 and CO_2) on the 5th day. Caffeine (15 mg/kg, i.p., -15 min) and SCH 58261 (1 mg/kg, i.p., -15 min) were administered on the 4th day of open field behavioral task (15 min) and on the 5th day of ergospirometry. The animals ran at increasing speeds until they reached exhaustion. The temperature at rest and after exercise was evaluated by IR thermography. The animals were perfused for immunohistochemistry of prefrontal cortex. Caffeine and SCH-58261 were psychostimulant (distance and average speed) for WT animals in the open field, but not for forebrain-A_{2A}R-KO animals. Caffeine and SCH-58261 were ergogenic for WT mice, that is, they increased 41.4±7.2% and 57.2±10.7% the running performance on the incremental running test. In addition, caffeine and SCH-58261 also increased 37±8.3% and 36.4±13.3% $\dot{V}O_2$max in WT mice, respectively. $\dot{V}CO_2$ had similar kinetics. But caffeine unchanged running power, submaximal and maximum $\dot{V}O_2$ and $\dot{V}CO_2$ of forebrain-A_{2A}R-KO animals. Acute physical activity increased cFos density in the prefrontal cortex of the animals. The different genotypes and treatments did not modify the body and tail temperature at rest and exercise-induced hyperthermia. Extracellular electrophysiology and high-resolution respirometry in striatum slices demonstrated the psychostimulant effects of caffeine. Our results suggest that the ergogenic effects of caffeine are mediated by A_{2A}R in the central nervous system.

Disclosures: A.S. Aguiar: None. **A.E. Speck:** None. **P.M. Canas:** None. **R.A. Cunha:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.08/TT5

Topic: E.09. Motor Neurons and Muscle

Support: FAPESP - Brazil - 2014/06892-3
CNPq - Brazil

Title: Neuronal preservation and reactive gliosis attenuation following neonatal sciatic nerve axotomy by a fluorinated cannabidiol derivate

Authors: *A. L. OLIVEIRA[1], M. PEREZ[2], L. P. CARTAROZZI[3], G. CHIAROTTO[4], F. S. GUIMARAES[5]
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Abstract: Lesion to the immature peripheral nervous system, such as the transection of a peripheral nerve, results in extensive degeneration of motoneurons and dorsal root ganglia (DRG) sensory neurons, mostly by apoptotic events. We have previously shown that cannabidiol

(CBD), the most abundant non-psychotropic molecule present in the *Cannabis sativa* plant, exhibits neuroprotective action when daily administered at a dose of 15mg/Kg. The present work shows that the use of 4'-fluoro-cannabidiol, HUF-101, a fluorinated synthetic version of CBD, significantly improves neuronal survival by 2-fold with only one-third of the dose. Furthermore, we show that HUF-101 administration significantly upregulates anti-apoptotic genes and block pro-apoptotic nuclear factors expression. Two-day-old Wistar rats were subjected to a unilateral section of the sciatic nerve and daily treated with HUF-101 (1, 2.5, 5 mg/Kg/day, i.p.) or vehicle solution for five days. The results were evaluated by Nissl staining, immunohistochemistry, and qRT-PCR. Neuronal counting revealed 47% rescue of spinal motoneurons and 79% of DRG neurons (HUF-101, 5mg/Kg). Such survival was associated with complete depletion of p53 and an elevation of 60-fold of BCL2 like 1 gene expression. Also, peroxisome proliferator-activated receptor gamma (PPAR-gamma) gene expression was downregulated by 80%. Neuronal preservation was coupled with a reduction in astroglial and microglial reaction evaluated nearby spinal motoneurons present in the ventral horn of the lumbar intumescence, and also higher preservation of synaptic covering. Overall, the current data strongly indicates the HUF-101 has potent neuroprotective effects, and such properties are particularly related to anti-apoptotic protection and reduction of astrogliosis.

Disclosures: A.L. Oliveira: None. **M. Perez:** None. **L.P. Cartarozzi:** None. **G. Chiarotto:** None. **F.S. Guimaraes:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); F.S.G. is a co-inventor of the patent “Fluorinated CBD compounds, compositions and uses thereof”. Pub. No.: WO/2014/108899. International Application No.: PCT/IL2014/050023..

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.09/TT6

Topic: E.09. Motor Neurons and Muscle

Support: KAKENHI JP26293397
KAKENHI JP15K15687
KAKENHI JP16K11488

Title: Activation of 5-HT_{2A} receptor enhances function of GluN2A-containing NMDA receptor via Src kinase in dendrites of rat jaw-closing motoneurons

Authors: M. DANTSUJI[1], S. NAKAMURA[1], K. NAKAYAMA[1], A. MOCHIZUKI[1], S. PARK[4], Y. BAE[4], M. OZEKI[2], *T. INOUE[3]

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Abstract: Jaw-closing masseter motoneurons (MMNs) receive both glutamatergic and 5-HT input, though the effect of 5-HT on glutamatergic input to MMN dendrites remains unknown. We examined the effects of 5-HT on glutamatergic responses in the dendrites of MMNs evoked by single- or two-photon laser photolysis of caged glutamate in brainstem slice preparations obtained from neonatal rats on postnatal day 2-5. Application of 5-HT induced membrane depolarization and enhanced glutamate responses. Furthermore, the 5-HT_{2A} receptor (5-HT_{2A}R) agonist TCB-2 mimicked enhancement of those glutamate responses, which was antagonized by ketanserin, a 5-$HT_{2A/2C}$R antagonist. In contrast, the 5-HT_{2B}R agonist BW723C86 and 5-HT_{2C}R agonist MK212 had no effect on glutamate responses. Blockade of NMDA receptors (NMDARs) by APV, but not AMPA receptors by NBQX, abolished 5-HT-induced enhancement. Furthermore, incubation with 5-HT significantly increased Src phosphorylation at tyrosine residue 416, while addition of the Src kinase inhibitor PP2 reduced 5-HT-induced enhancement. TCB-2 also enhanced NMDAR currents evoked by glutamate uncaging, whereas TCB-2-induced enhancement of NMDAR currents was abolished by the GluN2A antagonist PEAQX, but not the GluN2B antagonist ifenprodil. Additionally, glutamate responses evoked by two-photon uncaging of glutamate were enhanced when the uncaging loci were restricted to the vicinity of the puffed loci of TCB-2. Electron microscopic immunohistochemistry findings revealed that NMDARs and 5-HT_{2A}Rs were in close proximity to each other in the same dendrite. These results suggest that activation of 5-HT_{2A}Rs enhances the function of GluN2A-containing NMDAR in the vicinity via Src kinase. Such enhancement of glutamate responses by 5-HT may contribute to wide-ranging regulation of contractile forces of jaw-closing muscles.

Disclosures: M. Dantsuji: None. **S. Nakamura:** None. **K. Nakayama:** None. **A. Mochizuki:** None. **S. Park:** None. **Y. Bae:** None. **M. Ozeki:** None. **T. Inoue:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.10/TT7

Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant R01 NS091278

Title: Structural changes in spinal cord of newborns with muscle hypertonia after antenatal hypoxia-ischemia in rabbit cerebral palsy model

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Abstract: Newborn rabbit kits after global antenatal hypoxic-ischemic (H-I) injury exhibit motor deficits similar to humans with cerebral palsy, including muscle hypertonia. We previously reported that muscle hypertonia in newborns increased was associated with spinal circuit excitability and injury to descending white matter tracts. In the current study we tested several putative mechanisms previously implicated in spinal hyper- excitability in perinatal brain and spinal cord injury. Newborn P1 rabbit kits after E25 global hypoxic-ischemic brain injury with and without muscle hypertonia and naïve controls were used. Newborn kits received intramuscular injection of cholera toxin fluorescent conjugates to investigate primary afferents and motor neurons morphology. Motor neurons dendritic tree was examined using Sholl analysis on Golgi staining. Microglia activation and astrogliosis was examined on immune-stained cord sections with stereological methods. PCR and western blot of KCC2 transporter expression was performed during normal development at several time points and in newborns after injury. We found that motor neuron soma sizes and primary afferent density were not different between rabbit kits with and without hypertonia, either in neurons projecting to flexor or extensors muscles, in cervical or lumbar cord. Length of dendritic tree and ramification index were also not changed after H-I. Initially low KCC2 protein content in fetal naïve rabbit increased 6 fold after birth, reached maximum around P5-P11 and then declined with maturation. At P1, gene expression of KCC2 was lower in hypertonic kits, but the protein content was not different between the control and hypertonic groups either in cervical or in lumbar cord. While microglia was mostly present in activated form in control and hypertonic kits, we did not find difference in microglia numbers between the groups. There was a significant increase in astroglia in hypertonic group. In conclusion, we did not find structural evidence for increased primary afferent or dendritic tree size branching or motor neuron soma size that may explain spinal excitability and muscle hypertonia in rabbits after antenatal H-I. Since the phenotype is observed already in newborns we conclude that KCC2 is also unlikely related to motor deficits in the rabbit model, as previously suggested mechanism of spasticity in spinal cord injury. Astrogliosis, observed in hypertonic kit, may play a role in muscle hypertonia.

Disclosures: A. Drobyshevsky: None. **S. Synowiec:** None. **I. Goussakov:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.11/TT8

Topic: E.09. Motor Neurons and Muscle

Title: Predicting disease stage specific spinal motor neurons and glia in sporadic ALS

Authors: *F. SONG[1], F. DACHET[1], J. LIU[1], J. M. RAVITS[2]
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Abstract: Background: Recent observations of the location and spread of motor neuron degeneration in sporadic amyotrophic lateral sclerosis (sALS) patients suggests that neurodegeneration is radially graded, and regions of minimal motor neuron loss are remote from site of onset. Increasing evidence shows that neuroinflammation mediated by activated glia and infiltrated immune cells is involved in the progression. However, the mechanism of interaction between activated glia and motor neuron degeneration is unclear. **Objectives:** To determine the relationship between disease stage specific motor neurons and glial activation in sALS. **Methods:** We applied new bioinformatics tools to identify transcriptional profiles established by exon microarrays of motor neurons collected remote from site of onset with glia in the very close surrounding microenvironment by laser capture microdissection. We identified the relationship between motor neurons and glia from 12 sALS and 10 control patients. **Results:** Due to highly consistent and exact - inverse patterns of gene cluster being observed, we identified 5 clusters of co-expressed genes in sALS samples and 3 clusters in controls. Cellular interactome showed three stages of motor neurons interacting with different glia. Stages 2 and 3 motor neurons and groups 1 and 2 microglia/macrophage presented in sALS patients. While increased microglia/macrophage1 correlated best with decreased stage 2 motor neurons, the increased microglia/macrophage2 correlated best with decreased stage 3 motor neurons in 12 sALS patients. Increased MHC class II genes positively correlated with these increased groups 1 and 2 microglia/macrophage, suggesting they are activated. Tissue staining confirmed significantly increased microglia/macrophages activation in connection with motor neurons in the less affected microenvironment in sALS. The disease course in individual sALS patients inversely correlated with the quantity of stage 3 motor neurons. Identified gene pathways and biological changes included antigen processing and presentation and immune cell activation in microglia/macrophages, and induction of apoptosis and protein phosphorylation in stage 3 motor neurons. **Conclusions and discussion**: While the exact mechanism of how activated microglia/macrophages promote neurodegenerative progression is unclear, the new findings support the hypothesis that neuro-glia physical interactions are important in the ALS pathologic process, and targeting stage specific motor neurons and/or glia could be a useful therapy to slow disease progression in patients with sALS.

Disclosures: F. Song: None. **F. Dachet:** None. **J. Liu:** None. **J.M. Ravits:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.12/TT9

Topic: E.09. Motor Neurons and Muscle

Support: MEXT 26293397
MEXT 16K11489
MEXT 17H04373
MEXT 17K19775

Title: Effects of pharmacological agents administered for swallowing disorders on swallowing motor activity in nerves innervating infrahyoid and laryngeal muscles

Authors: T. MORIYA[1], K. NAKAYAMA[2], S. NAKAMURA[4], *A. MOCHIZUKI[3], T. SHIROTA[1], T. INOUE[5]
[2]Dept. of Physiol., [3]Dept. of Oral Physiol., [1]Showa Univ. Sch. of Dent., Tokyo, Japan; [4]Showa Univ., Tokyo, Japan; [5]Showa Univ. Sch. Dent., Tokyo, Japan

Abstract: Swallowing disorders are associated with increased risk of aspiration pneumonia, and often occur following acute cerebral infarction as well as in individuals with Parkinson's disease. Delayed triggering of the swallowing reflex has been reported in patients with damaged basal ganglia, who also exhibit impairments of dopamine and substance P metabolism. Thus, pharmacological agents that elevate dopamine and substance P concentrations have been suggested to prevent aspiration pneumonia and improve impaired swallowing processes. However, little is known about the effects of such agents on swallowing activities induced in motor nerves innervating the pharyngeal muscles. In the present study, we examined the effects of imidapril hydrochloride and cilostazol, often prescribed for swallowing disorders, on swallowing motor activity. Experiments were performed using arterially perfused decerebrate rats aged from postnatal day 21-33. We recorded efferent nerve activity in the vagal nerve (VN), hypoglossal nerve (HGN), and phrenic nerve (PN) using suction electrodes. Inspiratory motor discharges in each of those nerves were observed and occurred in a synchronous manner. Injection of 2.7 ml of distilled water into the oral cavity consistently inhibited inspiratory discharges in all of those nerves, and evoked synchronized swallowing burst discharges in the VN and HGN. Administration of imidapril (60 ng/ml) or cilostazol (2.5 μg/ml) to the perfusate increased the mean peak amplitude of orally evoked swallowing discharges in the VN, while the peak amplitude in the VN decreased over time in the non-administration group. The mean peak amplitudes of swallowing discharges normalized according to the amplitude of discharges preceding drug administration in both the imidapril and cilostazol administration groups were

significantly greater as compared to the non-administration group [imidapril (n=5): 116.0±15.6%, *P* = 0.017; cilostazol (n=8): 112.6±13.0%, *P* = 0.005; non-administration (n=5): 70.2±17.6%]. In contrast, neither imidapril nor cilostazol caused a significant change in swallowing activity frequency or burst duration. These results suggest that both imidapril and cilostazol administrations may improve impaired swallowing increasing pharyngeal muscle activities.

Disclosures: T. Moriya: None. **K. Nakayama:** None. **S. Nakamura:** None. **A. Mochizuki:** None. **T. Shirota:** None. **T. Inoue:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.13/TT10

Topic: E.09. Motor Neurons and Muscle

Support: The Lundbeck Foundation R140-2013-13648.
Danish Council for Independent Research: Pregraduate scholarship to SK

Title: Intramuscular injections of botulinum toxin cause axotomy-like changes in C-boutons on spinal motoneurones of adult rats

Authors: *C. F. MEEHAN, S. KLINGENBERG, D. B. JENSEN, K. P. DIMINTIYANOVA, J. WIENECKE
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Abstract: Large cholinergic boutons (C-boutons) on α-motoneurones are important modulators of neuronal excitability. Their activation increases excitability by decreasing action potential afterhyperpolarization (AHP). Experiments indicate that axotomy results in loss of C-boutons, which is consistent with studies reporting a prolongation of the AHP in fast spinal motoneurones following axotomy. Similar electrophysiological changes are also observed after intramuscular injections of Botulinum Toxin (Botox), including a prolongation of the AHP. The aim of the current experiments was therefore to investigate whether similar changes in C-bouton number or size could explain the AHP prolongation following intramuscular Botox administration.
In one group of 7 adult male Wistar rats, unilateral injections of Botox (mixed with the tracer Cholera Toxin subunit B conjugated to Alexa Fluor 488) were made into the gastrocnemius muscle. In a second group of 7 rats, the tibial nerve was dissected and the tracer was injected into the cut distal stump. Immunohistochemistry for vesicular acetylcholine transporter was used to detect C-boutons of labelled spinal motoneurones under these conditions and contralateral gastrocnemius motoneurones were used as internal controls. C-boutons were analysed on 102

axotomized motoneurones with 92 contralateral control motoneurones and 135 Botox motoneurones with 118 contralateral controls. All analysis was performed with blinding.
At 2 weeks post-axotomy we observed a significant decrease in C-bouton number by 40.4% ($P<0.0001$, n=194 cells). Linear regression confirmed that the number of C-boutons was influenced by soma size which itself was significantly decreased for axotomised motoneurones by 7.9% ($P=0.001$). The elevation of these regression slopes (soma size X C-bouton number) was significantly different confirming that the reduction in C-bouton number occurred irrespective of soma size. A significant difference was also found with respect to both C-bouton surface area by 23.4% ($P<0.0001$) and volume by 31.6% ($P<0.0001$). At 2 weeks post-Botox administration there was no significant difference in the number of C-boutons ($P=0.17$) but there were significant reductions in C-bouton surface area by 12.2% ($P=0.001$) and volume by 18.6% ($P=0.0008$).
This demonstrates that Botox administration results in somewhat similar but less extreme changes to C-boutons than observed post-axotomy. This is consistent with the electrophysiological changes in AHP that have been reported following both interventions.

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Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.14/TT11

Topic: E.09. Motor Neurons and Muscle

Title: The role of fscn1 in peripheral nerve regeneration

Authors: *T. OMURA[1], D. XU[2], Y. MIHARA[1], T. BANNO[1], A. OKAMOTO[1], Y. MATSUYAMA[1]
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Abstract: Through phenotypical analysis if axonal growth and full-genome expression profiling of nine genetically diverse inbred mouse strains, we found the potential role of fascin actin-bundling protein 1 (fscn1) in peripheral nerve regeneration. The purpose of the study was to examine the role in fscn1 using dorsal root ganglion (DRG) primary cultured neuron. Naïve and conditioned (sciatic nerve transection 5 days prior to harvest) L4 and 5 adult DRG from 8 weeks old C57BL/6 were grown and assayed on laminin coated plates. To evaluated whether fscn1 is necessary for axonal growth, we cultured conditioned DRG neurons for 15 hours in the presence or absence of FASCIN-G2(Xcess Biosciences In), a potent fscn1 antagonist at a concentration of

25, 50 (IC50), 75μM. Total axonal growth per neurons, longest neurite length and number of sprouting axons were cells were analyzed using NeuroMath and compared between the fscn1 treated group and the vehicle control group. With naïve DRG neurons, we confirmed significant reduction of total axonal growth and the longest neurite length with 50 and 75μM in a dose dependent manner. Similarly, conditioned neurons also exhibited significant decrease of total axonal growth longest neurite length with a concentration of 50 and 75μM. However, the number of sprouting axons was not affected by the inhibition of fscn1. The loss of function study using fscn1 inhibitor revealed that fscn1 is required for axonal elongation, but does not affect axonal sprouting. This is essential for clinical application as the increase in the total length and the extent of axonal growth is critical for faster innervation and improved recovery for the treatment of peripheral nerve injury, but additional sprouting may cause misdirection and co-contraction. We conclude that fscn1 is important for peripheral nerve regeneration.

Disclosures: T. Omura: None. **D. Xu:** None. **Y. Mihara:** None. **T. Banno:** None. **A. Okamoto:** None. **Y. Matsuyama:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.15/TT12

Topic: E.09. Motor Neurons and Muscle

Support: NSERC 386601

Title: Fatigue-associated changes in estimates of persistent inward current in human motor neurons

Authors: C. T. COMPTON, N. K. CECIRE, *J. M. KALMAR
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Abstract: Neuromuscular fatigue is associated with reduced supraspinal drive. Similarly, intracortical facilitation and muscle activation are reduced following concussion. Both fatigue and mild traumatic brain injury are associated with increased noradrenergic and serotonergic activity in animal models. Given that monoaminergic-dependent persistent inward currents (PIC) set spinal motor neuron (MN) gain, we speculate that PIC will increase during fatigue to compensate for supraspinal hypoexcitability and that this will be more pronounced in people with concussion. PURPOSE: To assess spinal MN excitability during fatigue in people with concussion and healthy controls. METHODS: 20 participants (10 concussion, average age 22.05 ± 2.25) completed two experimental sessions on two separate days (fatigue and rest, randomized and counterbalanced). On the fatigue day, paired motor unit analysis was used to estimate soleus

motor neuron PIC, before, during, and after an isometric plantarflexion fatigue protocol (5 sets of 50 3-s ankle plantarflexion contractions at 50% of maximal voluntary contraction). Excitability of the soleus motor neuron pool was assessed at rest using slopes of the H reflex recruitment curve before and after the protocol. On the rest day, estimates of PIC and H reflexes were made at the same time points, but the fatiguing contractions were omitted. A mixed ANOVA (group x day x time) was used to quantify the effects of fatigue and concussion on PIC and H reflexes, and a Fisher's LSD post-hoc analysis was used to detect differences between means. RESULTS: Soleus motor neuron PIC and resting H reflexes in people with concussion were not different from the controls at any time point. When the groups were collapsed, maximum voluntary torque declined to 92.6±8.67% ($p<0.001$) by the end of the fatigue protocol. PIC increased by the 3rd ($p<0.01$) and 4th ($p=0.026$) set of fatiguing contractions, returning to baseline by the end of the fatigue protocol ($p=0.562$). The slopes of the H reflex recruitment curves did not change. CONCLUSIONS: Although PIC may function to compensate for reduced drive or contractile failure early in the fatigue protocol, it does not appear to compensate for hypoexcitability in people with concussion. It is likely that increased monoaminergic drive seen during exercise activates soleus motor neuron PIC to enhance motor output. The increased gain provided by PICs may serve to enhance motor output during fatiguing muscle activity.

Disclosures: C.T. Compton: None. **N.K. Cecire:** None. **J.M. Kalmar:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.16/TT13

Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant R01NS076589-01
NIH Grant R01NS090622-01
VA Grant I01RX000815
VA Grant I01RX001807

Title: Motoneuron output during voluntary activity in humans with spinal cord injury

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Abstract: Evidence has shown that the excitability of resting spinal motoneurons increases in humans with spinal cord injury (SCI). The extent to which motoneuron excitability changes during voluntary activity after SCI remains largely unknown. To address this question, the ulnar

nerve was stimulated supramaximally at the wrist to evoke F waves in the first dorsal interosseous (FDI) and adductor digit minimi (ADM) muscles at rest and during 5% and 30% of maximal voluntary contraction into index finger abduction and little finger abduction in humans with and without chronic cervical SCI. In addition, we stimulated corticospinal axons directly by using high current electrical stimulation over the cervicomedullary junction to elicit motor evoked potentials (CMEPs) during the same conditions. We found higher persistence and amplitude of F waves at rest in the ADM compared with the FDI in controls. After SCI, both muscles showed higher persistence and amplitude of F waves compared with controls but to a similar extent. With increasing levels of voluntary contraction the amplitude of F waves and CMEPs increased in SCI participants but to a lesser extent than in control subjects in the muscles tested. These results indicate that the responsiveness of the motoneuron pool decreases during voluntary activity following SCI, which could alter the generation and strength of voluntary muscle contractions.

Disclosures: R. Vastano: None. **M.A. Perez:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.17/TT14

Topic: E.09. Motor Neurons and Muscle

Support: Reece foundation studentship

Title: Relative contributions of corticospinal and reticulospinal pathways to strength adaptation in non-human primates

Authors: *I. S. GLOVER, S. N. BAKER
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Abstract: It is well established that in addition to muscle hypertrophy, resistance training generates neural adaptations which may partially underlie strength gains. Previous work has focussed on changes in the corticospinal tract and intracortical inhibitory networks in M1. However, subcortical pathways could also play a part in neural adaptions. In this study, we investigated the changes in corticospinal and reticulospinal outputs during a period of unilateral strength training.
Two female rhesus macaques were trained to pull a loaded handle towards the body using their right hand; initial training used no additional loads, such that <5N was required to move the handle. Monkeys were then implanted bilaterally with EMG electrodes in 8 upper limb muscles as well as electrodes in M1, the pyramidal tract (PT) and medial longitudinal fasciculus (MLF)

for stimulation.
Recording sessions were carried out daily. A session involved performing 50 trials of the task without load, while M1, PT and MLF electrodes were stimulated in pseudorandom sequence. The monkeys then performed 50 trials at high load (up to 64N) without stimulation. The session ended with a further 50 trials while stimuli were given but without load.
The two animals completed 8 or 9 weeks of this protocol, preceded and followed by 2-week periods in which only unloaded trials were performed. We refer to the first week of strength training as week 0. Muscle responses to stimulation were assessed from averages of rectified EMG, and quantified as the area under the curve above baseline. Monkey L demonstrated a significant suppression of responses early in the training period (week 0 to 5), followed by a facilitation which started at week 6 and continued until the end of recordings. The observed changes were in a similar direction for M1, PT and MLF, but were proportionally much larger for the MLF stimulus (maximum increase 261% for MLF, 31% PT, 27% M1). In monkey N, we observed a similar early suppression for the M1 and PT stimuli (weeks 1 to 10), but not for MLF; there was no evidence of the late facilitation.
Our results suggest that changes in M1 responses may reflect underlying alteration of the spinal efficacy of both corticospinal and reticulospinal projections. The initial suppression of responses was unexpected, but robust in two animals. This may indicate that spinal circuits become transiently less dependent on descending drive to activate motoneurons in the early phase of strength training. The later response facilitation was seen in only one animal; it may reflect a secondary adaptation, rather than result from the strength training itself.

Disclosures: I.S. Glover: None. **S.N. Baker:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.18/TT15

Topic: E.09. Motor Neurons and Muscle

Title: Regulation of micturition by the activity of the anterior cingulate cortex in mice

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Abstract: Brain injury patients tend to have pollakisuria. Therefore, it has been believed that the cerebrum suppressed micturition in the storage phase and this suppression was released in the voiding phase. Recently, human imaging studies have shown that several brain regions including the anterior cingulate cortex (ACC) and the periaqueductal gray matter (PAG) were associated with micturition. Although the role of PAG has been extensively studied, it remains unclear how

ACC controls micturition. In this study, to elucidate the mechanisms for the control of micturition by ACC, we examined the change in the micturition interval time (MIT) induced by electrical and optogenetic stimulation of ACC in mice. MIT was defined as the time interval between peaks of voiding pressure. To measure MIT, we carried out cystometry through bladder catheter. First, we examined the contribution of ACC to MIT by lesion experiments. Electrodes were inserted into bilateral ACC, and we found that MIT was shortened by either the electrode insertion (N = 4 mice) or electrical lesion (N = 6 mice). These results are consistent with human pollakisuria induced by brain injury. Next, in order to further examine the contribution of ACC to micturition, we injected a $GABA_A$ receptor agonist, muscimol into both sides of ACC. After the injection of muscimol, MIT was extended (N=6 mice). Finally, we employed optogenetic stimulation of ACC neurons in order to directly demonstrate the causal relationship between the activity of ACC neurons and micturition. We found that photostimulation of excitatory layer 5 pyramidal neurons in ACC using channelrhodopsin-2 reliably induced micturition (N = 5 mice). On the other hand, photostimulation of parvalbumin-positive inhibitory interneurons in ACC significantly prolonged MIT (N = 6 mice). These results indicate that micturition could be induced by the activation of ACC. In contrast, the activation of parvalbumin-positive inhibitory interneurons in ACC causes extension of MIT. In conclusion, our results suggest that ACC plays a crucial role for the control of micturition and that the balance of excitation and inhibition in ACC may regulate micturition.

Disclosures: T. Mochizuki: None. **S. Manita:** None. **T. Mitsui:** None. **M. Takeda:** None. **K. Kitamura:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.19/TT16

Topic: E.09. Motor Neurons and Muscle

Support: NIH-NIAMS Grant AR-050520
NIH-NIAMS Grant AR-052345
Department of Defense Grant MR150091

Title: Can motor noise account for force variability?

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Abstract: Involuntary force variability is an inherent property of motor behavior. When exacerbated, it is a key contributor to performance errors and a feature of several neurological

conditions. Some propose that involuntary force variability arises primarily through the conversion of motoneuron firing patterns into muscle force, i.e. “motor noise.” This mechanism has been tested using a model of recruitment and rate coding developed by Fuglevand et al. (1993). However, this model has several drawbacks that limit its ability to simulate force variability. First, it was not designed to model explicitly the fusion of force twitches with increases in firing rate and concomitant saturation of calcium binding to troponin. Second, the model lacks a series elastic element (i.e., tendon), which damps out the effects of fluctuations of motoneurone firing by changing its length and, thereby, causing shortening and lengthening of the muscle fibers of what is an otherwise externally isometric system. We addressed these limitations by combining some elements of the Fuglevand model with physiological and mechanical features from a model by Song et al. (2008). This new model yields improved predictions of force and force variability. Upon close inspection, we show the amplitude and spectral features of force variability are significantly influenced by the passive viscoelastic properties of musculotendons. Importantly, this more physiological model of motor units produces a lower amplitude of force variability than previous models. Also, the spectral features of this new model resemble more closely what has been observed experimentally. These results question current thinking attributing the majority of involuntary force variability to peripheral motor noise, and highlight the importance of closed-loop behavior including afferent feedback, passive viscoelastic properties and voluntary error corrections.

Disclosures: A. Nagamori: None. **C.M. Laine:** None. **G.E. Loeb:** None. **F.J. Valero-Cuevas:** None.

Poster

497. Motor Neurons and Muscle: Activity, Sensory, and Central Control: Exercise, Injury, and Disease I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 497.20/DP10/TT17

Topic: E.09. Motor Neurons and Muscle

Support: DP1EY024503
BioCon HR0011-17-C-0026

Title: Neural and muscular dynamics of behaving Hydra under different environmental conditions

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Abstract: To understand the neural code, i.e., the relation between the activity of a nervous system and the behavior it generates, we study *Hydra vulgaris*, which, as a cnidarian, represents

some of the earliest nervous systems in evolution. Indeed, *Hydra* has a simple nervous system of 600-2,000 neurons, organized in three independent nerve nets in the ectoderm and endoderm, and which are distributed through the body of the animal but without any cephalization or ganglia. In recent work, we have genetically engineered the calcium sensor GCaMP6s in every neuron (Dupre and Yuste, 2017) or every muscle cell (Szymanski and Yuste, in prep.) of transgenic Hydra, and developed machine learning method to systematically analyze its behavior (Han et al, 2018). This makes it possible to reconstruct the entire neuronal and muscle activity of *Hydra* during behavior and analyze these databases to decipher the neural code. As a step in this direction, we have explored how freely-behaving *Hydra* responds to environmental stimuli and conditions that affect its survival, while measuring its entire neural and muscle activity dynamics. Experimental conditions include high osmolarity (50mM sucrose), high temperature (30 degree Celsius), scarce of food (1 week starvation), and smaller body size. We acquired movies using calcium imaging and then processed and analyzed the data to extract neural and muscle activity during spontaneous contraction and elongation using custom ImageJ and MATLAB code. To study changes in neuronal and muscle activity during different conditions, we focused on two previously identified non-overlapping circuits (Dupre and Yuste, 2017): contraction burst (CB) neurons that trigger body wall contractions and rhythmic potential 1 (RP1) neurons whose firing correlates with elongation. We found that activation of the muscle correlates to the activity of CB neurons during contraction and there was no difference in number of contractions or frequency of RP1 firing under different conditions. However, the frequency of CB firing decreased in high temperature or high osmolarity, (n = 3-7 replicates). These results indicate that *Hydra's* nerve net possess intrinsic control mechanisms to respond and adapt to the environment.

Disclosures: W. Yamamoto: None. **S. Han:** None. **R. Yuste:** None.

Poster

498. Motor Neurons: Development and Disease

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 498.01/TT18

Topic: E.09. Motor Neurons and Muscle

Support: FAPESP
CAPES
CNPQ

Title: Functional and Structural profile of abdominal-projecting motoneurons of rats submitted to sustained hypoxia

Authors: *M. P. SILVA[1], D. J. A. MORAES[1], L. G. H. BONAGAMBA[1], A. S. MECAWI[2], J. RODRIGUES[1], W. A. VARANDA[1], B. H. MACHADO[1]

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Abstract: Expiratory motoneurons work as an integrative center translating the complex brainstem neuronal respiratory inputs to effective muscles contraction, but their profile was not yet explored. Here, we characterized the abdomen-projecting motoneurons regarding their electrical, molecular and morphological profile using *in vitro* and *in situ* preparation from control and rats submitted to sustained hypoxia (SH), an experimental model presenting active expiration. Whole-cell patch clamp reveled two sub-populations of cells: spontaneous and silent motoneurons. SH (FiO2 0.1, 24 hours), selectively changed the excitability of spontaneous motoneurons: a) depolarization of the resting membrane potential (-69.3 ± 0.9 mV vs -66.5 ± 0.7 mV), b) enhancement of the firing frequency (7.6 ± 1 Hz vs 16.8 ± 3 Hz, n=18), and c) a reduction in the input resistance (0.35 ± 0.05 GΩ vs 0.18 ± 0.03 GΩ). However, these changes were abolished by synaptic blockers and were due to increases in the frequency (6 ± 1 Hz vs 2.2 ± 0.6 Hz, n= 11), as well in the amplitude (97 ± 10 pA vs 31 ± 5 pA) of excitatory postsynaptic currents. Three-dimensional reconstruction of spontaneous motoneurons revealed that hypoxia increased the surface area (349.4 ± 81 μm^2 *vs* 1119 ± 115 μm^2, p =0.013), soma volume (922.5 ± 109 μm^3 *vs* 4606 ± 1115 μm^3, p= 0.02), branching complexity (9892 ± 3542 *vs* 45800 ± 11760, p= 0.03) and the number of nodes of spontaneous motoneurons (3.25 ± 1 *vs* 13.6 ± 3, p=0.03). Interesting SH induced dendrites spines formation, which is absent in control conditions suggesting structural plasticity, which may contribute to changes observed in the electrophysiological properties of spontaneous motoneurons. These findings contribute for a better understanding of how abdomen-projecting expiratory motoneurons process the electrical inputs to ensure an appropriated respiratory activity in the control and mainly under hypoxic challenges.

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Poster

498. Motor Neurons: Development and Disease

Location: SDCC Halls B-H

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Program #/Poster #: 498.02/TT19

Topic: E.09. Motor Neurons and Muscle

Support: Lundbeckfonden grant no. DANDRITE-R248-2016-2518
EMBO Short Term fellowship 7375

Title: SorCS2 in motor neuron development and integrity

Authors: *P. B. THOMASEN[1,3], H. LOGIN[1], K. KJAER-SOERENSEN[2], J. TRANBJERG-JENSEN[1], S. BEEL[3], P. VAN DAMME[3], C. OXVIG[2], A. NYKJAER[1]
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Abstract: Motor neuron development is dependent on several mechanisms including axon guidance, growth cone collapse and synapse formation, and has been highly studied, yet all the proteins and pathways involved in this process and their interplay are still not fully described. Accumulating evidence implicates axon guidance proteins in neurological diseases such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy demonstrating that improper wiring during development may be lead to disease later on in life. Axon guidance proteins are not only important during development but also play a role in regeneration of nerves after injury. Further studies of axon guidance proteins and their function may clarify how dysregulation cause disease and could help towards developing new therapeutic strategies.
In my PhD project the function of the sorting receptor SorCS2 in motor neuron development and integrity is being studied through *in vitro* and *in vivo* studies in zebrafish and mice. We have found that SorCS2 is expressed in motor neurons in both zebrafish and mice. To study the role of SorCS2 in motor axon guidance we have knocked down expression of SorCS2 in zebrafish embryos by morpholino injections. We find that knockdown of SorCS2 results in abnormal length and aberrant branching in the primary motor neurons. Furthermore, acetyl choline receptor clustering is altered in knockdown embryos suggesting changes in neuromuscular synapse formation. Using the technique facial nerve crush injury, we similarly find that nerve outgrowth of SorCS2 knockout mice are significantly slower than wildtype mice. Together, the data suggests that SorCS2 plays an important role for motor neuron development and integrity, and ongoing studies aim at elucidating the molecular mechanisms underlying these phenotypes.

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Poster

498. Motor Neurons: Development and Disease

Location: SDCC Halls B-H

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Program #/Poster #: 498.03/TT20

Topic: E.09. Motor Neurons and Muscle

Support: NIH grant NS047357 (FJA)

Title: Spinal cord motor columns targeted by Foxp2 V1 interneurons

Authors: A. R. LANE[1], L. GOMEZ-PEREZ[1], J. B. BIKOFF[2], J. T. ANDERSON[1], T. M. JESSELL[3], *F. J. ALVAREZ[1]
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Abstract: Spinal V1 interneurons (V1s) are a diverse population of ventral horn inhibitory interneurons (INs) arising from the p1 domain and that transiently express the transcription factor En1 once they become postmitotic. V1s influence motoneuron (MN) activity and therefore motor output, but the distinctive V1 subpopulations remain to be fully characterized. Foxp2 V1s are one group that represents around 65% of all V1s when lineage labeled by intersectional genetics using $Foxp2^{flpo}$ :: $En1^{cre}$ mice with one R26 allele containing a dual conditional GFP and the other the Ai9 LSL-tdTomato (tdT). Because the tdT transgene in the Ai9 line is cre dependent but also is deleted by Flpo recombination, Foxp2 V1s only express GFP. In these animals 34.5% of V1s are tdT(+) Foxp2(-), 51.2% GFP(+) Foxp2(+) and 14.3% dual GFP/tdT labeled. We interpret dual GFP/tdT neurons as arising from transient expression of Foxp2 in embryo, while GFP "only" V1s represent neurons that upregulate Foxp2 during neurogenesis and many maintain expression until early postnatal age efficiently deleting tdT. All Foxp2 V1s have a fast spiking phenotype and are divided into lateral and medial groups according to timing of neurogenesis. Lateral Foxp2 V1s are further divided into dorsal and ventral groups, respectively expressing OTP and Foxp4 transcription factors. To gain insight into their function we identified their synapses by immunolocalizing VGAT to their genetically labeled axons and analyzed the targeting of different motor columns in the lumbosacral enlargement (T12 to S2) after counterstaining with choline acetyltransferase immunolabeling. The results show that Foxp2 V1s constitute ≥50% of the V1 input on the cell bodies of the lateral and medial motor columns (LMC and MMC) from lumbar (L)1 to L6, but contribute little input to the hypaxial motor column (HMC) in upper lumbar and lower thoracic segments. They also give few synapses to preganglionic sympathetic and parasympathetic neurons. Interestingly, most Foxp2 V1 synapses over autonomic MNs are GFP/tdT dual labeled. Overall, autonomic MNs received significantly lower density of V1 synapses than somatic MNs. We compared this pattern to calbindin V1 Renshaw cells (RC). RC synapses represent around 50% of all V1 synapses on the cell body of all upper lumbar (L1-L2) motor columns but were less abundant than Foxp2 V1 synapses on the lower lumbar (L4-L6) LMC and MMC and were absent on LMC distal motor pools (dorsolateral L6 MNs). Similarly to Foxp2 V1s, RCs did not significantly project to autonomic MNs. The results suggest that Foxp2 V1s mainly target somatic MNs and give significant input to both LMC and MMC, but not HMC MNs.

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Poster

498. Motor Neurons: Development and Disease

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 498.04/TT21

Topic: E.09. Motor Neurons and Muscle

Support: NIH NS091046
Answer ALS

Title: Transcriptomic and proteomic analysis of ALS iPSC-derived motor neuron cultures

Authors: R. G. LIM[1], V. VENKATRAMAN[2], J. WU[1], A. MATLOCK[2], J. KAYE[3], V. J. DARDOV[2], M. CASALE[1], E. FRAENKEL[4], T. THOMPSON[1], D. SAREEN[2], J. D. ROTHSTEIN[5], S. FINKBEINER[3], C. N. SVENDSEN[2], J. VAN EYK[2], *L. M. THOMPSON[6]
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Abstract: The NeuroLINCS Center is an NIH-funded multi-site collaborative effort between research groups with expertise in iPSC technology, disease modeling, imaging, OMICS methods, and computational biology focused on ALS. The NeuroLINCS team has generated a rich data set from RNA, protein, and epigenomic analyses using ALS and control iPSC-derived motor neurons. Gene level quantification of transcriptomic and proteomic data reveal specific cell signatures between C9orf72 and control iPSC-motor neurons even at the earliest timepoint. We further analyzed differential exon usage and alternative splicing to quantify transcript isoforms and ncRNA levels including: lnc-, circ-, and miRNAs in ALS and control samples. DeepBind motif analysis identified RNA binding proteins (RBPs) that could contribute to the altered exon usage and alt-splicing. The motifs of RBPs mislocalized in ALS autopsy tissue are highly represented, including: SRSF and hNRNP genes. Mislocalization and disruption of the normal function of these RBPs could play a role in the transcriptomic dysregulation seen in the i-MNs from *C9ORF72* ALS patients. Predicted protein isoforms are also analyzed in the matching proteomics data set to determine if isoforms were translated and if there were quantity changes between *C9ORF72* ALS and control. WGS was carried to identify genetic variants that could be associated with or modifying our ALS disease signatures. eQTL analysis is being used to 1) identify genetic variant that could be confounding our gene expression signatures 2) stratify our ALS samples by uniquely modifying the signatures 3) as prior knowledge for anchoring nodes for network-based causal inference modeling. Another way we are integrating the genomic data with other data sets is to investigate if DNA coding variants are expressed in i-MNs and if these predicted protein isoforms were sequentially identified based on the actual peptide sequence within the proteomic data to confirm that genetic variants are being expressed and assess their

proportional representation among other proteins. This approach to OMICS data integration helps us understand how genetic SNPs impact the cellular protein milieu. These approaches are being extended to samples generated through Answer ALS, which is creating 1,000 unique stem cell lines from ALS patients and healthy controls. We show preliminary data on the first 500 lines using RNASeq and SWATH proteomics.

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Poster

498. Motor Neurons: Development and Disease

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 498.05/TT22

Topic: E.09. Motor Neurons and Muscle

Support: NIH LINCS

Title: Early proteomic changes in a genetic form of ALS

Authors: *V. J. DARDOV[1], .. NEUROLINCS CONSORTIUM[4], C. N. SVENDSEN[2], J. VAN EYK[3]
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Abstract: Amyotrophic lateral sclerosis (ALS) is an adult onset neurodegenerative condition in which loss of upper and lower motor neurons occurs due to cell death, which ultimately leads to impaired muscle function and eventually death. iPSC derived motor neurons allow for the interrogation of the discrete molecular effects of specific genetic perturbations within the context of ALS. The goal of this study was to identify disease specific proteomic signatures using three different timepoints along differentiation as a means to identifying the minimal or initiating ALS pathways. We carried out cell wide proteomic analysis (data independent acquisition-MS, DIA-MS) on iPSC derived motor neurons generated from patients with a single homogenous genetic driver (C9) and compared those to control lines (n=4 for each) at three differentiation time-points: Day 18, Day 32 and Day 90. Of the DDA-MS peptide library consisting of ~ 5000 cell specific proteins, DIA-MS data quantified ~3700 proteins across the three timepoints. In addition, there were 84, 322 and 924 differentially expressed proteins in Day 18, 32 and 90, respectively. Of these, 11 proteins overlapped at all three time points, with just over half of the Day 18 differentially expressed protein being unique to that timepoint. Importantly the proteome signature at day 18, comprised of nuclear pore and ECM proteins were observed and expanded in

the later more complex differentiations. With longer differentiation times, there was an enrichment in the number of known ALS associated proteins, as well as proteins associated with the nuclear pore and cytoskeleton. We speculate that the large increase in the number of differential proteins with the length of the differentiation protocol may reflect i) disease progression, ii) neuronal cell maturity or iii) appearance of other cell types (development of a microenvironment). Moreover, this initial proteomic signature is already present at Day 18, suggesting early cellular dysfunction as a result of mutations in C9.

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Poster

498. Motor Neurons: Development and Disease

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Program #/Poster #: 498.06/TT23

Topic: E.09. Motor Neurons and Muscle

Support: CIRM

Title: The effect of increasing the length of differentiation on ALS phenotypes seen in human iPSC-derived motor neurons

Authors: *M. G. BANUELOS[1], B. MANDEFRO[3], K. KUROWSKI[3], H. TROST[3], S. HUANG[3], B. SHELLEY[3], L. THOMPSON[4], E. FRAENKEL[5], J. ROTHSTEIN[6], S. FINKBEINER[7], J. VAN EYK[3], N. ANSWER ALS CONSORTIUM[2], D. SAREEN[2], C. SVENDSEN[2]
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Abstract: The Answer ALS project entails creating 1,000 unique stem cell lines from ALS patients and healthy controls. These stem cells and their derived brain and spinal cord cells can then be used *in vitro* to model the disease in a large scale. We have been optimizing the differentiation protocols and in this study asked the question: what is the effect of increasing the time and complexity of the differentiation protocol on phenotypic differences seen between ALS and control lines? We used 12 lines for this study, that included sporadic ALS patients (n=4), familial ALS patients with a C9ORF mutaion (n=2), C9ORF isogenic corrected controls (n=2) and healthy controls (n=4). The first motor neuron protocol was performed in three different stages: (Stage 1) Neuroepithelial induction using base media supplemented with CHIR99021, SB431542, and LDN193189, (Stage 2) motor neuron precursor generation using Retinoic Acid to induce caudalization, (Stage 3) terminal motor neuron maturation using neurotrophic growth

factors such as GDNF and BDNF. Motor neuron cultures were collected at 18, 32 and 60 days of differentiation. In addition, a longer differentiation protocol was used that included embryoid body formation, rosettes, sphere expansion and platedown of cells for 21 days of motor neuron maturation. At the end of each protocol, differentiated motor neurons were collected and distributed to 5 collaborating sites: Thompson lab at the University of California, Irvine for RNA analysis, Fraenkel lab at the Massachusetts Institute of Technology for DNA/Epigenetic analysis, Finkbeiner Lab at the University of California, San Francisco for imaging analysis, Rothstein Lab at Johns Hopkins University for perturbation analysis and Van Eyk lab at Cedars-Sinai for protein analysis. Here, data is presented from this collaborative study aimed at determining the optimal time of differentiation for detecting phenotypic differences between ALS and control lines.

Disclosures: M.G. Banuelos: None. **B. Mandefro:** None. **K. Kurowski:** None. **H. Trost:** None. **S. Huang:** None. **B. Shelley:** None. **L. Thompson:** None. **E. Fraenkel:** None. **J. Rothstein:** None. **S. Finkbeiner:** None. **J. Van Eyk:** None. **N. Answer ALS Consortium:** None. **D. Sareen:** None. **C. Svendsen:** None.

Poster

498. Motor Neurons: Development and Disease

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 498.07/TT24

Topic: E.09. Motor Neurons and Muscle

Support: Answer ALS

Title: Answer ALS iPSC and Motor Neuron Repository at the Cedars-Sinai RMI iPSCCore

Authors: *L. PANTHER, H. TROST, R. CHENG, E. GOMEZ, C. LIU, L. ORNELAS, J. ORTIZ SANCHEZ, M. BANUELOS, S. HUANG, K. KUROWSKI, D. WEST, I. PSC CORE, M. N DIFFERENTIATION CORE, A. NSWER ALS CONSORTIUM, C. SVENDSEN, D. SAREEN
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Abstract: The Answer ALS project entails creating 1,000 unique stem cell lines from ALS patients and healthy controls. These stem cells and their derived cells of the brain and spinal cord can be used to model the disease on a large scale. This allows scientists a deeper look at the mechanisms of a fatal neurodegenerative disease like ALS.
The iPSC Core at Cedars-Sinai is leading the generation of these unique iPSCs and their derived motor neurons (MNs) from samples collected across multiple clinical sites in the US along with deep clinical data. These cells are being utilized in big data projects and large-scale omics investigations. The iPSC Core has already received 692 unique patient blood samples. Over 600

of these samples were collected from ALS patients with mutations like *C9ORF72, SETX* and *SOD1,* while others were from healthy controls without any neurological diseases and some with diseases such as primary lateral sclerosis and spinal muscular atrophy. We have successfully reprogrammed over 300 PBMCs into iPSCs; over 66 of these lines are control samples, 17 with C9ORF72 ALS, 3 with SOD1 ALS while the remaining lines are from sporadic ALS patients. The PBMCs are reprogrammed using non-integrating episomal plasmids and undergo extensive testing and optimization to ensure their pluripotency, quality and genetic integrity. After we have completely reprogrammed the Answer ALS samples, the iPSC Core will have one of the largest biorepositories of ALS iPSC lines which, along with the de-identified clinical data, will be available for distribution throughout the world.
Of the 300 iPSC lines, 126 have been successfully differentiated into MNs; 42 being controls and the remaining 84 are from ALS patient iPSC lines. The method used to differentiate iPSC lines into MNs involves an 18-day process split into 3 different stages: neuroepithelial induction using media supplemented with CHIR99021, SB431542, and LDN193189 (Stage 1), MN precursor generation using Stage 1 media with Retinoic Acid for inducing caudalization (Stage 2) and terminal MN maturation using media supplemented with neurotrophic factors such as GDNF and BDNF (Stage 3). At the end of the protocol differentiated neurons are collected and distributed to 5 collaborating sites; Thompson lab at the University of California, Irvine for transcriptomics (RNA-seq), Fraenkel lab at the MIT for epigenomics (ATAC-seq), Finkbeiner Lab at the UCSF for longitudinal imaging analysis, Rothstein Lab at Johns Hopkins University for perturbation analysis and Van Eyk lab at Cedars-Sinai for proteomics.

Disclosures: L. Panther: None. **H. Trost:** None. **R. Cheng:** None. **E. Gomez:** None. **C. Liu:** None. **L. Ornelas:** None. **J. Ortiz Sanchez:** None. **M. Banuelos:** None. **S. Huang:** None. **K. Kurowski:** None. **D. West:** None. **I. PSC Core:** None. **M. N Differentiation Core:** None. **A. nswer ALS Consortium:** None. **C. Svendsen:** None. **D. Sareen:** None.

Poster

498. Motor Neurons: Development and Disease

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 498.08/UU1

Topic: E.09. Motor Neurons and Muscle

Support: UCI/NIH Grant U54 NS091046

Title: Comparison of differentiation protocols for cortical forebrain neurons from ALS patient and control iPSC lines

Authors: *V. J. GARCIA[1], A. N. COYNE[2], I. EPSTEIN[3], R. G. LIM[4], H. HEMMATI[1], U. HUSSAIN[2], J. KALRA[3], S. FINKBEINER[5], J. D. ROTHSTEIN[2], L. M. THOMPSON[6], C. N. SVENDSEN[7], N. NEUROLINCS CONSORTIUM[7]

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Abstract: Amyotrophic lateral sclerosis (ALS) and Frontotemporal Dementia (FTD) comprise a spectrum of neurodegenerative diseases. ALS is characterized by a loss of neurons in the spinal cord, brainstem and cortex. Specific cortical neuron subtypes are implicated, including deep layer V pyramidal neurons that project to the spinal cord, as well as layer II/III interneurons that regulate the excitatory activity of projection neurons. In contrast, FTD is characterized by a loss of neurons in the frontal and temporal cortices. Mutations in the gene C9*orf*72 have been identified as playing a role in both diseases. In a collaborative effort across three Institutes (NeuroLINCS), we have used 3 protocols to differentiate 12 human induced pluripotent stem cell (iPSC) lines (6 C9*orf*72 ALS, 2 isogenic-corrected C9*orf*72 ALS, and 4 control) into robust and reproducible cortical forebrain neurons. Here, we compare differentiation protocols, each of which employ varying components and time in culture. We first use immunocytochemistry to assay the diversity of cell types produced with each protocol, including deep layer pyramidal neurons, interneurons and glia. We also evaluate the neuronal cultures for their transfection efficiency and the ability to perform longitudinal single-cell imaging. In addition, we perform RNA-seq and protein analysis for di-peptide repeats, which are pathologically produced in ALS and FTD patients. Finally, we evaluate the signatures present in the C9*orf*72 patient-derived cortical neurons compared to control cell lines. Our work presents a platform for future, multi-omic evaluation of neurodegenerative diseases. This project paves the way to extend our integrated analysis beyond ALS to assess FTD and other neurodegenerative disorders like Alzheimer's Disease. This will position NeuroLINCS as a resource for the broader scientific community.

Disclosures: V.J. Garcia: None. **A.N. Coyne:** None. **I. Epstein:** None. **R.G. Lim:** None. **H. Hemmati:** None. **U. Hussain:** None. **J. Kalra:** None. **S. Finkbeiner:** None. **J.D. Rothstein:** None. **L.M. Thompson:** None. **C.N. Svendsen:** None. **N. NeuroLINCS Consortium:** None.

Poster

498. Motor Neurons: Development and Disease

Location: SDCC Halls B-H

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Program #/Poster #: 498.09/UU2

Topic: E.09. Motor Neurons and Muscle

Support: NIH K99AG056678-01 grant

ALSA 11000 GE232 grant
NIH U54NS091046-01 grant
NIH UG3NS105703-01 grant

Title: Spatial reconstruction of the spinal cord from iPSC models of ALS with single cell RNA-seq

Authors: *R. HO[1], M. J. WORKMAN[1], M. KELLOGG[2], V. MONTEL[2], M. G. BANUELOS[1], S. HUANG[1], D. WEST[1], I. KHREBTUKOVA[2], L. WATSON[2], K. TAYLOR[2], C. N. SVENDSEN[1]
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Abstract: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder characterized by motor neuron (MN) death, typically presented in late adulthood, and resulting in an average lifespan of five years after diagnosis. Of ALS cases, 90 percent are of unknown genetic cause (sporadic ALS), and ten percent are attributed to genetic mutations (familial ALS). Onset of motor symptoms is variable among patients, presumably due to differing rates of degeneration among MN sub-types. Living central nervous system tissue is not accessible from patients to perform functional genomic and molecular research, which hinders pinpointing genetic or environmental mechanisms that cause MN degeneration. *In vitro* modeling of ALS with patient-derived induced pluripotent stem cells (iPSCs), which harbor the relevant genetic context of patients, can potentially capture the underlying causes of ALS in a patient-specific manner. We published that iPSC-derived MNs differentiated *in vitro* exhibit bulk transcriptomic expression profiles that globally resemble *in vivo* fetal spinal tissues. However, these bulk transcriptomic techniques represent averaged gene expression profiles among heterogeneous cell types and thus may not accurately reflect distinct pathologies of individual cells. Here, we describe our application of single cell RNA-seq (scRNA-seq) to assay individual cell transcriptomes with the goal of producing a high-resolution, three-dimensional anatomical map of cellular identities and physiologies within iPSC-derived spinal tissue cultures in ALS patient and control samples. This cellular atlas of the human spinal cord will provide 1) a valuable resource for stem cell and neuroscience research communities, 2) new avenues of investigation to resolve variable clinical phenotypes of ALS, and 3) specific molecular mechanisms to target by specialized treatment options for patients. Classifying iPSC-differentiated cells as *in vivo* spinal cell types using individual transcriptomes enables discovery of dysregulated pathways occurring in distinct MNs or other cell types. This single-cell approach with patient-specific iPSC models of ALS may resolve the variable motor deficits among patients, improve understanding of disease etiology and progression, and thus enable precision treatments for ALS.

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Poster

498. Motor Neurons: Development and Disease

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 498.10/UU3

Topic: E.09. Motor Neurons and Muscle

Support: ALSFAC
Robert Packard Center
MDA
ALSA
NINDS
American Airlines

Title: Precision Brain Health: Answer ALS is a population based mult-iomics program to indentify ALS subgroups, biomarkers and druggable pathways

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Abstract: Answer ALS was conceived and organized as a comprehensive multi-omics approach to ALS to ascertain, at a population level, the various clinical-molecular- biochemical subtypes of ALS. This national program was initiated to identify and follow 1000 ALS and ALS/FTD patients nationwide along with a cohort of >100 matched control patients. Patients were recruited at 8 national ALS centers and followed longitudinally over one year. In addition, a smartphone-based system was employed to collect deep clinical data including fine motor activity, speech, breathing and linguistics/cognition. In collaboration with IBM Watson, analytics of speech pattens reveals a strong correlation between clinical progression indices and speech. In parallel, iPS motor neurons were blood-derived from each patient and these cells underwent multi-omic analytics including: whole genome sequencing, RNA transcriptomics, ATAC-Seq, proteomics, metabolomics, high content imaging and longitudinal high throughput single cell analysis. HIPPA compliant cloud data bases were employed to store all data. Open access to early raw data is being instituted as well. More than 750 ALS patients have already been enrolled and > 400 iPS cell lines have already been generated from these patients, along with > 350 whole

genomes sequenced. Integrated clinical and biological signatures are now being generated using bioinformatics, statistics and computational biology to establish patterns that may lead to a better understanding of the underlying mechanisms of disease. We hope to begin identification of biological subgroups from the first 130 sALS and fALS iPS motor neuron lines. Interestingly, definite subgrouping was readily identified even with an initial small subset of ~30 patients and appears to be influenced by co-analyses of clinical and biological data sets. C9 patients were found have prominent defect in nuclear transport, chromatin remodeling and RNA metabolism as fundamentally altered pathways with candidate pathways modulating drugs identified. For some subgroups, antisense oligonucleotides targeting relevant pathways could mitigate molecular injury- reverting cells towards control patient profiles. Relevant pathways and molecular targets are being verified in post mortem brain tissue as well as fly models. A web portal for open source sharing of all data are being developed for widespread community based data analytics. These studies demonstrate distinct reliably identifiable subgroups among the sporadic and familial patients and the great utility in iPS based approaches to disease pathophysiology and therapy discovery.

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Poster

498. Motor Neurons: Development and Disease

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 498.11/UU4

Topic: E.09. Motor Neurons and Muscle

Support: NSF - GRFP

Title: VCP is involved in axonal mitochondrial motility

Authors: *A. E. GONZALEZ
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Abstract: In neurons, mitochondria must be transported sizable distances through the axon to localize to areas like the bouton, where synaptic growth, signaling, and Ca2+ buffering require mitochondria for energy. Mitochondrial transport is especially critical in motor neurons as the axon can extend up to a meter in length. Movement of mitochondria along the axon is mediated by Miro, which anchors mitochondria to a motor complex and to microtubules. Miro responds to diverse cellular signals to dynamically mediate the movement of mitochondria. These signals include intracellular Ca^{2+}, glucose, and mitophagic triggers including PINK1 and Parkin

interactions, which link Miro to neurodegenerative disease. We have recently discovered a connection between Miro and VCP/p97. VCP is a highly conserved, ubiquitous, essential, and abundant ATPase. The hexameric structure and enzymatic activity of VCP enables it to perform mechanical work in cells, with its most widely studied function being facilitation of protein degradation through the ubiquitin-proteasome system (UPS). VCP function has been implicated in a mitochondrial process called mitophagy, the selective autophagy of damaged mitochondria. This process is regulated by the PINK1/Parkin pathway which tags outer mitochondrial membrane (OMM) proteins and initiates mitophagy. VCP is required for the removal and degradation of OMM protein Mitofusin2 (Mfn2) which is an essential step required to complete mitophagy. VCP also localizes to mitochondria and regulates Mfn2 levels in healthy conditions. While VCP disease mutants have been studied in artificially damaged conditions, the function of VCP in mitochondrial pathways remains unstudied in healthy conditions. We looked at the role of VCP in axonal mitochondrial transport, hypothesizing that VCP may regulate Miro similarly to Mfn2. We found that while VCP does not play a role in regulating the speed of individual mitochondria, it does play a role in the number of mitochondria in axons. We hypothesize that loss of VCP function reduces the number of mitochondria transported from the cell body into the axon by lowering Miro levels, and thus reducing anchoring of mitochondria on microtubules. Our results suggest that VCP has a role in regulating Miro in healthy conditions. Further, the long axons of motor neurons that are particularly susceptible to mitochondrial transport defects could suffer most from the molecular dysregulation of VCP and Miro. As evidence of defective mitochondrial dynamics continues to emerge in ALS and other neurodegenerative disease research, our research on the basic biology of VCP may enlighten us to VCP functions important for disease pathogenesis.

Disclosures: A.E. Gonzalez: None.

Poster

498. Motor Neurons: Development and Disease

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 498.12/UU5

Topic: E.09. Motor Neurons and Muscle

Support: DOD grant W881XWH-15-10229

Title: Does time make a difference? The effect of the administration of follistatin on re-innervated skeletal muscle fiber recovery after 3 vs 6 months of denervation

Authors: *M. S. SHALL[1], J. E. ISAACS[2], S. MALLU[2], G. PATEL[2]
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Abstract: The objective is to evaluate the effect of Follistatin on the recovery of skeletal muscle strength and skeletal muscle fiber diameter after different periods of denervation time and re-innervation.
Rationale: Functional recovery following traumatic peripheral nerve injury is often suboptimal despite appropriate treatment. Due to the slow rate of axonal regeneration (1-3 mm/d), the target muscle may undergo significant atrophy before the axon attempts reinnervation. Follistatin influences muscle regeneration at several levels including directly inhibiting myostatin, a signal transduction protein that regulates muscle mass by inhibiting muscle regeneration. As a result, Follistatin stimulates muscle fiber hypertrophy and hyperplasia in normal animal models.
Methods: Transection of the tibial nerve in the hindlimb of Sprague-Dawley rats, followed by delayed (3 or 6 month) repair (utilizing microsurgical nerve suturing with nerve graft) induced partial recovery of the muscle with mild or moderate residual strength deficits due to irreversible atrophy. Recombinant protein and recombinant DNA were synthesized (and the DNA packaged in adeno-associated viral vectors) in the Virginia Commonwealth University (VCU) Biological Macromolecule Core Facility. The Follistatin protein was delivered, after reinnervation, to the gastrocnemius muscle utilizing an Alzet (Cupertino, CA, USA) implantable drug delivery system. Treatment effects on the muscle were evaluated by cryosectioning the muscles after evaluation of muscle force. Muscle fiber types identified with Immunohistochemistry allowed differential evaluation of three primary muscle fiber types.
Results: The muscles of the animals that were denervated 3 months and repaired, followed by Follistatin treatment, exerted about the same force as experimental animals without Follistatin treatment and had about the same size muscle fibers. Muscles that were denervated 6 months before reinnervation and treatment with Follistatin protein developed significantly more force than denervated animals without treatment. The muscle fibers expressing type IIa and IIb myosin heavy chains were larger in diameter in the experimental animals that were treated with either type of Follistatin than control animals that received no Follistatin.
Conclusions: In this rodent model of delayed peripheral nerve repair, we found that Follistatin, administered 1 month after reinnervation had a greater facilitating effect after 6 months than 3 months of denervation on the recovery of type IIa and IIb muscle fibers and muscle force.

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Poster

499. Neurophysiologic Effects of Early-Life Stress

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 499.01/UU6

Topic: F.04. Stress and the Brain

Support: FAPESP 2017/11339-0
FAPESP 2014/17959-1

NIH R01- MH115914

Title: Early life stress and neurodevelopment: Contributions of glucocorticoid plasticity to maturational timing

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Abstract: Early life stress (ELS) is associated with increased risk for later emotional disturbance and precocious development of the HPA-axis. ELS leads to an earlier emergence of contextual fear inhibition (Pattwell et al., 2012) and accelerated maturation of the hippocampus. We posit that corticosterone (CORT) plays a functional role in regulating the timing of maturation of regions underlying threat learning and expression, including the hippocampus, amygdala, and prefrontal cortex. Our working hypothesis is that elevations in plasma levels of CORT can impact the timing of maturational processes, and that blocking elevation in CORT associated with ELS will buffer against ELS effects on the timing of brain and behavioral maturation. To test those hypotheses, we used a limited bedding model of ELS from P4-P11. Control and ELS animals were administered either saline (Naïve) or metyrapone (MET; 50mg/kg) on P12. At P18, P21 or P28 separate groups of mice were exposed to a single session of fear conditioning followed 24 h later by a single context test (Bath et al.,2016). Analysis of freezing behavior in the context test revealed that MET treatment blocked the acceleration in contextual fear inhibition in ELS reared mice at P22, with no diference between groups at P19 or P29. This effect was observed in both female and male mice. Interestingly, in control male pups treated with MET a significant reduction in freezing was observed at P22 and increased freezing at P29 when compared to Naïve, indicative of MET effects on typical development.
We discuss these data in the context of complementary approaches assessing ELS and MET effects on the timing of neurotrophic factor and glucocorticoid receptor expression in the brains of these mice. Based on the current results, CORT is likely playing an important role in the timing of both typical development and ELS-associated shifts in behavior and brain maturation. Importantly, blocking the ELS-associated increase in CORT in ELS mice may represent an interesting strategy to buffer stress effects on the timing of brain maturation and possibly decrease risk for pathological emotional outcomes.

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Poster

499. Neurophysiologic Effects of Early-Life Stress

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 499.02/UU7

Topic: F.04. Stress and the Brain

Support: NRF Grant 2016M3C7A1905385

Title: The ^{1}H MRS study for the measurement time dependency of acute stress response

Authors: *Y. HWANG[1], M.-H. LEE[2,3], C.-S. YUN[1], Y. KIM[4], H.-M. BAEK[4], B. HAN[1], D. KIM[1]
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Abstract: Proton magnetic resonance spectroscopy (^{1}H-MRS) has been widely used in study for the acute stress (AS) response. This response to AS is a complicated process that varies depending on the individual characteristics, which may cause variation of the amount of each metabolite over individuals measured at the same time after AS exposure. However, most stress studies using ^{1}H-MRS have been performed based on the measurement at particular time. Therefore, the existing measurement method of MRS data for AS study needs to be improved to reflect the individual differences in AS response. There has not yet been an assessment of AS and its impact on the brain's metabolic response over time, which is critical to deepening our understanding of brain metabolism. In this study, we explore the physiological response to AS by quantifying metabolites in the hippocampus over time using ^{1}H-MRS. Twenty-four C57BL/6N mice (18-25g, 6~7 weeks, and male) were involved in this study and randomly assigned into control (12 mice) and AS (12 mice) groups. In order to examine the AS response, the each mouse in AS group was physically restrained in 50mL conical tubes for 2 hours. The MRS data were acquired in the hippocampus at 9.4T Bruker MRI/MRS system with PRESS. Data acquisitions were performed at 30min, 60min, 90min and 120min after AS exposure. The data were analyzed using Linear Combination Model (LCModel) with a simulated basis set including 17 metabolites and group comparisons were carried out employing the nonparametric t-test for each data obtained at particular time and repeated measure analysis of variance for all data. Our findings are as follows: The stress group shows significantly higher concentration than control group in Alanine (Ala) and Glutamate (Glu) at 30min, Ala, Glu, and total Creatine (tCr) at 60min, Ala at 90min, and Glucose (Glc) at 120min ($p<0.05$). In the group analysis for all data, the stress group shows significantly higher concentration in only Glu and Ala than control group ($p<0.05$). The findings of present study show that the results of MRS data analysis vary depending on the measurement time. Therefore, this study suggests that the analysis through the measurements over time is required in the AS studies using ^{1}H-MRS.

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Poster

499. Neurophysiologic Effects of Early-Life Stress

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 499.03/UU8

Topic: F.04. Stress and the Brain

Support: Conacyt 241911

Title: Chronic lead exposure promotes epigenetic changes in serotoninergic receptors and aggressive behavior in mice

Authors: *L. G. GARCIA-LARA[1], A. J. HERNÁNDEZ-CORO[1], J. MARTÍNEZ-LAZCANO[2], B. E. SÁNCHEZ-HERNÁNDEZ[3], S. MONTES[1], C. RÍOS CASTAÑEDA[1], F. PÉREZ-SEVERIANO[1]
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Abstract: Exposure to lead (Pb), during early stages of life, affects the normal brain development causing neuronal and behavioral changes, such as aggressiveness, hyperactivity and learning impairments. Previously, we have demonstrated the interaction between a decreased serotonin turnover (5-HT) and the aggressiveness in mice exposed to Pb. To elucidate the mechanism that leads to the alteration of the 5-HT1A and 5-HT1B receptors by exposure to Pb from pregnancy to different postnatal ages (P7, P14, P28 and P72). We set breeding litters of C57BL6 mice and they were given *ad libitum* either tap water as control or lead acetate solution (250 ppm) and we dissected the hippocampus and cortex of both groups for protein and RNAm detection levels of 5-HT1A and 5-HT1B receptors. Furthermore, methylation levels were analyzed in the 5-HT1A and 5-HT1B promoter region and we found low methylation especially in the 5-HT1B promoter. For the evaluation of the aggressive behavior, the resident-intruder test was performed on mice of both groups at P72 and we found that the mice exposed to Pb with respect to the control show higher aggressive behavior. Therefore, chronic lead exposure from the gestation to an adult stage predisposes to an aggressive behavior probably due to the methylation and expression impairments that could affect the response of 5HT1A and 5HT1B receptors.

Disclosures: L.G. Garcia-Lara: None. **A.J. Hernández-Coro:** None. **J. Martínez-Lazcano:** None. **B.E. Sánchez-Hernández:** None. **S. Montes:** None. **C. Ríos Castañeda:** None. **F. Pérez-Severiano:** None.

Poster

499. Neurophysiologic Effects of Early-Life Stress

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Topic: F.04. Stress and the Brain

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Molly Towell Perinatal Research Foundation
August-Wilhelm Scheer Program, TUM, Germany

Title: Chronic maternal stress during pregnancy alters fetal development

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Abstract: Maternal stress before and during pregnancy (prenatal stress, PS) is a key risk factor affecting in utero and postnatal child development. We hypothesized that PS impacts the heart rate variability signature of autonomic nervous system (ANS) stress axis activity in mother and fetus. We recorded abdominal electrocardiogram (aECG) in a cohort of stressed (n=49) and non-stressed (n=55) pregnant women, identified by Cohen Perceived Stress Scale questionnaire (PSS-10) administered on 28th week of gestation. Using validated mathematical algorithms, we extracted maternal (mECG) and fetal (fECG) signal from aECG. We then studied maternal and fetal ECG-derived heart rate variability (HRV) properties, a measure of fetal autonomic nervous system (ANS) activity, using a novel multidimensional HRV analysis approach (DYNAMO). Traditional HRV measures from HRV Task Force were calculated for comparison (SDNN, RMSSD, SDSD, pNN50, IQRNN and HTI). Maternal hair cortisol was measured at birth: Cortisol levels from 3 cm hair reflected up to three months of prior chronic stress exposure. (Clinical Trials NCT 033891 78). Maternal hair cortisol levels differed significantly between both groups objectifying the results of PSS-10. We show that such HRV approach distinguishes stressed from non-stressed fetuses one month following PSS-10 assessment. Notably this result

is best seen in fetal HRV and less clearly in maternal HRV. The traditional HRV measures did not provide a clear separation of the two groups. This suggests a direct transgenerational transmission of PS onto fetal ANS and stress axis. Our finding show a persistent effect of PS identified in the last trimester. Our study provides a proof-of-principle for deploying non-invasive aECG technology for early identification of mothers and fetuses at risk of altered neurodevelopmental trajectories to allow for planned early postnatal interventions

Disclosures: M.C. Antonelli: None. **H. Wu:** None. **C. Shen:** None. **P. Su:** None. **B. Haller:** None. **A. Mueller:** None. **G. Berg:** None. **B. Fabre:** None. **J. Weyrich:** None. **C. Zelgert:** None. **M.G. Frasch:** None. **S.M. Lobmaier:** None.

Poster

499. Neurophysiologic Effects of Early-Life Stress

Location: SDCC Halls B-H

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Klingenstein foundation
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Title: Drd3 signaling in the lateral septum mediates early life stress-induced social dysfunction

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Abstract: Children exposed to adverse experiences (e.g., physical abuse, emotional neglect, etc.) during a critical period in their development are more likely to have social dysfunction later in life. Those experiences, collectively referred to as early life stress (ELS), can induce psychiatric symptoms associated with diseases like autism spectrum disorder (ASD), schizophrenia, and major depression. Little is known, however, about the relevant molecular signaling within a specific neural substrate that governs ELS-induced social dysfunction. Here, we identify dopamine receptor 3 (Drd3)-expressing-LS ($Drd3^{LS}$) neurons as a critical component mediating the detrimental effects of ELS on social behavior. Employing an early social deprivation (ESD) stress paradigm, we found that Drd3 signaling in the LS is significantly down-regulated in mice exposed to ESD stress, and that this is accompanied by abnormal social behaviors such as reduced social preferences and severe communication deficits. Using in vivo Ca^{2+} imaging, we

found that social stimuli produce significantly less activity in $Drd3^{LS}$ neurons of ESD mice than in controls. Notably, optogenetic activation of $Drd3^{LS}$ neurons rescues this ESD-induced social impairment. Pharmacological treatment with the Drd3 agonist PD128907, which increases the activity of $Drd3^{LS}$ neurons, also normalizes the abnormal social behaviors of ESD mice. Taken together, our findings identify Drd3 signaling in the LS as a critical mediator of the ELS-induced social impairments in adulthood. Drd3 in the LS may therefore constitute an important therapeutic target for the treatment of the severe social impairments commonly observed in numerous neuropsychiatric disorders.

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Poster

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Topic: F.04. Stress and the Brain

Support: NSF IOS 1557451

Title: Effects of birth and birth-mode on markers of inflammation in the mouse brain

Authors: *A. CASTILLO-RUIZ, M. MOSLEY, Y. C. HOFFIZ, R. BURCH, N. G. FORGER
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Abstract: Birth is an inflammatory event, with the onset of parturition marked by inflammation at the fetal/maternal interface. As the fetus traverses the vaginal canal and enters the outside world, it experiences changes that under any other circumstance could elicit an immune response: hypoxia, mechanical pressure, and a new environment filled with microorganisms. In agreement, we previously found that perinatal mice show dynamic changes in peripheral pro-inflammatory cytokines, with TNF-α showing high levels pre- and postnatally, and IL-6 showing highest levels just before birth. In contrast, the anti-inflammatory IL-10 tripled within 3h of birth. Whether this peripheral response extends to the brain's immune system, and whether the inflammatory response to birth is altered by birth mode has not been addressed. To answer these questions, we focused on microglia, the resident immune cells of the nervous system. Microglia respond to immune challenges by increasing their soma size and morphing into an activated, amoeboid state. We examined microglial soma size at embryonic day (E)18.5 and E19 and *ex utero* at postnatal day (P)0 (3h after birth), P1, and P3 in mice born vaginally or by Cesarean section. Brains were immunohistochemically stained for the microglial marker ionized calcium binding adaptor molecule 1. We found a significant increase in microglial soma size between E19 and P1 in vaginally-born animals that was sustained at P3 in the paraventricular nucleus of

the hypothalamus, a region with a central role in the stress response and brain-immune interactions. Remarkably, this effect was prevented in mice born by Cesarean section. Given that soma size is a marker of microglial activation, our findings suggest that microglia in Cesarean born mice are less activated. We are currently assessing whether these results extend to other brain regions and are examining brain cytokine expression in mice born vaginally or by C-section. In addition, to test the role of the peripheral IL-10 peak seen 3h after birth (above) on the brain's immune system, we are examining brain cytokine expression and microglial soma size in perinatal IL-10 knockout mice. Taken together, our results indicate that vaginal birth triggers an immune response in the newborn's body and brain and that some aspects of this response are altered by birth mode.

Disclosures: A. Castillo-Ruiz: None. **M. Mosley:** None. **Y.C. Hoffiz:** None. **R. Burch:** None. **N.G. Forger:** None.

Poster

499. Neurophysiologic Effects of Early-Life Stress

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Topic: F.04. Stress and the Brain

Support: NIH MH57440

Title: The impact of stress on the dopamine system is dependent on the state of the critical period of plasticity

Authors: *F. V. GOMES[1], X. ZHU[1], A. A. GRACE[2]
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Abstract: Background: Unregulated stress exposure occurring during sensitive periods of development leads to the emergence of circuit deficits consistent with schizophrenia in the adult. If accurate, one would predict that re-opening the sensitive period in the adult could make it susceptible to a similar disruption. **Methods:** Male rats were submitted to a combination of footshock (FS) and restraint stress (RS) during adolescence (PD31-40) or adulthood (PD65-74). The activity of dopamine neurons in the ventral tegmental area (VTA) and the pyramidal in the ventral hippocampus (vHipp) were evaluated 1-2 or 5-6 weeks post-stress. We also evaluate if the administration of the HDAC inhibitors valproic acid (VPA; 300mg/kg) and SAHA (25mg/kg), which are known to re-instate the critical period in adults, would recreate an adolescent phenotype of susceptibility to stress. **Results:** The adolescent stress increased VTA dopamine population activity 1-2 and 5-6 weeks post-stress, these changes seem to be driven by an increased vHipp activity. FS+RS in adult rats decreased dopamine population activity 1-2 weeks post-stress, but not after 5-6 weeks. Interestingly, VPA treatment altered the impact of

adult stress. When rats were treated with VPA or SAHA, FS+RS increased VTA dopamine population activity, similar to that observed with adolescent stress. **Conclusion:** Timing of the stress is a critical determinant of the pathophysiology that is present in the adult. While adolescent stress could led to changes that recapitulates the MAM model of schizophrenia, adult stress induced changes observed in animal models of depression. Re-opening the sensitive period in the adult restores vulnerability to stress-induced pathology resembling schizophrenia.
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Poster

499. Neurophysiologic Effects of Early-Life Stress

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Topic: F.04. Stress and the Brain

Support: NIH grant K08 MH086812
Carver Charitable Trust
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Title: Embryonic GABAergic proliferation as a contributing mechanism in prenatal stress effects

Authors: *J. J. DEWITT, S. J. LUSSIER, E. C. MENEZES, J. S. ARMER, H. E. STEVENS
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Abstract: *Background*: Prenatal maternal stress increases risk for psychiatric outcomes in offspring, such as autism spectrum disorder (ASD), schizophrenia, Tourette syndrome, and ADHD. One mechanism that has been implicated both as an effect of prenatal stress and in psychiatric pathology is the alteration of the GABAergic neuron development. Human studies also implicate increased neuronal progenitor proliferation in macrocephalic ASD, but it is unclear if this is affected by prenatal stress. This study evaluates the effects of prenatal stress on GABAergic progenitor proliferation, developing striatal GABAergic populations, and striatal-dependent behaviors. *Methods*: A standard prenatal stress protocol used three times daily restraint stress beginning on embryonic day 12 in CD1 mouse dams bred to CD1 males heterozygous for a GAD67GFP transgene. Male offspring performed habit-learning, motor learning, and motor activity as adults. We examined GAD67GFP+ cellular outcomes in embryonic and postnatal brain using immunocytochemistry. With *in vivo* and *in vitro* methods, we manipulated maternal stress physiology, placental growth factors upregulated by stress, and embryonic GABAergic progenitor proliferation and assessed outcomes. *Results*: Motor activity

and motor and habit learning were disrupted in in adulthood. These behavioral changes correlated with increased GABAergic neuron density in mature caudate putamen, a region dominated by inhibitory neuronal populations. In embryonic brain, prenatal stress resulted in increased GABAergic progenitor proliferation, ganglionic eminence proliferative zones, and ventral GABAergic populations. Repetitive maternal exposure to interleukin-6 (IL6) but not corticosterone, also increased GABAergic populations in embryonic brain. These findings were matched in neurospheres. Neurosphere cultures were also used to develop methods for increasing GABAergic proliferation *in vivo*. *Conclusion*: Motor activity and habit learning were altered in male offspring after prenatal stress, reflecting what is seen in children with ASD and Tourette syndrome. These behavioral changes were associated with significant differences in GABAergic populations in the caudate putamen after prenatal stress, neurobiology implicated in several psychiatric disorders. Prenatal stress and maternal and placental physiological stress factors perturbed proliferation of GABAergic progenitors. These findings implicate interactive mechanisms in maternal and placental physiology during stress in disrupting the normal control of embryonic growth and represent important contributions to psychiatric disorders.

Disclosures: J.J. Dewitt: None. **S.J. Lussier:** None. **E.C. Menezes:** None. **J.S. Armer:** None. **H.E. Stevens:** None.

Poster

499. Neurophysiologic Effects of Early-Life Stress

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Topic: F.04. Stress and the Brain

Support: National Institute of Health Grant R01MH115914 (KGB)
National Science Foundation Graduate Research Felloships Program
COBRE Pilot Award (NIH P20- GM103645 to J.S. and K.G.B.)

Title: Effects of early life stress on infantile amnesia and early development

Authors: *R. A. APONTE-RIVERA[1], A. JOHNSEN[1], G. MANZANO NIEVES[1], S. N. BASKOYLU[1], K. G. BATH[2]
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Abstract: Early life adversity is associated with increased predisposition for mental health disorders later in life. By looking at development, we can determine how early life adversity may alter neurodevelopment in ways that increase susceptibility to affective disorders. This experiment focuses on the development of memory as a means of probing for differences in emotional learning between typical and adverse-life subjects. Mouse models of early life stress (ELS) can carry crucial translational implications on memory formation in the traumatized brain,

especially in the ability to transition from child-like (infantile) to adult-like forms of memory. In order to visualize this transition behaviorally, we consider the period of infantile amnesia in order to compare development between ELS and control mice. We subjected mice to a limited-bedding paradigm as a model for ELS and measured fear recall of a tone-shock pairing at 17 (within the typical infantile amnesia window) days of age. Current results demonstrated the absence of infantile amnesia in 17-day-old ELS mice, suggesting a shortened period of infantile amnesia and an acceleration towards adult-like memory in ELS mice. In corroborating this biologically, ELS mice demonstrate higher levels of neurogenesis in the amygdala. From this data, we conclude that ELS mice demonstrate accelerated memory development, and that the greater tonic levels of neurogenesis in ELS mice are responsible for the accelerated, "strengthened" memory effect.

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Poster

499. Neurophysiologic Effects of Early-Life Stress

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Topic: F.04. Stress and the Brain

Support: National Institute of Health Grant R01MH115914 (KGB
COBRE pilot award (NIH P20- GM103645 to J.S. and K.G.B.)

Title: The effects of early life stress on central and peripheral immune development in male and female mice

Authors: *M. E. GALLO[1], T. CAMPBELL[2], A. OLANIYAN[3], K. G. G. GALLO, 02901-1821[4]
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Abstract: Exposure to early life stress (ELS) increases the lifetime risk for pathology and profoundly impacts neural development. To model ELS, we take advantage of a limited bedding and nesting (LBN) paradigm to induce alterations in maternal behavior and stress in the pups. To further characterize the behavioral effects of this ELS model on mother-pup interactions, we utilize a 24/7 video monitoring setup over the entire ELS manipulation to assess maternal behaviors including nesting, eating, drinking, kicking and walking. Critically, we observe LBN dams expressed increased interactions with their nest as indexed by nest entries/exists and circadian dependent differences in time spent on nest during the dark-light transition and the light period. Utilizing this model, we assess the effects of ELS on central and peripheral immune development. Recent work has linked chronic exposure to stress to regional changes in neuron-

microglial activation and changes in inflammatory responses, positing a role for the activation of the immune system in the sculpting of neural development. Utilizing immunohistochemistry, we assess the effects of ELS on microglia/macrophage specific binding protein (IBA-1) expression in regions implicated in maternal and social behaviors at postnatal days 8, 12 and 16 (during and following our LBN manipulation). Using real time qPCR, we characterize expression of relevant proinflammatory responses, including IL-6, IL-1 and CD34, in these regions. To assess peripheral immune responses, we quantify peripheral blood lymphocytes during and following the LBN manipulation.

Disclosures: **M.E. Gallo:** A. Employment/Salary (full or part-time):; Brown University. **T. Campbell:** None. **A. Olaniyan:** None. **K.G.G. Gallo:** A. Employment/Salary (full or part-time):; Brown University. F. Consulting Fees (e.g., advisory boards); Prothera Biologics.

Poster

499. Neurophysiologic Effects of Early-Life Stress

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Topic: F.04. Stress and the Brain

Support: NSERC RGPIN-2016-06146

Title: Prenatal stress affects communication patterns and modulates corticosterone and pro-inflammatory responses to an adult social stressor in male and female mouse offspring

Authors: ***N. D. OSBORNE**[1,2], T. CHARLTON[4], C. GROULX[4], K. CONNOR[5], M.-C. AUDET[1,2,4,3]
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Abstract: Early life experiences may affect behavioral and cognitive development and modulate responses to stressors encountered later in life. In rodent models, adult social stressors known to promote depressive- and anxiety-like behaviors elicit stress hormone hypersecretion, gut microbiota changes reflective of a pro-inflammatory gut environment, and pro-inflammatory cytokine activation in circulation and in stress-sensitive brain regions. The objective of this study was to investigate whether a prenatal maternal stressor would modulate inflammatory activation and membrane permeability status along specific regions of the gut-brain axis in adult males and females exposed to an acute social stressor. Communication patterns in the developing offspring were also examined. Pregnant C57BL/6 mice experienced physical restraint (30 minutes, three times daily) during the second trimester of their pregnancy or were left undisturbed. Ultrasonic vocalizations were recorded at early (postnatal day [PD] 2) and late (PDs 9-11) neonatal stages and before weaning (PD21). In adulthood, male and female offspring experienced an acute social

stressor or were not manipulated (no stressor condition) and were sacrificed 90 minutes after for the determination of plasma corticosterone levels and mRNA expression of pro-inflammatory cytokines and tight junction proteins in the prefrontal cortex and the jejunum. Prenatally stressed litters emitted more ultrasonic vocalizations than non-stressed litters at PD2, while the calls produced had comparable peak maximum frequencies. As pups from both prenatally stressed and non-stressed litters aged, call rates decreased while peak maximum frequency increased. Elevations of plasma corticosterone levels and of prefrontal expression of interleukin (IL)-6 apparent after the adult stressor were limited in prenatally stressed males, but not in females. Curiously, prefrontal expression of the tight junction protein claudin-5 was upregulated in prenatally stressed males (irrespective of whether they experienced an adult social stressor) but was reduced after the adult social stressor only in females. In the jejunum, IL-1β and IL-6 mRNA was increased in prenatally stressed offspring, an effect that appeared limited when these mice were acutely stressed in adulthood. These findings suggest that prenatal stress may alter offspring's communicative development and modulate corticosterone as well as gut and brain cytokine responses to a subsequent stressful experience in a sex-specific fashion.

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Poster

499. Neurophysiologic Effects of Early-Life Stress

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Support: NIH/NIDA Grant R24DA029989
NIH/NIMHD Grant G12MD007592

Title: Maternal separation induces long-lasting changes in anxiety and protein expression in specific brain regions, but not conditioned place preference to methamphetamine

Authors: *J. N. HAMDAN[1], S. SAUCEDO[2], G. A. LODOZA[1], J. A. SIERRA FONSECA[2], R. J. FLORES GARCIA[3], L. E. O'DELL[4], K. L. GOSSELINK[5]
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Abstract: Maternal deprivation is a strong psychological stressor that can cause long-lasting neurological and behavioral changes which may lead to difficulties with social integration; subsequent outcomes can include school- or work-related challenges, increased criminal behavior, and even the manifestation of mental illness. The goal of this study was to determine long-lasting changes in the brain and behavior of rats that result from maternal deprivation in the

form of maternal separation (MatSep). Male Wistar rats were removed from their dams for 3h/d from postnatal day (PND) 2 to PND14 and were assessed in adulthood (PND 70-95). Proteins involved in dopaminergic signaling [dopamine transporter (DAT), dopamine receptor-1 (D_1), dopamine receptor-2 (D_2), tyrosine hydroxylase (TH)] or synaptic plasticity [D_1, post-synaptic density 95 (PSD95), NMDA receptor-1 (NMDAR), and α-synuclein] were evaluated by Western blot. Brain regions in which the levels of these proteins were quantified included the prefrontal cortex (PFC), hippocampus, caudate-putamen (CPu), and the nucleus accumbens (NAcc). Rats were also exposed to a light-dark box test for anxiety-like behavior, and for conditioned place preference to different doses of methamphetamine (1.0 mg/kg and 0.1mg/kg). Preliminary data show a significant increase in the expression of D_1 and PSD95 in the NAcc ($p=0.040$ and 0.016, respectively), a significant decrease in the expression of NMDAR in the CPu ($p=0.026$), a significant decrease in the expression of DAT, D_1, and D_2 in the hippocampus, and a significant increase in the expression of D_2 in the PFC. No changes were seen in drug sensitivity caused by MatSep, but a significant decrease was seen in stressed rats in the amount of time spent in the light side of the light-dark box. Together, these data suggest that plasticity and reward systems can undergo significant changes without affecting certain relevant behavioral outputs. The impacts of early life stress are long-lasting and can be seen in multiple brain regions in adult animals, months after the stress was experienced. This study will also include a more in-depth analysis of changes caused by MatSep on protein expression and behavior following the administration of methamphetamine.

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Poster

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Topic: F.04. Stress and the Brain

Support: CAPES
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Title: Social isolation in early adolescence induces long-term changes in dopaminergic system and increases the susceptibility to food addiction in adulthood

Authors: *C. LAMPERT[1], N. S. COUTO-PEREIRA[1], D. M. ARCEGO[1], A. S. VIEIRA[1], E. GARCIA[1], D. A. VENDITE[1], R. M. M. DE ALMEIDA[2], M. E. CALCAGNOTTO[1], C. DALMAZ[1]
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Abstract: Exposure to early life stress, such as social isolation (SI), is able to prompt changes in sensitive brain circuitries, essentially in the mesolimbic dopaminergic system and increase the risk for psychiatric disorders later in life. SI can stimulate the consumption of rewarding substances, like drugs of abuse and palatable foods. However, most studies analyze long periods of SI and very little is known about the effects of a brief social isolation in a sensitive period of development and its association with palatable foods on the reward system sensitization. Therefore, the aim of this study was to analyze the effects of a short period of SI combined with a chronic access to a high sugar diet (HSD) on sweet food seeking behavior, and possible alterations in dopaminergic parameters and synaptic function in the nucleus accumbens (NAc). We used female Wistar rats that were socially isolated from post-natal days (PND) 21 to 35 and received chronic HSD until PND 60. After five days of washout, on PND 65, the habituation protocol of the sweet food seeking task (using Froot Loop®) was performed. The habituation session lasted 5 days under food restriction, and the test session was conducted on the 6th day in a fed state. During the habituation and test sessions, we analyzed the latency to reach the food, the latency to start eating and the amount consumed. Another subset of animals was killed on PND 65 to determine the dopaminergic parameters on NAc using western blotting. In addition, the excitatory synaptic transmission on NAc neurons was studied in slices using Whole cell-patch clamp. We found that animals that were socially isolated after weaning increased sweet food seeking (p=0.004) as well as the amount of Froot Loop® consumed (p=0.025) in a fed state, indicating a binge eating-behavior. In the same way, SI animals showed a reduced basal immunocontent of D2R (p=0.024) in the NAc, indicating an increase in dopaminergic signaling in the NAc. The electrophysiological properties of synaptic transmission are still being analyzed. This study highlights that a short post-weaning social isolation is able to induce long-term changes in the NAc dopaminergic system and increase sweet food seeking behavior. These results emphasize the importance of stressful experiences during a short period of development on reward circuit programming and susceptibility to food addiction later in life.

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Poster

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Topic: F.04. Stress and the Brain

Support: NIH Grant MD007592
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Title: Early life stress induces retinal microglia activation and retinal layer alterations across the lifespan of female rats

Authors: *M. CHAVEZ[1,2], M. GRIGORUTA[1], J. SIERRA[2], K. L. GOSSELINK[2], A. MARTINEZ[1]
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Abstract: Early life stress (ELS) in mammals is associated with neuronal and glial alterations in central nervous system (CNS). ELS has different consequences including learning, memory, behavior, and morphological disorders during brain lifespan, depending on sex. Early Maternal Separation (MatSep) is considered as an ELS chronic model for newborns and is associated with proinflammatory immune response activation. Several studies indicate that MatSep-stressed animals experience both microglia and proinflammatory cytokine activation in adolescent and adulthood life. Retinal tissue is part of the CNS but MatSep stress effects have not yet been described. The objective was to evaluate MatSep-stress effects in retinas from female rats of three different ages: adolescence, adulthood, and aged. Newborn pups were separated from their mother for 3 hours per day on 13 consecutive days (PND 2-14), then were grown to three different age groups: 49 (adolescent) or 75 (adult) days old, or 17 months old (aged). Rats were sacrificed, their eyes enucleated and treated for immunofluorescence analysis. Retinal sections (12 µm) were cut on a cryostat and incubated with antibodies for 1) microglia activation: IBA-1, CD45; and 2) neuroprotective function: DJ-1. To evaluate the retina architecture, retinal layer thickness was determined for Control and MatSep groups at different ages. 10 retinal sections per animal (N=3 animals for group/age) were stained with DAPI. The thickness of the outer nuclear layer (ONL), inner nuclear layer (INL), and total retina was measured with Zen Blue® 2011 software. Results are shown as mean ± SEM. Our results suggest that retinas from the MatSep group have higher IBA-1 and CD45 expression depending on age. Maximum expression of both markers was observed in the aged group. On the other hand, DJ-1 expression in Control and MatSep groups was similar in adolescent and adult retinas but decreased in aged rats. Moreover, retinal thickness for the MatSep group showed more than 30% reduction in adult and old rats. MatSep-stress is a condition that affects retinal architecture predominantly in adult and aged rats, which also increase the expression of microglia activation mediators.
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Poster

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Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 499.15/UU20

Topic: F.04. Stress and the Brain

Support: University of Richmond

Title: Long-term neurobiological effects of early-life challenges on cognition and stress responsivity in adult female rats

Authors: *M. H. KENT[1], M. BROOKS[1], D. KOVALEV[1,3], S. SCAROLA[3], D. VAVRA[2], K. POKORNY[2], K. G. LAMBERT[1]
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Abstract: In humans, poverty and unpredictable environments have been associated with negative socioemotional and developmental outcomes (Blair et al., 2016). Accordingly, the current study utilized a rodent model to assess the effects of restricted resources and unpredictable threats [simulating a poverty/low socioeconomic status (SES) model] on socioemotional neurobiological functions. In this model, female rats were raised in four different conditions defined by availability of materials for nest building, standard resources for control (CON) and restricted resources for (LOW), along with the presence (T) or absence (NT) of threat (predator cues) throughout the lactation period. Following weaning, offspring were pair-housed, according to group assignments (LOW/NT; LOW/T; CON/NT; CON/T, n=8 each group) in standard housing conditions for 1 year. Female adult offspring were assessed on multiple behavior tasks to assess the cognitive and emotional effects of rearing environment. During a learning task, CON/T rats on average took longer to reach the reward baited well compared to the CON/NT while there was little difference between the LOW groups. The same difference was observed for the percentage of rewards eaten. This difference could indicate a difference in vigilance between the T and NT groups in the CON group. An uncertainty task revealed increased vigilance behaviors in the T rats demonstrated by increased rearing responses. The same trend for increased vigilance--like behavior was seen in a novel environment task where T rats explored more than NT rats. When a novel male confined to a plastic container was introduced the NT rats interacted more with the container and spent more time engaged in nose to nose interactions with the novel male. However, when the female cage mate was placed in the plastic container the T rats spent more time rearing (information gathering) while the NT rats spent time directing attention toward the restricted conspecific (ie, digging). Further, CON/T rats spent the most time interacting with the confined cage mate especially when compared to the CON/NT. Histology data revealed a trend in increased oxytocin-ir in the supraoptic nucleus in

NT rats BDNF-ir was increased in CON rats, specifically in the CA3 area of the hippocampus. Interestingly, lower body weights and longer tail lengths in CON animals were observed in adulthood. In sum, behavioral and neurobiological data suggest long-term socioemotional effects in adult animals exposed to stressful conditions during the limited time of lactation.

Disclosures: M.H. Kent: None. **M. Brooks:** None. **D. Kovalev:** None. **S. Scarola:** None. **D. Vavra:** None. **K. Pokorny:** None. **K.G. Lambert:** None.

Poster

499. Neurophysiologic Effects of Early-Life Stress

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 499.16/UU21

Topic: F.04. Stress and the Brain

Support: International Associated Laboratory (LIA) France/Italy "Prenatal Stress and Neurodegenerative Diseases", University of Lille – CNRS UMR8576 and Sapienza University of Rome - IRCCS Neuromed. Co-directed by Pr S Maccari and Pr F Nicoletti

Title: Early life stress causes dopaminergic dysfunction in the basal ganglia motor circuit and related behaviours in adult and aged rats

Authors: *S. MACCARI[1,2,3], S. MORLEY-FLETCHER[2], J. MARROCCO[5], A.-R. ZUENA[6], D. BUCCI[3], A. PITTALUGA[7], M. CANNELLA[3], M. MOTOLESE[3], G. BATTAGLIA[4], J. MAIRESSE[8], H. BOUWALERH[2], G. VAN CAMP[2], R. VERHAEGHE[3], F. NICOLETTI[6,4]
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Abstract: Perinatal stress (PRS) in rats has an established value as a model for stress-related disorders endowed with face, construct, and pharmacological validity. A comorbidity exists between stress-related disorders and disorders of the extrapyramidal motor system (e.g., Parkinson's disease). We decided to examine how PRS influences neurochemical and behavioral parameters related to basal ganglia motor function. We were surprised to find that adult (4-month old) PRS rats (i.e., the adult offspring of dams exposed to multiple episodes of restraint stress during pregnancy causing reduced maternal care) showed a reduction in depolarization-evoked dopamine (DA) release in the corpus striatum, as assessed by measurement of ^{3}H-DA efflux from superfused isolated synaptosomes, associated with an increase in steady-state DA levels in

the striatum. Immunoblot analysis of the high affinity DA transporter (DAT) suggested that the reduction of DA release found in PRS rats was not due to degeneration of nigro-striatal DAergic terminals. Interestingly, PRS rats showed increased A_{2A} adenosine receptor mRNA levels and A_{2A} receptor-mediated cAMP formation in the striatum, with no changes in the transcripts of mGlu4 and mGlu5 metabotropic glutamate receptors. As a behavioral correlate of these findings, adult PRS rats showed a defective striatal motor performance in the grip strenght, and pasta matrix reaching tests. We extended the analysis to aged (20-month old) PRS rats, which also showed a reduction in the evoked release of ^{3}H-DA from striatal synaptosomes and a defect in striatal motor function (pasta matrix, and ladder rung walking tests) with respect to age-matched unstressed controls. D1 receptor protein levels were also largely reduced in the striatum of aged PRS rats. Our findings suggest that early life stress may cause abnormalities in the basal ganglia motor circuit that could enhance the risk for development of extrapyramidal motor disorders.

Disclosures: S. Maccari: None. **S. Morley-Fletcher:** None. **J. Marrocco:** None. **A. Zuena:** None. **D. Bucci:** None. **A. Pittaluga:** None. **M. Cannella:** None. **M. Motolese:** None. **G. Battaglia:** None. **J. Mairesse:** None. **H. Bouwalerh:** None. **G. Van Camp:** None. **R. Verhaeghe:** None. **F. Nicoletti:** None.

Poster

499. Neurophysiologic Effects of Early-Life Stress

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 499.17/UU22

Topic: F.04. Stress and the Brain

Support: International Associated Laboratory (LIA) France/Italy “Prenatal Stress and Neurodegenerative Diseases”, University of Lille – CNRS UMR8576 and Sapienza University of Rome - IRCCS Neuromed. Co-directed by Pr S Maccari and Pr F Nicoletti

Title: Consequences of a double hit of stress during the perinatal period and midlife in female rats: Mismatch or cumulative effect?

Authors: *G. VAN CAMP[1], H. BOUWALERH[2], J. MAIRESSE[3], E. GATTA[4], P. PALANZA[5], S. MACCARI[2,6], S. MORLEY-FLETCHER[2]
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Abstract: A double exposure to stressful events during critical developmental periods and later in the adult life is crucial in shaping individual variability in coping strategies. In males, it has been shown that exposure to stressful events in early life strongly programs an individual's phenotype. Here, we extended the study to middle-aged female rats using the model of perinatal stress (PRS). We investigated different outcomes following exposure in later life to an unpredictable chronic mild stress (uCMS) condition for six weeks. We showed for the first time an accelerated ageing in the estrous cycle associated with a reduction in estradiol levels in PRS rats. In middle-aged female rats PRS also reduced motivational and risk-taking behavior, caused an impaired regulation of plasma glucose and insulin levels following a glucose challenge, and disrupted the feedback regulation of the hypothalamic-pituitary-adrenal axis after acute stress. Interestingly, all PRS-induced alterations were modified by exposure to uCMS while controls were not affected by uCMS, except for a slight and transient reduction in body weight. PRS females displayed a reduced body weight gain across the entire duration of the uCMS procedure. Remarkably, the effects of uCMS on PRS females were still observed up to two months after its termination and the females displayed heightened rhythms of locomotor activity and enhanced sensitivity to reward with respect to controls exposed to uCMS. Globally, our findings indicate a mismatch hypothesis for many parameters of the PRS female adult phenotype that are subjected to both an early and late experiences and suggest that early stressed individuals may be programmed with a more dynamic phenotype than non-stressed individuals.

Disclosures: H. Bouwalerh: None. **J. Mairesse:** None. **E. Gatta:** None. **P. Palanza:** None. **S. Maccari:** None. **S. Morley-Fletcher:** None.

Poster

499. Neurophysiologic Effects of Early-Life Stress

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 499.18/VV1

Topic: F.04. Stress and the Brain

Support: International Associated Laboratory (LIA) France/Italy "Prenatal Stress and Neurodegenerative Diseases", University of Lille – CNRS UMR8576 and Sapienza University of Rome - IRCCS Neuromed. Co-directed by Pr S Maccari and Pr F Nicoletti

Title: Early life stress induces an impairment of glutamatergic transmission: Effects of pharmacological strategies at adulthood

Authors: *S. MORLEY-FLETCHER, G. VAN CAMP[1], J. MARROCCO[2], J. MAIRESSE[3], E. GATTA[4], H. BOUWALERH[5], A.-R. ZUENA[6], C. CLARISSE[7], Y. GUERARDEL[7], A. PITTALUGA[8], C. GABRIEL-GRACIA[9], E. MOCAER[9], S. BRETIN[9], F. NICOLETTI[10,6], S. MACCARI[11,10]

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Abstract: Perinatal stress (PRS) in rats has an established value as a model for stress-related disorders which is caracterized by an impaired synaptic activity including glutamatergic transmission with reduced depolarization-evoked glutamate release selectively observed in the ventral hippocampus and reduced expression of SNARE proteins and mGlu5 and mGlu2/3 receptors. The defective glutamate transmission is causally related to reduced risk-taking behavior in several behavioral tests. We wanted to assess the effects of different interventional strategies in reversing this PRS-induced profile on glutamate transmission by chronically treating (3 weeks, i.p.) adult PRS animals with antidepressants (fluoxetine, agomelatine, and the novel AMPA receptor enhancer, S 47445) or by targeting the stress/antistress balance with the oxytocin receptor agonist, carbetocin. We found that the three different treatments reversed the deficit in glutamate release and in the expression in SNARE proteins, and corrected abnormalities in risk-taking behavior, motivational behavior, and cognitive function, as assessed by the elevated plus maze, light-dark box, splash test, and social memory test. There was significant correlation between glutamate release and behavioral changes in the various experimental groups. We are currently performing a glycomic characterization in the hippocampus of PRS rats to unravel the molecular events that drive phenotypic changes focusing on post-translational modifications of proteins. Taken together, our findings suggest that PRS causes long-lasting changes in glutamatergic transmission in the hippocampus that involve, at least in part, modifications in the presynaptic machinery mediating glutamate release. Interestingly, this “glutamatergic synaptopathy” was corrected by antidepressant and anti-stress drugs. These findings support the hypothesis that abnormalities in glutamatergic neurotransmission lie at the core of stress-related disorders.

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Poster

499. Neurophysiologic Effects of Early-Life Stress

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 499.19/VV2

Topic: F.04. Stress and the Brain

Support: NIMH Grant 1R01MH107556-01
MilliporeSigma Neuroscience Discovery Grant

Title: Effects of early life stress on AMPA receptor composition and cocaine conditioned place preference are sex-specific and driven by TNF

Authors: *P. GANGULY, J. A. HONEYCUTT, J. ROWE, L. RYLL, C. DEMAESTRI, H. C. BRENHOUSE
Northeastern Univ., Boston, MA

Abstract: Early life adversity can contribute to the propensity for developing neuropsychiatric diseases, including substance abuse disorders. In rodents, early stressors such as repeated maternal separation (MS) impact neural development, including important effects on ionotropic glutamate receptors in brain regions critical for behavioral regulation. Notably, previous reports suggest that neuroimmune signaling molecules, including the pro-inflammatory cytokine tumor necrosis factor (TNF), regulates AMPAR subunit composition. Indeed, increased TNF levels are reported to reduce GluA2-positive AMPARs, which are associated with increased excitotoxicity. Since MS can lead to TNF elevation, we hypothesized that AMPAR subunit composition is altered after MS. Furthermore, AMPAR activity in both the prefrontal cortex (PFC) and nucleus accumbens (NAc) contributes to drug-cue association. Therefore, we tested whether MS induced TNF elevations in these regions prompt AMPAR subunit composition changes, thereby affecting cocaine-induced conditioned place preference (CPP). Here, we (a) studied the contribution of MS to selective loss of GluA2 subunit in the PFC and NAc of male and female rats, (b) tested the specific role of soluble TNF in MS-induced GluA2 loss, and (c) examined the role of MS in cocaine-induced CPP and possible amelioration via pharmacological disruption of TNF signaling. Male and female rats were reared either under control or MS conditions. During adolescence (P40), animals were subcutaneously administered soluble TNF inhibitor XPro1595 (Xencor, Inc) or vehicle. Subsequently, they were tested for cocaine-induced CPP. PFC and NAc were extracted for qPCR analysis of TNF, GluA1, and GluA2, and western blot analyses on membrane fractions of GluA1, GluA2, and TNFR1. We observed elevated TNF gene expression in both PFC and NAc of MS males, but not females, compared to controls. GluA2 gene and protein expression were reduced in both regions of MS male rats, and XPro1595 treatment protected against such loss. MS males also formed a greater preference for a cocaine-paired environment, which returned to baseline levels after XPro1595 administration. Taken together,

this work is the first to show a sex-specific mechanistic link between TNF signaling and changes in GluA2 expression and drug-cue conditioning, thereby providing further evidence for a role of MS and neuro-immune activity changes in cortical and striatal AMPARs. Moreover, manipulation of the TNF signaling pathway represents a novel approach for influencing response to rewarding effects of drug use.

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Poster

499. Neurophysiologic Effects of Early-Life Stress

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 499.20/VV3

Topic: F.04. Stress and the Brain

Support: 1R01MH107556-01

Title: Altered corticolimbic connectivity in a rat model of early adversity: Evidence from fMRI and neuroanatomical tracing suggests sex-dependent effects of early experiences

Authors: *J. A. HONEYCUTT[1], C. DEMAESTRI[1], X. CAI[2], R. MEHTA[1], P. P. KULKARNI[2], C. F. FERRIS[2], H. C. BRENHOUSE[1]
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Abstract: Adverse early life experiences significantly alter behavioral and neural trajectories, and such disruptions during early developmental periods likely set the course for aberrant brain maturation. Indeed, children with a history of early life stress (ELS) often exhibit deleterious effects, manifesting as maladaptive behaviors, cognitive impairment, and/or increased risk of mental illness later in life. Evidence in ELS human populations points to a role of atypical corticolimbic circuit development leading to changes in connectivity between limbic (i.e. amygdala, hippocampus) and the prefrontal cortex (PFC). Importantly, children with a history of ELS show patterns of precocially mature corticolimbic functional connectivity (FC) which is comparable to adolescent patterns. While these findings indicate compelling influences of early adversity on neural circuit maturation, the underlying neurobiological substrates remain poorly understood. Recent work from our group utilizing a rat model of ELS via maternal separation reveal sex- and age-dependent effects on amygdala-derived axonal innervation of the PFC. Specifically, we have reported that juvenile ELS females show patterns of axonal innervation comparable to adolescent and adult controls, with ELS-dependent changes in males not appearing until later in development. To explore whether these neuroanatomical changes confer alterations in corticolimbic connectivity, we utilized resting state FC and anisotropy assessments

to directly compare ELS and control males and females from juvenility to adolescence. Here, we present data delineating sex- and age-dependent effects of resting FC which suggest thatmay help explain how females with a history of adversity may be more vulnerable to later psychiatric illness resulting from alterations in FC driven by precocial maturation of amygdala-derived PFC innervation. Furthermore, we present behavioral data suggesting that these neural alterations may also be predictive of anxiety-like behaviors mediated by corticolimbic circuitry. Taken together, this data provides evidence for a critical role of early experience, and provides putative preliminary mechanistic insight into the underlying etiology of adversity-induced vulnerability.

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Poster

499. Neurophysiologic Effects of Early-Life Stress

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 499.21/VV4

Topic: F.04. Stress and the Brain

Support: NIMH Grant 1R01MH107556-01
Graduate Thesis/Dissertation Research Grant

Title: Early life stress leads to sex-specific alterations in the formation of perineuronal nets around parvalbumin-expressing interneurons in the developing rat prefrontal cortex

Authors: *K. R. GILDAWIE, J. A. HONEYCUTT, H. C. BRENHOUSE
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Abstract: Early life experiences play a vital role in the development of the brain and its molecular components. Consequently, early life adversity can have disruptive effects on behavioral and neural development, especially in the prefrontal cortex (PFC), a late-maturing region with many subcortical connections involved in emotion regulation. Research demonstrates that the formation of extracellular structures, such as perineuronal nets (PNNs), that enwrap certain neuronal subtypes throughout the central nervous system, is essential for proper neurodevelopment. Indeed, PNN formation coincides with the closure of developmental critical periods, potentially playing a role in the emergence of neuropsychiatric disorders. Early life stress via maternal separation (MS) is reported to have sex-specific effects on presence of parvalbumin (PV), which is expressed in fast spiking GABAergic interneurons that PNNs preferentially surround in the PFC. To determine the impact of MS and sex on PNN and PV formation in the PFC, male and female rat pups were separated from their dams for 4 hours per day from postnatal day (P) 2-20. At distinct developmental time points of juvenility (P20), adolescence (P40), early adulthood (P70), and adulthood (P120) rats were perfused and brains

were collected, cryoprotected, and sliced on a freezing microtome to 40 µm slices. Tissue sections containing the prelimbic (PL) and infralimbic (IL) PFC were stained for *Wisteria floribunda* agglutinin, a plant lectin that has an affinity for PNNs, and anti-PV to visualize PV neurons. Z-stacks were obtained (8 stacks per section) using fluorescent microscopy in 4 consecutive sections of the PFC and ImageJ was used to manually count PNNs, PV cells, and PNNs surrounding PV cells in the PL and IL. Results demonstrate sex- and age-specific effects of MS on PNN number in the PFC, where females displayed a distinct reduction in the number of PNNs surrounding PV cells following MS. Notably, this effect is not observed in PNNs surrounding non-PV cells. These findings have implications for the role of aberrant PNN and PV development in neural and cognitive dysfunction seen in humans and animals that have experienced early life adversity.

Disclosures: K.R. Gildawie: None. **J.A. Honeycutt:** None. **H.C. Brenhouse:** None.

Poster

499. Neurophysiologic Effects of Early-Life Stress

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 499.22/VV5

Topic: F.04. Stress and the Brain

Title: The association between maternal alcohol consumption in pregnancy and offspring brain morphology: A population-based MRI study

Authors: *T. SHARP[1], E. WALTON[1], C. RELTON[1], T. PAUS[2], L. ZUCCOLO[1]
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Abstract: The neurodevelopmental consequences of Foetal Alcohol Spectrum Disorder are well characterised, with microcephaly and cognitive deficits consistently reported resulting from significant prenatal alcohol exposure (PAE). There is a gap in the literature, however, regarding the impact of in utero alcohol exposure in non-clinical populations. Here we describe the results of our exploratory study assessing the association of PAE with global and region of interest (ROI) measures of cortical surface and thickness in two population-based cohorts.
Data from mother-adolescent pairs were meta-analysed from two populations; prospective birth cohort the Avon Longitudinal Study of Parents and Children (ALSPAC, n=455) in the UK and the cross-sectional Saguenay Youth Study (SYS, n=998) in Canada. Data on maternal alcohol consumption were collected via structured questionnaire, and offspring grouped as exposed or unexposed. MRI scans were obtained during adolescence (mean 19.6 years ALSPAC, 15.2 years SYS), and processed using the FreeSurfer v5.3 pipeline. Brain-based outcomes were defined as total cortical surface (tCS), mean cortical thickness (mCT), and 34 regions-of-interest (ROI) in both measures. A wide range of covariates relating to the prenatal and postnatal environment were examined as potential confounders. Our final model adjusted for sex, age and gestational

age of the child, and maternal smoking in pregnancy, parity, and socioeconomic indicators. To allow assessment of a dose-response relationship, additional analyses were conducted in ALSPAC using low (<1 unit/week) and moderate (1 to 6 units/week) alcohol measures. Regression models produced little evidence against the null hypothesis in all analyses. In the adjusted model, exposed offspring showed a 398mm2 difference in tCS in ALSPAC (95% CI -3024mm2 to 3820mm2 p=0.82), and a 492mm2 difference in SYS (95% CI -1835mm2 to 2819.17mm2 p=0.68), with a pooled estimate of 462mm2 (95% CI -1503mm2- 2383mm2 I2< 0.00%). Exposed offspring showed a 0.009mm difference (95% CI -0.014mm to 0.031mm p=0.46) in mCT in ALSPAC, and a 0.003mm difference in SYS (95% CI -0.019 to 0.012 p=0.69), with a pooled estimate of 0.001mm (95% CI -0.012mm to 0.013mm I2=<0.00%). Low and moderate exposure measures were not associated with differences in either tCS or mCT. No ROIs were associated with any alcohol measures after correction for multiple testing.
We found little evidence to suggest PAE is associated with alterations in brain morphology in adolescents in the general population. This analysis will be expanded to incorporate other population cohorts, where increased power may allow detection of evidence of effect.

Disclosures: T. Sharp: None. **E. Walton:** None. **C. Relton:** None. **T. Paus:** None. **L. Zuccolo:** None.

Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.01/VV6

Topic: F.04. Stress and the Brain

Support: NIH Grant K99MH115096
NIH Grant P50 MH096890
Hope for Depression Research Foundation

Title: Transcriptional priming by enduring chromatin modifications after early life stress

Authors: *C. J. PENA[1], Y.-H. E. LOH[1], L. FARRELLY[1], B. GARCIA[2], I. MAZE[1], L. SHEN[1], E. J. NESTLER[1]
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Abstract: Child maltreatment and other forms of early life stress increase the lifetime risk of depression and other mood, anxiety, and drug disorders by 2-4 -fold. Studies in humans and animals suggest that early life stress sensitizes individuals to stress later in life, leading to a first appearance or synergistic worsening of depression-like symptoms only after additional stress. To study the molecular correlates of lifelong stress vulnerability, we recently established a “two-hit”

stress paradigm in mice in which early life stress in a sensitive window increases susceptibility for depression-like behavior, but only after experience of an additional stressor in adulthood. This latent behavioral vulnerability is accompanied by latent transcriptional alterations in key brain reward regions that are implicated in depression, including the ventral tegmental area (VTA; Peña et al., *Science*, 2017). We hypothesized that such latent transcriptional alterations would be primed by post-translational histone modifications. In order to profile all possible long-lasting histone modification changes, we performed bottom-up mass spectrometry on isolated histone tail fragments from adult standard-reared and early life stressed male mice. The proportions of 14 histone H3 and H4 modifications were altered by early life stress, a majority of which are associated with permissive gene expression states. Among these, early life stress increased H3K4me3 and H3K4me1, marks of active and primed cis-regulatory elements. ChIP-seq for H3K4me1 revealed 201 differentially enriched peaks (FDR<0.05 and >20% fold-change), a majority of which were increased by early life stress. Interestingly, there is greater correspondence between H3K4me1 enrichment and expression of nearest-genes after additional adult stress than after early life stress alone, in support of a priming hypothesis. This research suggests novel epigenetic mechanisms mediating the long-lasting effects of early life stress within brain reward circuitry.

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Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.02/VV7

Topic: F.04. Stress and the Brain

Support: NIH Grant P50 MH096889
NIH Grant R01 MH73136
NIH Grant R01 NS28912
Hewitt Foundation for Medical Research

Title: Unexpected transcriptional programs underlie enduring memory deficits after early-life adversity

Authors: *J. L. BOLTON[1], A. SCHULMANN[1], M. M. CURRAN[1], L. REGEV[1], N. KAMEI[1], A. SINGH-TAYLOR[1], S. JIANG[2], J. MOLET[1], A. MORTAZAVI[2], T. Z. BARAM[1]
[1]Dept. of Anat. & Neurobio., [2]Developmental and Cell Biol., Univ. of California-Irvine, Irvine, CA

Abstract: Premise: Adverse early-life experiences are associated with lifelong cognitive deficits and risk of dementia, yet the underlying mechanisms remain unclear.
Methods: We imposed early-life adversity by rearing rat pups in simulated poverty, assessed hippocampus-dependent memory in adulthood, and probed enduring changes in gene expression and their contribution to memory deficits.
Results: Adversity provoked poor spatial memory in adult male rats, associated with over a hundred differentially expressed (mostly downregulated) genes in dorsal hippocampus. Transcription-factor target enrichment identified the stress-hormone receptor GR (glucocorticoid receptor) and, unexpectedly, the repressor neuron-restrictive silencer factor (NRSF/REST), as candidate upstream regulators. Blocking NRSF function transiently *after* the adversity period rescued hippocampus-dependent memory without influencing other behaviors.
Conclusions: These studies identify a novel role for NRSF-mediated repression of crucial neuronal genes in early-life adversity-induced hippocampal dysfunction and enduring cognitive deficits. A better understanding of these mechanisms will enable the development of better therapeutics and preventative interventions for at-risk children.

Disclosures: J.L. Bolton: None. **A. Schulmann:** None. **M.M. Curran:** None. **L. Regev:** None. **N. Kamei:** None. **A. Singh-Taylor:** None. **S. Jiang:** None. **J. Molet:** None. **A. Mortazavi:** None. **T.Z. Baram:** None.

Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.03/VV8

Topic: F.04. Stress and the Brain

Support: Hope for Depression Research Foundation
NIH/NINDS R00NS080911

Title: Variations in maternal care influence the epigenomic and transcriptomic landscape of the rat dentate gyrus

Authors: *W. I. DOYLE[1], X. WEN[2], C. L. KEOWN[1], J. DIORIO[2], M. MEANEY[3], E. A. MUKAMEL[1], T.-Y. ZHANG[2]
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Abstract: Maternal care has profound impacts on the development and function of the brain in mammals. Maternal care in rats affects synaptic plasticity and neurogenesis in the dentate gyrus (DG), a brain region involved in learning and stress-related behaviors. Offspring of high licking/grooming (high LG) mothers have enhanced learning and memory, and decreased

corticosterone response to acute stress, compared to offspring of low licking/grooming (low LG) mothers. We examined the effects of maternal care in the dorsal and ventral DG on gene expression (transcriptome RNA-sequencing). In parallel, we generated DNA methylome (whole genome bisulfite sequencing) and hydroxymethylome (Tet- assisted bisulfite sequencing) data to address the potential epigenomic contribution to the lasting effects of maternal care. RNA-sequencing indicated that maternal care is associated with significant changes in the expression of genes related to synaptic plasticity and function, dendrite complexity, and gene regulation in both the dorsal and ventral DG. These effects were similar in the two poles of the DG. Consistent with our previous work in mice, we also found that the dorsal and ventral DG have substantial differences in gene expression and DNA methylation, with higher levels of methylation at non-CG dinucleotides in ventral compared to dorsal DG. We also identified over 30,000 differentially methylated regions (DMRs) where CG dinucleotides were hypomethylated in the dorsal DG. These results demonstrate that maternal care can lead to changes in expression of genes crucial for proper neuronal activity, which may be in part explained by DNA methylation differences.

Disclosures: W.I. Doyle: None. **X. Wen:** None. **C.L. Keown:** None. **J. Diorio:** None. **M. Meaney:** None. **E.A. Mukamel:** None. **T. Zhang:** None.

Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.04/VV9

Topic: F.04. Stress and the Brain

Support: NIH Grant P50 MH096889

Title: Intra-individual methylome signatures distinguish early-life experiences

Authors: *N. KAMEI[1], S. M. JIANG[2], J. L. BOLTON[1], G. A. SANCHEZ[1], A. MORTAZAVI[2], T. Z. BARAM[1]
[1]Anatomy/Neurobiology and Pediatrics, [2]Developmental and Cell Biol., Univ. of California, Irvine, Irvine, CA

Abstract: Premise: Genetic and environmental factors interact during sensitive periods early in life to influence mental health and disease. These influences involve modulating the function of neurons and neuronal networks via epigenetic processes such as DNA methylation. However, it is not known if DNA methylation changes outside the brain provide a predictive ‘epigenetic signature’ of early-life experiences in an individual child that may serve as a marker for vulnerability or resilience to mental illness. **Methods:** To obviate the massive variance among individuals, we employed a novel intra-individual approach by directly comparing two timed samples from the same individual rat in groups exposed to distinct early-life experiences with

defined onset and duration. We have previously established that these diverse experiences provoke specific phenotypic outcomes later in life. Specifically, we imposed 'simulated poverty' by raising pups for a week (from postnatal day [P]2 to P10) in cages with limited bedding and nesting materials (LBN). This manipulation disrupts the care provided by the rat dam to her pups and results in profound yet transient stress in the pups, devoid of major weight-loss or physical changes. This transient experience provokes significant and life-long deficits in memory and generates emotional measures of anhedonia and depression. Genomic DNA was isolated from each buccal swab. Reduced Representation Bisulfite Sequencing (RRBS) libraries were created and analyzed for intra-individual methylome changes using Support Vector Machine learning (SVM) algorithms. **Results:** Methylation levels of samples collected on P10 or P2 reflected the effect of age. However, inter-individual comparisons of P10 samples did not distinguish the early life experience of each individual rat. In contrast, **intra-individual** methylation changes of paired DNA samples from the same individual rat reflected the impact of diverse neonatal experiences. Using a support vector machine learning algorithm, we identified a DNA methylation signature that enabled predicting the type of early life experience of individual rats in a validation cohort. **Conclusions:** Our observations in rats--that distinct early-life experiences generate specific individual methylome signatures in accessible peripheral cells--should be readily testable in humans.

Disclosures: N. Kamei: None. **S.M. Jiang:** None. **J.L. Bolton:** None. **G.A. Sanchez:** None. **A. Mortazavi:** None. **T.Z. Baram:** None.

Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.05/VV10

Topic: F.04. Stress and the Brain

Support: Society for Research in Child Development Victoria Levin Award

Title: Early life emotional neglect predicts shorter telomere length in adulthood

Authors: *P. CINTORA[1], H. K. LAURENT[2]
[1]Neurosci., [2]Neuroscience, Psychology, Univ. of Illinois at Urbana Champaign, Urbana, IL

Abstract: Telomere length has gained increased attention as a potential risk marker for neuropsychiatric disorders. Telomeres, the protective caps at the end of chromosomes, naturally shorten with cellular aging, eventually leading to cellular dysfunction and death. Acceleration of this shortening process has been associated with early life adversity. However, there are multiple forms of adversity, and most studies to date have narrowly focused on abuse or trauma. Here, we study the associations between childhood maltreatment subtypes of neglect and abuse and

telomere length in a sample of 48 low-income women who took part in a study of mother-infant stress regulation. Self-reported experiences of neglect and abuse on the Childhood Trauma Questionnaire were used to predict mothers' telomere length in saliva samples collected when their infants were 18 months old. Of the five subtypes of childhood maltreatment, only history of emotional neglect predicted shorter telomere length in adulthood [Beta = -.318, p= .027], which was independent of concurrent depression and anxiety symptoms. Our results indicate that emotional neglect may have long lasting impacts that are biologically based as indicated by telomere shortening. Research examining the biological mechanisms by which neglect may accelerate telomere shortening and how that impacts later psychological health are warranted.

Disclosures: P. Cintora: None. **H.K. Laurent:** None.

Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.06/VV11

Topic: F.04. Stress and the Brain

Support: CIHR
NOSM RDF

Title: Transcriptome analysis of prenatal glucocorticoid exposed offspring demonstrates altered circadian rhythm signaling

Authors: S. THARMALINGAM, S. KHURANA, *T.-C. TAI
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Abstract: Prenatal glucocorticoid (GC) exposure is associated with the development of hypertension in adults. We have previously demonstrated that antenatal dexamethosone (DEX) administration in Wistar-kyoto dams results in offspring with elevated systolic, diastolic, and mean arterial pressure, along with increased plasma epinephrine levels (Nguyen 2015). Permanent molecular programming of the adrenal gland in the hypothalamic-pituitary-adrenal (HPA) axis has been implicated with cardiovascular disorders. In order to elucidate the molecular mechanisms responsible for prenatal DEX-mediated hypertension, whole-transcriptome analysis of the adrenal gland in male offspring of DEX exposed Wistar-kyoto dams were analyzed using Rat Gene 2.0 ST GeneChip (Thermo Fisher Scientific). This array covers over 27,000 protein coding transcripts from 24,000 Entrez genes, with a median of 22 probes per gene thereby providing excellent genome wide coverage. Differential gene expression analysis of DEX exposed offspring compared with saline-treated controls revealed 84 significantly differentially expressed genes; 55 upregulated genes and 29 downregulated genes (criteria: fold-change <-1.5 and >1.5; p-value <0.05; false discovery rate < 0.1). Global network

analysis demonstrated that genes involved in circadian rhythm signaling were most robustly dysregulated. Here, DEX exposed offspring demonstrated 2-fold increased expression of BMAL1 and Npas2, while Per1, Per2, Per3, Cry1, and Cry2 were all downregulated (verified using qPCR analysis). BMAL1 and Npas2 dimerize and function as molecular transcription factors with a wide variety of downstream effects including control of blood pressure regulation. Interestingly, BMAL1 knockout animals demonstrate reduced blood pressure during the active phase. Furthermore, BMAL1-Npas2 complex also increases expression of Per and Cry genes, which are negative regulators of BMAL1 and Npas2. Therefore, these results suggest that the adrenal gland of DEX exposed offspring demonstrate abnormal circadian rhythms. Thus, altered circadian rhythm signaling may provide a mechanism by which prenatal GC exposure may program for hypertension later in life.

Disclosures: S. Tharmalingam: None. **S. Khurana:** None. **T. Tai:** None.

Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.07/VV12

Topic: F.04. Stress and the Brain

Title: Development and characterisation of mice carrying the humanised FKBP5 gene

Authors: V. NOLD[1], N. DENOIX[1], B. HENGERER[1], *K. A. ALLERS[2]
[1]CNS Discovery Res., [2]Boehringer Ingelheim Pharma Gmbh & Co. KG, Biberach An Der Riss, Germany

Abstract: The *fkbp5* gene codes for the protein FKBP51, which is a potent regulator of glucocorticoid and NFkB signaling. A common SNP located in *fkbp5* is rs1360790, which imparts a profound influence on the stress response. This is likely due to an altered chromatin conformation in carriers of the T- allele, resulting in greater transcription upon glucocorticoid response element activation. Furthermore, the risk of developing psychiatric disorders after childhood trauma is higher in carriers of rs1360790-T as compared to carriers of the ‘resilience’ allele (rs1360790-C), as shown by an increased incidence of disorders in carriers of the ‘risk’ allele. This gene × environment interaction is suggested to be mediated via demethylation of *fkbp5*, which further promotes transcription in the already more highly responsive form of *fkbp5*. These SNPs are not present in rodents. In collaboration with Taconic, our aim was to develop humanised mouse lines carrying the ‘risk’ or ‘resilience’ allele. A locus replacement strategy was used: Targeting constructs for either the murine or human gene were obtained by cloning the SNP variants into the sequence. Via homologous recombination, the constructs were inserted in the genome of murine embryonic stem cells (ESC). Construct-positive ESC clones were selected using resistance factors included at the ends of the constructs and confirmed by PCR analyses.

The selected ESC clones were inserted in blastocysts via microinjection to generate chimeric mice. In these chimeras, the resistance factors were deleted in vivo via flip-recombinases. Breeding of chimeric mice with wildtype-mice resulted in heterozygous progeny which was HE × HE mated to obtain homozygous transgenic mice carrying the human *fkbp5* gene containing either the 'risk'-allele rs1360790-T or the 'resilience'-allele rs1360790-A. A well-known feature of *fkbp5* regulation is its induction by glucocorticoid receptor agonists, which makes detection of *fkbp5*-RNA after stimulation of the glucocorticoid receptor an ideal test of a functionally responsive gene. Upon generation of heterozygote mice, primary splenocytes were isolated to test for a functional response upon glucocorticoid stimulation. In this assay, the mouse and human alleles were both stimulated in a dose-responsive manner to an equal extent (~10 fold change). This study demonstrated that the human allele is detectable at basal levels and is also functionally responsive. Hence, this mouse model may provide an ideal system in which to further characterize the gene × environment interactions of the known human SNP rs1360790-T with childhood adversity that impart significant risk for psychiatric disorders.

Disclosures: V. Nold: A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma. **N. Denoix:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma. **B. Hengerer:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma. **K.A. Allers:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma.

Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.08/VV13

Topic: F.04. Stress and the Brain

Support: NIMH RO1 MH106565
5T32MH067631-13

Title: Epigenetic regulation and gene gxpression analysis of glucocorticoid receptor exon 1f and fkbp5 in adolescent suicide

Authors: *H. S. RIZAVI, D. R. GRAYSON, H. ZHANG, G. PANDEY
Univ. Illinois Chicago, Chicago, IL

Abstract: Suicide has been steadily rising for the past 10 years and is at its highest peak in 30 years, since collection of data began. This rise is particularly high among teens 12-18 and college-age youth. An impaired feedback inhibition of the HPA axis is a strong predictor for suicide. Glucocorticoid receptor (GR), a key mediator of HPA axis regulation and a transcription factor is considered to engage several responsive genes that can drive lasting molecular and cellular changes. GR also directly induces expression of FKBP5 which is a negative regulator for

GR sensitivity to cortisol. Growing number of studies have shown that gene-environment interactions ultimately affect and influence genetic predispositions for suicide. Epigenetic modifications continuously modulate the transcriptional changes that could lead to lasting functional changes. Our aim was to determine the epigenetic modifications occurring at the proximal promoter region of GR-1F and FKBP5 and the regulatory consequence on the respective genes. In addition, we examined the expression of genes that control DNA methylation, DNA methyltransferases (DNMTs), and demethylation, ten-eleven translocation proteins (TETs) and growth arrest- and DNA-damage-inducible proteins GADD45, as potential contributors to the altered levels of DNA methylation (5mC) and hydroxymethylation (5-hmC). We found an increase in 5mC and a decreased level of 5hmC at the GR1F promoter which is accompanied by a significant decrease in expression of GR1F. We also find a decreased amount of 5mC and an increase in the levels of 5hmC at the proximal promoter region of FKBP5, and a total increase in expression of FKBP5. These results are accompanied by an increase in DNMT1 and DNMT3a expression, decrease in TET1 and TET2 and a decrease in Gadd45β. Collectively these results identify possible causes to the disturbed balance that contributes to prolonged activation of HPA axis in PFC and provide insight to the molecular pathology of teenage suicide.

Disclosures: H.S. Rizavi: None. **D.R. Grayson:** None. **H. Zhang:** None. **G. Pandey:** None.

Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.09/VV14

Topic: F.04. Stress and the Brain

Support: NICHD 1R01HD087509-01

Title: Prevention of aberrant DNA methylation induced by maternal maltreatment in early life

Authors: *N. PHILLIPS[1], T. S. DOHERTY[2], T. L. ROTH[3]
[1]Psychological and Brain Sci., [3]Psychology, [2]Univ. of Delaware, Newark, DE

Abstract: Early life adversity can increase risk for the development of psychological disorders such as depression and anxiety. One prominent form of early life adversity is child maltreatment. Poor maternal care can alter methylation patterns of several genes, and these altered patterns are often followed by maladaptive behaviors later in life Previously, our lab demonstrated that negative caregiving received by rat pups results in aberrant methylation and decreased gene expression of the brain-derived neurotrophic factor (*Bdnf*) gene in the prefrontal cortex (PFC) across the lifespan and that aberrant methylation can be rescued in adulthood via daily administration (7 days) of a DNA methyltransferase inhibitor (DNMTi), zebularine. Further, we and others have found that maltreated pups grow up to maltreat their own offspring. The present

study aimed to investigate whether DNMTi, 5-aza-deoxycytidine (5-azaD), can prevent aberrant methylation of *Bdnf* exon IX in the PFC of Long-Evans (*Rattus norvegicus*) pups if delivered at the time of negative caregiving. Using a scarcity adversity paradigm and a within-litter design, male and female pups were exposed either to normal care from their biological mom, normal care from a nurturing foster dam, or negative care from a stressed foster dam for 30 minutes per day from postnatal days 1-7. Results indicate that a 0.5 mg/kg dose of 5-azaD normalized *Bdnf* methylation such that there were no differences between maltreated pups given 5-azaD and their control counterparts Methylation levels in females given this dose exhibited high variability. Thus, we also tested the effects of a 1mg/kg dose to ensure effectiveness. We found that the 1 mg/kg dose of 5-azaD significantly reduced *Bdnf* methylation in the infant maltreated female PFC, and normalized methylation in the infant maltreated male PFC. These findings indicate that a pharmacological intervention can prevent changes in the epigenome due to early adverse experiences. If this prevention persists into adulthood, it could potentially prevent the development of adversity-induced maladaptive behaviors. Thus, we plan to measure if this prevention of methylation persists into adulthood and if that persistence is associated with the amelioration of adversity-induced behavioral phenotypes. [NICHD (1R01HD087509-01 to TLR]

Disclosures: N. Phillips: None. **T.S. Doherty:** None. **T.L. Roth:** None.

Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.10/VV15

Topic: F.04. Stress and the Brain

Support: CIHR Project grant to N.M

Title: Child abuse, neuroinflammation, and blood-brain barrier integrity: A preliminary postmortem investigation

Authors: *M. WAKID[1], A. TANTI[1], P.-É. LUTZ[2], C. NAGY[1], D. ALMEIDA[1], M. DAVOLI[1], G. TURECKI[1], N. MECHAWAR[1]
[1]Douglas Mental Hlth. Univ. Inst., Montreal, QC, Canada; [2]Nociception et Douleur, Inst. Neurosciences Cellulaires Intégratives, Strasbourg, France

Abstract: Introduction: There is increasing evidence supporting the hypothesis that major depression is associated with increased neuroinflammation and permeability of the blood-brain barrier (BBB). Our group recently reported that in the dorsal anterior cingulate cortex (dACC) of depressed suicides, there is a significantly higher proportion of blood vessels surrounded by a high density of macrophages compared to matched controls. The aim of the current project is to examine whether a history of child abuse is associated with even more pronounced changes in

the expression of neuroinflammatory and BBB markers. Methods: Well-characterized postmortem dACC samples from adult depressed suicides with a history of severe child abuse and from matched healthy controls having died suddenly were processed for RNAseq. Results: A preliminary comparative transcriptome analysis revealed a significant downregulation of certain genes coding for tight junction proteins, including tight junction protein 1 (TJP1), tight junction protein 2 (TJP2) and occludin (OCLN) in depressed suicides with a history of child abuse compared to controls. Discussion: Tight junctions, which underlie the physical barrier created by neurovascular endothelial cells of the BBB, provide neuroprotection for complex cellular interactions at the neurovascular unit. Our preliminary finding indicate that some key genes for the establishment and maintenance of tight junctions are disrupted in dACC samples from depressed suicides with a history of child abuse. We speculate that this observation is associated with our previous findings of increased macrophages surrounding blood vessels in the dACC of depressed suicides. Experiments are under way to validate these results, assess their specificity with regards to child abuse, and explore BBB integrity with additional molecular and histological approaches. Keywords: child abuse, major depressive disorder, suicide, tight junction, blood brain barrier, neuroinflammation

Disclosures: M. Wakid: None. **A. Tanti:** None. **P. Lutz:** None. **C. Nagy:** None. **D. Almeida:** None. **M. Davoli:** None. **G. Turecki:** None. **N. Mechawar:** None.

Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.11/VV16

Topic: F.04. Stress and the Brain

Support: NIH Grant HD091376
NIH Grant MH099910
NIH Grant ES028202
NIH Grant MH104184
NIH Grant MH108286

Title: Epigenetic programming of chromatin accessibility by stress during puberty

Authors: *K. E. MORRISON, T. L. BALE
Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Adverse childhood experiences are one of the greatest predictors for affective disorder presentation for women. However, few animal models exist that address female-specific risk factors or unique periods across the lifespan. As the pubertal transition is marked by dynamic hormonal changes and ensuing reorganization of the brain, it represents a window of sex-specific

vulnerability to adverse experiences. Periods of hormonal flux in the female lifespan, including pregnancy, exacerbate the risk for affective disturbances and promote stress dysregulation, a key feature of affective disorders. We have established a translationally relevant mouse model in which pubertal adversity leads to broad stress dysregulation in adulthood that is dependent upon hormonal status. Our previous work in humans and mice has shown that increases in allopregnanolone are necessary to produce the blunted HPA axis response in stressed females. Allopregnanolone likely acts on a reprogrammed GABA system within the paraventricular nucleus of the hypothalamus (PVN), as RNA-Seq analysis of the PVN during pregnancy revealed alterations to GABA system gene expression by pubertal stress. However, it is unclear what is responsible for long-term reprogramming of the GABA system. Prior RNA-Seq also revealed that females stressed during puberty had increased expression of a host of immediate early genes at baseline during pregnancy. Immediate early gene expression requires that their promoters be accessible to the intracellular cascades that initiate their transcription. These data suggest that, even at baseline, the chromatin in the PVN of pubertally stressed females is in a more open, permissive state. Thus, we utilized ATAC-Seq, a technique which allows for the direct assessment of chromatin openness and interrogation of which genes are available for transcription, to assess pubertal stress-induced epigenetic programming. Female mice were exposed to chronic variable stress from postnatal days 21-34 and were sacrificed during adulthood, either in virgin or pregnant state. ATAC-Seq signal intensity in the PVN was assessed for effects of pubertal stress and hormonal state, allowing for the identification of any alterations to the chromatin accessibility landscape. Together, these studies provide novel insight into the mechanisms underlying female-relevant risk factors for stress dysregulation, a central endophenotype of affective disorders.

Disclosures: K.E. Morrison: None. **T.L. Bale:** None.

Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.12/VV17

Topic: F.04. Stress and the Brain

Support: NIH Grant R37 MH108286-04

Title: Sperm RNA payload: Extracellular vesicle delivery of stress to the next generation of mice and men

Authors: *C. P. MORGAN[1,2], J. CHAN[3], D. S. BERGER[3], N. V. BHANU[3], B. A. GARCIA[3], C. N. EPPERSON[3], T. L. BALE[2]
[1]Baltimore, MD; [2]Univ. of Maryland Sch. of Med., Baltimore, MD; [3]Univ. of Pennsylvania Perelman Sch. of Med., Philadelphia, PA

Abstract: Paternal preconception exposures to environmental stressors, including metabolic, immune, and perceived threats are associated with increased disease risk in subsequent generations. Studies in rodent models implicate the germ cell transfer of epigenetic information in programming these intergenerational effects. Though the cellular mechanisms responsible for encoding paternal experiences in sperm are still being characterized, small non-coding RNAs (sncRNA) delivered to sperm by extracellular vesicles (EV) seem to play a key role. We have developed a model of paternal preconception stress in which chronically stressed mice sire offspring with a significantly blunted stress response and broad hypothalamic transcriptional changes. In our current studies, we identified a mechanism by which stress alters the sncRNA content of sperm to influence offspring development, focusing on the known role of EVs in delivering RNA cargo to sperm in the male reproductive tract. Analyses of mouse paternal reproductive tissues following stress revealed a convergence in stress-responsive sncRNA between sperm and the caput epididymis, pointing to this tissue as a nexus for somatic cell shaping of sperm sncRNA content. We modeled this *in vitro* using corticosterone treatment of cultured epididymal epithelial cells and found that this 'stress in a dish' reproduced lasting changes in the sncRNA content of secreted EVs. In addition, chronic corticosterone affected the histone codes of these cells, alterations that were also found in our mouse model of paternal stress. Together, these preclinical data support a lasting epigenetic mechanism by which stress experience alters programming of the caput epididymis, transmits this information to maturing sperm via secreted EVs, ultimately influencing early embryo development. To maximize the translational potential of this work, we developed a broad framework to determine the content and variability in EVs and sperm sncRNA over time relative to perceived stress in healthy human subjects. Using proteomics and RNA-sequencing to characterize the sncRNA content of sperm collected monthly from healthy human subjects for 6 months, we examined changes in semen content relative to perceived stress at each donation. Analyses to determine the normal within and between individual variability of sperm RNA content over time and to identify populations of sncRNA that covary with measures of perceived stress were completed. These studies offer an exciting novel mechanism by which the environment dynamically regulates sperm epigenetics, furthering our understanding of paternal contributions to offspring development and disease risk.

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Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

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Topic: F.04. Stress and the Brain

Support: NIH Grant MH108286
NIH Grant MH104184
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NIH Grant ES028202
NIH Grant GM110174

Title: Epididymal extracellular vesicles signal paternal stress programming of sperm and offspring neurodevelopment

Authors: *J. CHAN[1], B. M. NUGENT[2], K. E. MORRISON[2], E. JASAREVIC[2], N. V. BHANU[1], B. A. GARCIA[1], T. L. BALE[2]
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Sch. of Med., Univ. of Maryland, Baltimore, MD

Abstract: Evidence that paternal preconception exposures can shape offspring behavior and physiology prompts new consideration for the molecular mechanisms underlying offspring neuropsychiatric disease risk. As potential modes of transmission, germ cell epigenetic marks have been described to respond dynamically to stress in the paternal environment and subsequently transmit this information at fertilization. In particular, mechanistic examination has implicated small noncoding RNA populations in sperm, including microRNA (miRs) and tRNA-derived fragments, as causal mediators of offspring programming. Yet, despite the exciting potential for sperm small RNAs, how stress in the paternal environment is signaled from somatic tissues to transcriptionally inert sperm and how these signals may persist remain unknown. Here, we address these questions using our established mouse model of paternal stress, where specific sperm miRs altered by chronic stress reprogrammed adult offspring hypothalamic-pituitary-adrenal (HPA) stress reactivity. In the current studies, we describe the involvement of the caput epididymis, a somatic tissue that secretes extracellular vesicles (EVs) to deliver miRs from epididymal epithelial cells to maturing sperm, in relaying stress signals to sperm. Using an *in vitro* model, we demonstrate that administration of chronic glucocorticoids to DC2 mouse caput epididymal epithelial cells altered EV miR content both acutely and long after treatment ended, mimicking the timing of miR changes in paternal stress sperm. These EV changes corresponded with upstream increases in glucocorticoid receptor (GR) levels and modifications to histone post-translational marks in caput epididymal cells both in DC2 cells *in vitro* and in our mouse model *in vivo*, suggesting a potential mechanism that promotes enduring alterations to EV and subsequently sperm miRs. Further, we demonstrate the crucial role of GR in paternal stress transmission by caput epididymal epithelial-specific transgenic knockdown, which prevented offspring HPA stress axis dysregulation. Lastly, to determine the mechanism by which GR reduction rescued transmission, we analyzed the caput epididymal epithelial-specific translatome and found enhanced mitochondrial capacity and reversal of chromatin-modifying processes as potential modes of cellular resilience to stress. Our studies establish the paternal caput epididymis as an important somatic tissue upstream of offspring brain programming, and provide insight into the cellular mechanisms that can impact and prevent intergenerational transmission of offspring neuropsychiatric disease risk.

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Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

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Program #/Poster #: 500.14/VV19

Topic: F.04. Stress and the Brain

Support: P50-MH099910
MH 104184
MH 091258
MH 087597
MH 073030
MH 108286
NIH NRSA F32 MH 109298

Title: The pregnancy gut microbiome as a translational biomarker of maternal adversity and offspring immune programming

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Abstract: Maternal adversity during pregnancy, such as stress, diet, and infection, influence fetal neuroimmune development and is a risk factor for neurodevelopmental disorders, including autism and schizophrenia. To examine the hypothesis that sex-specific neuroimmune development is influenced by early pregnancy stress alterations to the maternal gut microbiome and microbiota-derived metabolites, we used our established mouse model of early prenatal stress (EPS), in which male, but not female, offspring demonstrate lasting health outcomes. Longitudinal modeling revealed that stress experience disrupted gut microbiota. Functional profiling revealed stress disruption of microbial metabolic pathways. Comparisons of amino acids, bile acids, and short chain fatty acids (SCFAs) from embryonic day (E)18.5 maternal and fetal tissues demonstrated parallel stress-mediated decreases in amino acids and SCFAs in maternal cecum and E18.5 brain. As these metabolites regulate innate immune development, we determined how altered metabolite availability impacts the E18.5 fetal brain immune compartment and observed sex-specific alterations in the frequency and activational patterns of resident and infiltrating immune cells. Sex-specific transcriptomes were also examined using RNA-Seq and ATAC-Seq on E18.5 immune cell populations. Reconstitution experiments were used to examine the casual contribution of maternal gut microbiota-derived metabolites to rescue

aspects of the EPS phenotype in adulthood. Finally, to establish the translational relevance of our results, pregnant women who had experienced either a low (<2) or high (>2) number of adverse childhood events (ACEs) during the preadolescent window were recruited at 21 to 32 weeks of pregnancy. Gut microbiota composition, pro-inflammatory cytokine profiles, and cortisol levels following acute stress were measured in low and high ACE pregnant women. Similar to our results in our EPS mouse model, the maternal gut microbiome was significantly altered in high ACE women relative to low ACE women during pregnancy. Further, pro-inflammatory cytokines were positively correlated with inflammation-associated microbiota in high ACE women, providing an important link between early life adversity and peripheral inflammation during pregnancy. Taken together, our results demonstrate stress reprogramming of the neuroimmune compartment via maternal gut microbiota-derived metabolites. Further, as the maternal gut microbiota is readily accessible, these studies demonstrate high translational potential and implicate a novel biomarker of ACEs and subsequent health outcomes in the offspring.

Disclosures: E. Jašarevic: None. **L. Hantsoo:** None. **C. Howard:** None. **C.N. Epperson:** None. **T. Weinkopff:** None. **T.L. Bale:** None.

Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.15/VV20

Topic: F.04. Stress and the Brain

Support: NIH Grant ES028202
NIH Grant MH099910
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NIH Grant MH108286

Title: Maternal stress and brain development: Can stress in mice model the stress-induced racial disparity in infant health?

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Abstract: Maternal lifetime exposures to perturbations such as stress, infection, and malnutrition increase risk for offspring disease. African American infants in the U.S. have significantly worse health outcomes than non-Hispanic white infants. Increased risk of low birth weight (LBW) and preterm birth (PTB) is correlated with indicators of stress, as well as childhood and lifetime

perceived racism specifically in African American mothers, independent of socioeconomic, medical, and behavioral risk factors. While maternal insults during pregnancy directly impact fetal development, the mechanisms by which lifelong stress experience can alter germ cell programming and affect offspring neurodevelopment are unknown. We have established a model of maternal preconception stress (MPS), where adult female mice were exposed to chronic (4 week) or lifelong (from weaning) stress. Two weeks post-stress, females were mated to naïve male mice. Stress-relevant behaviors and physiological were assessed in adult offspring of MPS dams. Female, but not male, MPS offspring showed enhanced stress reactivity, supporting our hypothesis that stress experienced prior to pregnancy induces long-term changes along the reproductive tract to alter sex-specific fetal development. Transcriptional changes in the placenta regulate sex-specific programming in response to stress, through differential expression of the X-linked gene, OGT (O-glycosyl transferase), and its regulation of the repressive histone mark, H3K27me3. We therefore examined differences in placental histone post-translational modifications (PTMs) using an unbiased mass spectrometry approach. Female placentas from MPS dams showed decreased H3K27 methylation and increased acetylation, suggesting increased broad permissive transcription in response to stress. We then conducted transcriptomic analysis of the placenta and fetal brain via RNA-sequencing to examine the transcriptional consequences of MPS programming. Finally, we investigated the role of the oocyte in encoding the lasting molecular alterations of MPS at the single cell level via RNA-sequencing. Together, these studies bring to attention the importance of female lifetime and preconception experiences on germline, placental, and offspring brain development, and highlight its potential contribution to the stress-induced racial disparity in infant health outcomes.

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Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.16/VV21

Topic: F.04. Stress and the Brain

Support: American Society of Primatologists Legacy Award
NIH Grant R24OD011180

Title: From bowel to brain: Gut microbiota diversity and chronic HPA axis activity across development in rhesus monkeys

Authors: *A. M. DETTMER[1], J. ALLEN[2], V. A. VARALJAY[2], R. M. JAGGERS[2], S. J. SUOMI[3], J. S. MEYER[4], M. T. BAILEY[2]
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Abstract: Objective and rationale: Within days of birth, mammals undergo commensal intestinal bacterial colonization that remains throughout life. This commensal colonization is critical for immune function, nutrient processing, and central nervous system (CNS) functioning. One major component of the CNS, the hypothalamic-pituitary-adrenal (HPA) axis, synchronizes the body's stress response system and matures throughout the postnatal period, a time at which intestinal bacterial colonization also occurs. Studies in rodents have demonstrated a bidirectional pathway of communication between the gut and the brain such that gut microbiota program the HPA axis early in life, as well as stress reactivity throughout the lifespan; conversely, stress also alters the integrity of intestinal microbiota. Moreover, behavioral and physiological responses to stressful situations are impacted when the bacterial status of the gut is manipulated, either by infection, treatment with probiotics, or genetic modification. However, all these studies have been conducted in rodents and have relied on short-term samples to assess HPA axis functioning. Though it is established that nursery-reared (NR) monkeys exhibit higher long-term cortisol concentrations than mother-peer-reared (MPR) monkeys, nonhuman primates are notably absent from the literature demonstrating that gut microbiota program the HPA axis early in life. Methods: We tested the hypothesis that gut microbial diversity would relate to chronic HPA axis activity, as measured in hair cortisol concentrations (HCCs), across early development in rhesus monkeys (*Macaca mulatta*, N=19-35; 10-21 female). We obtained DNA samples from rectal swabs and hair samples on the day of birth and at six intervals throughout the first year of life. We used t-tests to explore rearing differences in relative quantities of intestinal bacteria genera, and Pearson's correlations to assess relations between relative percentages of bacteria and HCCs. Results: NR infants had lower relative *Lactobacillus* than MPR infants at 30d ($t(1)=3.39, p=0.002$) and 6mos ($t(1)=1.98, p=0.03$), and higher *Bifidobacterium* at 30d ($t(1)=-2.50, p=0.01$). Relative levels of *Lactobacillus* ($r=0.48, p=0.06$) and *Streptococcus* ($r=0.53, p=0.03$) at 6mos were positively correlated with changes in HCCs from 6-9mos for NR infants. These are the first findings in neonatal nonhuman primates to show that gut microbial diversity, from birth, is associated with altered chronic HPA axis activity. Support: This research was supported by the Legacy Award from the American Society of Primatologists (to AMD), and by the National Institutes of Health (#R24OD011180).

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Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.17/VV22

Topic: F.04. Stress and the Brain

Title: A functional role of somatic retrotransposition in schizophrenia-associated sensory motor gating deficits

Authors: *J. A. ERWIN[1], A. SARKAR[2], A. PAQUOLA[1], E. TIETZE[1], M. WANG[2], I. GALLINA[2], J. HERDY[2], S. PARYLAK[2], F. H. GAGE[2]
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Abstract: The brain is a genomic mosaic due to somatic mutations occurring throughout neural development. Endogenously encoded Long Interspersed Element-1 (LINE-1 or L1) is a mobile element that generate somatic mosaicism in the human hippocampus and other regions. While it has been hypothesized that aberrant somatic L1 activity could mediate environmental factors that contribute to neurological disorders, evidence of L1 activation and the functional consequences of L1 mediated somatic mosaicism has remained elusive. Herein, we investigate the functional role of inflammation-driven somatic L1 retrotransposition in contributing to neurological disorders. Maternal immune activation (MIA) during embryonic neurogenesis increases the risk of developing schizophrenia and autism and correlates with increased L1 copy number in mouse and macaque brain. Here, we demonstrate that MIA induced pro-inflammatory cytokine IL-6 activates transcription and retrotransposition of mouse and human L1 in hippocampal neural progenitor cells. We established an in vivo mouse model to manipulate levels of L1 retrotransposition during MIA. Mice exposed to fetal MIA with high levels of L1 retrotransposition demonstrate impaired sensorimotor gating. Attenuation of L1 retrotransposition during fetal MIA specifically restores sensorimotor gating function. Offspring subjected to fetal MIA while attenuating L1 retrotransposition retain the strong pro-inflammatory immune response. Therefore, somatic retrotransposition specifically mediates attentional abnormalities associated with schizophrenia and autism. We performed targeted single cell DNA sequencing to identify somatic L1-assciated variants (SLAVs) induced by MIA in mouse. MIA results in an increased number of SLAVs in hippocampal neurons, an increased percentage of highly variable neurons harboring 15-60 SLAVs per cell, and enriched genomic variation near genes expressed at the time of MIA. These results suggest that L1 genomic variation mediates an important environmental risk factor for aberrant neural development and that properly tuned levels of somatic mosaicism are essential for healthy cognitive function.

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Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

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Program #/Poster #: 500.18/WW1

Topic: F.04. Stress and the Brain

Support: NIH Grant R01MH115914
NIH Grant P20- GM103645

Title: Early life stress accelerates amygdala development while delaying prefrontal connectivity

Authors: *G. MANZANO-NIEVES[1], M. BRAVO[2], A. JOHNSEN[3], H. SHIN[6], R. A. APONTE-RIVERA[4], K. G. BATH[5]
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Abstract: Early life stress (ELS) is associated with an increased risk for later development of emotional pathology such as depression and anxiety. The origins of pathology are thought to be rooted in atypical development of circuits regulating emotional responding, including the amygdala. Here we used a mouse model of ELS, in the form of maternal bedding restriction, and tested the effect on amygdala development, and the development of freezing behavior in a tone-associated fear conditioning paradigm. Previous work has established that tone-associated freezing develops as early 15 days of age and stays relatively stable across early development. Here, we found that mice reared under ELS conditions show an unexpected and significant decrease in freezing behavior at 21 days of age. This decrease in freezing behavior was associated with a precocious maturation and an increase in the density of Parvalbumin (PV)-positive cells in the basal amygdala (BA). In addition, we found that ELS mice had a delay in prefrontal to basolateral amygdala projections. To test if the increase in PV-cells was related to suppressed freezing behavior, we took advantage of optogenetic techniques to silence this population of cells in the BA during acquisition and testing phase in the conditioning paradigm. We found that silencing BA PV cell restored normal levels of freezing behavior in ELS reared mice. These results have implications for understanding the effects of ELS on the ontogeny of circuit development and its impact on the development and expression of fear associated responding.

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Poster

500. Early-Life Stress: Molecular Mechanisms and Cellular Effects

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 500.19/WW2

Topic: B.01. Neurotransmitters, Transporters, and Signaling Molecules

Support: NSERC Discovery

Title: The impact of chronic early life social isolation on receptor expression and receptor tyrosine kinase transactivation in the hippocampus and prefrontal cortex

Authors: N. GONDORA[1], C. POPLE[2], M. ROBINSON[1], J. G. MIELKE[3], *M. A. BEAZELY[4]
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Abstract: Exposing mammals to social isolation in early life can affect brain development and lead to changes in adult behavior. In rats, social isolation during adolescence induces changes reflective of neuropsychological disorders, such as depression. However, the molecular mechanism(s) underlying these outcomes have not yet been elucidated. In the Chronic Early Life Social Isolation Study (CELSI), we explored the impact of social isolation on the expression of key proteins both implicated in neuroplasticity and potentially related to the observed behavioral effects of social isolation: the TrkB receptor and the NMDA receptor. At post-natal day 21, 20 male and 20 female Sprague-Dawley rats were separated into either group (N=3 animals/cage) or isolation housing. After seven weeks, the animals were sacrificed and the hippocampus (HP) and prefrontal cortex (PFC) were extracted, homogenized, and analyzed via immunoblotting. Differences in receptor subunit expression between the control (group housed) and stressed (isolated) animals were observed, including sex-specific and region-specific variation. To explore the relationship between chronic stress (early life isolation) and acute chemical stress, brain slices obtained from the CELSI rats were exposed to corticosterone, a steroid stress hormone. We have previously demonstrated cross-talk signaling between the 5-HT7 serotonin receptor and receptor tyrosine kinases including TrkB. Slices treated with the 5-HT7 receptor agonist, LP 12, or corticosterone, demonstrated increased TrkB receptor phosphorylation. The transactivation pathway is of particular interest because of its potential to harness neuroprotective potential and to buffer against various neuronal insults. We have also demonstrated in the HT22 cell-line, (a hippocampal cell-line) that corticosterone affects both cell-viability and receptor tyrosine kinase (RTK) transactivation. This data will form the basis for

subsequent work to improve our understanding of the molecular neurodevelopmental responses to chronic early-life stress.

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Poster

501. Water and Salt Balance and Thirst

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 501.01/WW3

Topic: F.09. Thirst and Water Balance

Support: Hellman Fellowship

Title: Circuitry for water seeking motivation in *Drosophila*

Authors: D. LANDAYAN[1], J. ZHOU[1], *F. W. WOLF[2]
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Abstract: Thirst is an evolutionarily ancient motivational state that is hard-wired and critical for survival. How thirst circuits in the brain coordinate the appropriate goal-directed behavior, and how it can do so in the presence of opposing behavioral states such as hunger, is not well understood. We show that a persistent state of thirst is evoked by the precise activation and inactivation of overlapping central brain neuronal circuit elements in Drosophila. In a neuronal activation screen, we identified a subset of glutamatergic neurons that evoke robust thirst-related behaviors, including water seeking and intake; we named these neurons Durstig, the German for thirsty. These central brain neurons function downstream of sensory input and internal osmotic sensors to drive seeking to either open or inaccessible water. Importantly, activation of Durstig neurons overrides food seeking in water replete but hungry flies. We also identified neuropeptide F receptor (NPFR)-expressing neurons that appear to function as a water seeking homeostat. Neurons expressing NPFR, the invertebrate homolog of the NPY receptor, also promote insatiable hunger and voracious feeding. Like Durstig neurons but independent of them, activation of NPFR neurons overrides food seeking in water replete but hungry flies. Thus, neural circuit elements that regulate hunger and thirst are tightly integrated. These studies provide an entry point for mapping the fundamental homeostatic thirst neurons and the hierarchical wiring of neural circuits that encode opposing motivational states.

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Poster

501. Water and Salt Balance and Thirst

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

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Topic: F.09. Thirst and Water Balance

Support: NRF Grant 2016R1C1B2007319
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KHIDI Grant HI15C2887
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KIST 0409-20180017

Title: A neural circuit signaling water intake and quenching thirst

Authors: *S.-Y. KIM, D.-Y. KIM, G.-R. HEO, J. SOH, M. KIM, H. KIM, S. JUNG, M. LEE, J. PARK, H.-E. PARK
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Abstract: Water intake is a basic physiological response that restores fluid homeostasis in thirsty animals. Water ingestion is detected in the oral/oropharyngeal cavity and gastrointestinal (GI) tract, and this signal is communicated to the central thirst neurons to quench thirst. This signaling is thought to involve serially connected nuclei including the parabrachial nucleus (PB). However, the key circuit elements and precise circuit organization remain unclear. Here we show that a genetically defined subpopulation of neurons in the PB signals water intake and quenches thirst. By monitoring deep-brain calcium dynamics, we show that the PB neurons are selectively activated by water intake in a time-locked manner. These responses are induced by wet solids or aqueous liquids as well, but not by dry solids or non-aqueous liquids. Interestingly, this activation is stronger when animals are water-deprived, suggesting that animal's internal state is already integrated into the water intake signal at or before the PB. Optogenetic stimulation of the PB neurons selectively suppressed water intake, whereas chemogenetic inhibition of the same population augmented water intake in water-deprived mice. Taken together, our study provides a circuit mechanism to explain how water intake signals from the periphery are transmitted to the thirst centers and quench thirst.

Disclosures: S. Kim: None. **D. Kim:** None. **G. Heo:** None. **J. Soh:** None. **M. Kim:** None. **H. Kim:** None. **S. Jung:** None. **M. Lee:** None. **J. Park:** None. **H. Park:** None.

Poster

501. Water and Salt Balance and Thirst

Location: SDCC Halls B-H

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Topic: F.09. Thirst and Water Balance

Support: Major Research Plan of the National Natural Science Foundation of China (91432306)

Title: Modulation of drinking behavior through central amygdala GABAergic neurons

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Abstract: Drinking behavior is a repetitive licking movement with a constant frequency. Recent studies indicate that central amygdala (CeA) play a role in ingestive behavior and the mechanism is still poorly understood. Here, we validated a new circuit from CeA GABAergic neurons to Midbrain nucleus. The activity of this pathway increased during drinking period recorded by fiber photometry in mice. Furthermore, photo-stimulation of this projection effectively induced a licking behavior and promoted water consumption in mice. These results demonstrate that CeA GABAergic projection to midbrain has a crucial role in modulating drinking behavior.

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Poster

501. Water and Salt Balance and Thirst

Location: SDCC Halls B-H

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Topic: F.09. Thirst and Water Balance

Support: Merit Review 5 I01 BX001000-06 award from the Department of Veterans Affairs.
Center on Genetics of Transport and Epithelial Biology at the University of Cincinnati.

Title: Carbonic anhydrase II deletion confers salt appetite in genetically engineered mice

Authors: M. VARASTEH KIA[1], S. BARONE[1], K. ZAHEDI[1], *M. SOLEIMANI[1,2]
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Abstract: Salt appetite, salt craving or salt intake in excess of physiological needs is regulated by a number of physiological mechanisms including neuronal and hormonal pathways. Excess salt intake is a major health problem and a risk factor in the pathogenesis of hypertension, which consequently can lead to heart disease and stroke. Few genetic factors are implicated in the pathogenesis of salt appetite. Here we demonstrate that mice with the genetic inactivation of carbonic anhydrase 2 (CAII) display significant salt appetite as judged by their preference for salted water (280 mM NaCl added to the drinking water) over regular tap water, when both options are provided (daily salted water intake of 2.80 ml in WT and 5.2 ml in CAII KO mice, $p<0.01$, $n=5$). Wild type littermates showed preference for regular water (daily tap water intake of 4.21 ml in WT and 2.15 ml in CAII KO mice, $p<0.03$, $n=5$). The excess salt intake is observed in the absence of any vascular volume depletion or kidney dysfunction in CAII KO mice (as judged by comparable kidney renin expression and blood creatinine and BUN concentration in WT and CAII KO mice). When only provided the salted water (280 mM salt added to the drinking water), CAII null animals showed a robust increase in daily water intake vs. WT mice (20.54 ml/day in KO mice vs. 11.83 ml/day in WT, $p<0.001$, $n=5$) as well as an increase in sodium excretion (0.192 mmol/g in CAII KO vs. 0.0716 mmol/g in WT, $p<.01$, $n=5$). The expression levels of kidney sodium and water absorbing channels ENaC and AQP-2 showed robust increases in response to enhanced salt intake in CAII KO mice vs. wild type littermates despite their lower expression levels under baseline states. The AVP expression levels in pituitary gland significantly increased in CAII KO mice vs. WT littermates when receiving salted water for 10 days ($p<0.05$), despite their comparable expression levels at baseline conditions. When given the option of tap water and salted water, male CAII KO mice exhibited remarkable propensity toward salted water intake vs. female KO mice. Systolic blood pressure after 10 days of salted water intake showed a tendency toward higher values (systolic blood pressure of 145 +/- 3.9 in CAII null mice vs. 135 +/- 3.2 in WT) as verified by a computerized tail cuff method, but did not achieve statistical significance ($p=0.07$). We propose that CAII plays an important role in regulating salt intake and its inactivation can cause salt appetite, specifically in male animals, and may provoke a salt sensitive hypertension.

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Poster

501. Water and Salt Balance and Thirst

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Program #/Poster #: 501.05/WW7

Topic: F.09. Thirst and Water Balance

Support: UKY Research Funds to JS

Title: Estradiol regulation of fluid intake following 24 hour water deprivation

Authors: *J. A. HOWELL, J. SANTOLLO
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Abstract: Thirst is an essential component of maintaining body fluid homeostasis and is necessary to restore osmolality and volume in cases of dehydration. Estradiol (E2) decreases daily fluid intake and intake in response to dehydration in females, but the mechanism(s) underlying this effect is unclear. To explore the mechanism(s) that underlie E2's inhibitory effect on fluid intake we first aimed to expand the previous finding that E2 decreases water intake stimulated by 24 h deprivation by examining drinking microstructure. Then, we aimed to determine which estrogen receptor subtype mediates the decreases in intake. Because activation of ERα decreases water intake stimulated by the hormone angiotensin II we hypothesized that activation of ERα, but not ERβ, decreases water intake stimulated by 24 h fluid deprivation. Using a repeated-measures design, ovariectomized (OVX) rats (n=9) were injected with estradiol benzoate (EB, 10 µg) or vehicle for two consecutive days. Twenty-four hours after the second injection, rats were water deprived or retained fluid access as a control. The following day, water was returned and total intake was measured for 1 h. In addition, licks during the test period were recorded using a contact lickometer. As expected, after water deprivation EB-treated rats drank significantly less than oil-treated rats ($p < 0.05$). Furthermore, there was no difference in the number of licks per burst. After water deprivation, oil-treated rats had significantly more bursts (defined as at least two licks with an interlick interval of less than 1 s) than EB-treated rats ($p < 0.05$) suggesting that estradiol reduces intake by increasing post-ingestive feedback signals. Next, to investigate the estrogen receptor subtype mediating this effect, a second group of OVX rats (n = 10) were water deprived or retained fluid access as a control. The following morning, rats were injected with 200µg PPT (ERα agonist), 250µg DPN (ERβ agonist) or vehicle and 3.5 h later water was returned from deprived animals and intake and licks were measured for 1 h. Preliminary data suggests no difference in intake after agonist treatment. This could suggest that the anti-dipsogenic effect of E2 after water deprivation is the result of synergistic activation of both ERα and ERβ receptors and ongoing research is testing this hypothesis.

Disclosures: J.A. Howell: None. **J. Santollo:** None.

Poster

501. Water and Salt Balance and Thirst

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Topic: F.09. Thirst and Water Balance

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16SDG27260001
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R01 DK100699

Title: Disinhibition of sodium appetite by Htr2c in the lateral parabrachial nucleus

Authors: *S. PARK[1], C. LIU[2,3], K. W. WILLIAMS[2], J.-W. SOHN[1]
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Abstract: The drive for sodium intake, sodium appetite, is a powerful form of motivation which is required for the maintenance of blood volume. This form of motivation is capable of making animals and humans ingest otherwise aversive concentrations of sodium. However, in the absence of fluid imbalance, this manifestation of sodium appetite is normally suppressed to prevent homeostatic deviations. Although molecular and neural mechanisms underlying the promotion of sodium appetite have received attention recently, those that act to inhibit sodium appetite have remained relatively obscure. Here we report a genetically defined population in the lateral parabrachial nucleus (LPBN), marked by the expression of Htr2c, which acts to inhibit sodium appetite. Chemogenetic inhibition of these neurons leads to increases in sodium intake whereas chemogenetic activation reduces sodium intake during times of sodium depletion. Interestingly, inhibition of these neurons is also capable of increasing food intake but only when sodium is present in the diet. Furthermore we show that Htr2c hyperpolarises these neurons through KATP channels and that removal of Htr2c from LPBN neurons decreases sodium intake in mice. Collectively these results reveal a genetically distinguishable population of neurons in the LPBN that act to suppress sodium appetite. Given the pernicious link between sodium intake and cardiovascular disease, as well as the non-compliancy of patients on low-sodium diets, our study may also provide potential drug targets aimed at inhibiting sodium appetite.

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Poster

501. Water and Salt Balance and Thirst

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Topic: F.09. Thirst and Water Balance

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Title: Neural circuits underlying sodium homeostasis

Authors: *S. LEE, V. AUGUSTINE, Y. ZHAO, H. EBISU, Y. OKA
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Abstract: Maintaining the balance of internal fluid is indispensable for survival. Fluid homeostasis mainly regulates the amount of water and sodium in extracellular fluids to achieve a proper balance. Sodium is the major cation that determines the osmolality of the extracellular fluid. As such, the ingestion of sodium is strictly regulated by both peripheral sensory signals and central appetite signals. However, the underlying neural mechanism is still poorly understood. Recent rodent studies have shown that some types of neurons in the lamina terminalis (LT) and nucleus tractus solitaries (NTS) are causally related to sodium intake. Nevertheless, these studies have highlighted the highly complicated and shared neural circuits between sodium appetite. Here we show the neural population in the hindbrain that exclusively regulates sodium appetite. We will also discuss how these neurons optimizes sodium intake based on peripheral signals.

Disclosures: S. Lee: None. **V. Augustine:** None. **Y. Zhao:** None. **H. Ebisu:** None. **Y. Oka:** None.

Poster

501. Water and Salt Balance and Thirst

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 501.08/WW10

Topic: F.09. Thirst and Water Balance

Support: NIH Grant: NIHP Thirst

Title: Functional annotation of molecular cell types in the mammalian thirst system

Authors: *A.-H. POOL[1], Y. OKA[2]
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Abstract: Thirst is an instinctive behavioral state that elicits a series of robust behavioral adjustments geared towards restoring body fluid homeostasis. Osmotic stress in mammals is detected by two circumventricular organs - OVLT and SFO - and relayed to higher order brain centers where the need signal is converted to adaptive behavioral and endocrine responses. Here we explored the cellular logic for decoding the need signal at the second order thirst nucleus MnPO. Single cell RNA-seq uncovered 8 distinct transcriptomic cell types within the nucleus. In

functional characterization of these cells we revealed that one of the four excitatory cell types is water deprivation activated and can drive the full thirst behavioral repertoire. Another excitatory cell type encodes heat stress whereas one of the 4 inhibitory neuronal classes is responsible for liquid consumption related suppression of drinking behavior. Anatomical output mapping of the thirst driving cell type revealed a candidate map of only a few hypothalamic and extrahypothalamic targets identifying sites for decoding the thirst signal into behavioral subprograms. Current analysis reveals the logic of decoding physiological cues at the second order thirst relay.

Disclosures: A. Pool: None. **Y. Oka:** None.

Poster

501. Water and Salt Balance and Thirst

Location: SDCC Halls B-H

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Program #/Poster #: 501.09/WW11

Topic: F.09. Thirst and Water Balance

Support: INCT - NanoBiofar
CNPq
FAPEMIG
CAPES
UFOP

Title: Central angiotensin II induces sucrose intake dissociated from water intake

Authors: *M. H. PAES[1], L. M. CARDOSO[2], L. B. OLIVEIRA[3]
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Abstract: Ang II acts on the regulation of different ingestive behaviors, including sucrose intake. However, the increase in sucrose intake could be a consequence of thirst induced by ANG II. Thus, this study aimed to distinguish the effect of Ang II on the thirst from its stimulatory effect on sucrose intake. Therefore, male Wistar rats weighing 300330g were anesthetized with ketamine (80 mg/kg) and xylazine (7 mg/kg) and a stainless steel cannula was implanted directed to the right lateral ventricle (LV) in the animal's brain. During recovery period (five days), water, 2% sucrose solution and food were ad libitum. To the ingestive test, food, water and sucrose were removed and the rats received LV injection of 1 μL of PBS (control) or ANG II (0.4 nmol/μL). After 15 minutes, they had free access to water and its intake was measured at 15, 30, 60, 90 and 120 minutes. At 105 minutes (after water offer) the animals received central injection (1μL on LV) of vehicle or the antagonists (losartan 50nmol/μL or PD 123319 30nmol/μL). 15 minutes later, 2% sucrose solution was also offered to the animals.

Water and sucrose intakes were measured at 135, 150, 180, 210 and 240 minutes. At the end of 4 hours, the animals received food, water and 2% sucrose solution *ad libitum*. The results are expressed as means±SEM. Two way RMANOVA and pos test Tukey's were used for statistical analyses. Differences were considered significant at p&It0.05. In the first two hours of experiment, ANG II, as expected, increased water intake, satiating thirst (PBS 0.5 ± 0.18 vs ANG II 14.5 ± 1.77 mL/120min). After the second injection, sucrose intake in the group receiving ANG II was higher than the control group and this effect was abolished when Losartan or PD 123319 were injected (PBS + PBS 0.5 ± 0.29 vs PBS + ANG II 5.5 ± 1.21 vs losartan + ANG II 0.1 ± 0.10 vs PD123319 + ANG II 0.3 ± 0.28 mL/120min). In the last two hours of the experiment, no differences were observed for water intake among treatments. These results suggest that central ANG II induces sucrose intake independent of its effect on thirst.

Disclosures: M.H. Paes: None. **L.M. Cardoso:** None. **L.B. Oliveira:** None.

Poster

501. Water and Salt Balance and Thirst

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Topic: F.09. Thirst and Water Balance

Support: NIH Grant R00HL125805
NIH Grant R01HL139868
NIH Grant R01HL136595
AHA Grant 17GRNT33660969

Title: Neurons within the subfornical organ that express angiotensin type 1a receptors stimulate fluid consumption and hypothalamic-pituitary-adrenal axis activation

Authors: *A. R. ALLEYNE[1], K. CAHILL[2], Y. TAN[3], A. D. DE KLOET[5], E. G. KRAUSE[4]
[2]Pharmacodynamics, [3]Dept. of Pharmacodynamics, [4]Dept Pharmacodynamics, [1]Univ. of Florida, Gainesville, FL; [5]Physiol. and Functional Genomics, Univ. of Florida, Col. of Med., Gainesville, FL

Abstract: Circulating angiotensin II elicits behavioral and physiological responses to decreased blood pressure or hypovolemia by activating angiotensin type-1a receptors (AT1aR) in circumventricular organs that lack a blood brain barrier. In particular, the subfornical organ (SFO) contains neurons that express AT1aR and are implicated in the maintenance of body fluid homeostasis. This study used mice with Cre recombinase expression directed to the AT1aR gene to functionally phenotype neurons in the SFO that express AT1aR. Initial studies combined genetic reporting with RNAscope *in situ* hybridization to reveal that the majority of AT1aR neurons in the SFO are glutamatergic. Next, Cre-inducible adenoassociated virus that expresses

channelrhodopsin-2 (ChR2) or enhanced yellow fluorescent protein (eYFP) was delivered into the SFO of AT1aR-Cre mice, and subsequently, a chronic dwelling fiber optic was implanted. Relative to controls expressing eYFP, *in vivo* optogenetic stimulation of AT1aR neurons in the SFO significantly increased water and 0.3M NaCl consumption. Interestingly, optical excitation of the same population of neurons also significantly elevated plasma levels of corticosterone. Taken together, these results suggest that neurons in the SFO that synthesize AT1aR drive water and sodium intake as well as activation of the hypothalamic-pituitary-adrenal axis.

Disclosures: A.R. Alleyne: None. **K. Cahill:** None. **Y. Tan:** None. **A.D. de Kloet:** None. **E.G. Krause:** None.

Poster

501. Water and Salt Balance and Thirst

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 501.11/WW13

Topic: F.09. Thirst and Water Balance

Title: Renal expression of aquaporin 2 in the offspring of rats that consumed sugared water during pregnancy and lactation

Authors: *V. VELAZQUEZ[1], L. NICOLÁS[2], E. CUEVAS[2], A. ORTEGA[3], F. CASTELÁN[4], J. RODRÍGUEZ ANTOLÍN[2]
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Abstract: The urinary tract achieves the elimination of toxic substances from the organism, particularly in the kidneys. Among the several types of aquaporins (AQPs) expressed in different parts of the organism, seven (AQP1,-2,-3,-4,-6,-7, and -8) are differentially expressed in the kidney. These are highly relevant for the water transport across the renal tubules. Particularly, AQP2 is located on the collecting duct where the urine will be diluted or concentrated because of actions triggered by the anti-diuretic hormone (ADH) including the trafficking of AQP2 containing vesicles to the apical membrane. The high consumption of sugared beverages is related to metabolic diseases, including type 2 diabetes mellitus frequently linked to renal failure. The aim of this project was to determine the effect of sugared water consumption during pregnancy and lactation on the renal AQP2 in the adult male offspring. We use Wistar female rats that were mated and divided in a control group fed with standard diet and tap water, and the experimental group fed with standard diet and 5% sucrose diluted in tap water (sugared water). At weaning, two male rats were randomly selected per litter; one of them had free access to simple water while the other had free access to the sugared water. After four months, male rats were sacrificed and the AQP2 expression was analyzed by immunohistochemistry and Western

blot. In contrast to the group that consumed tap water, the group that consumed sugared water during pregnancy, lactation and postnatal life showed an overexpression of AQP2. It seems that the consumption of sugared water, even in low concentration, is able to modify the renal AQP2 expression. These findings could be directly related to water transport in the renal tubules altering the function of the upper urinary tract.

Disclosures: V. Velazquez: None. **L. Nicolás:** None. **E. Cuevas:** None. **A. Ortega:** None. **F. Castelán:** None. **J. Rodríguez Antolín:** None.

Poster

501. Water and Salt Balance and Thirst

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Program #/Poster #: 501.12/WW14

Topic: F.09. Thirst and Water Balance

Support: FAPESP (2015/234677)
CNPq (425586 / 2016-2)
CNPq (308099/2017-6)

Title: Pressor and dipsogenic responses induced by central angiotensin II in rats treated with high fat diet

Authors: J. M. SÁ, R. M. BARBOSA, L. A. DE LUCA, Jr., J. V. MENANI, E. COLOMBARI, *D. S. COLOMBARI
UNESP Sch. of Dent., Araraquara, Brazil

Abstract: The activity of the renin-angiotensin system may increase in obesity. We have previously demonstrated that the central blockade of angiotensin type 1 receptor of high fat diet (HFD)-fed rats abolished the increase in arterial pressure observed in these animals. In the present study, we tested the pressor and dipsogenic responses to central angiotensin II (ANG II) in rats fed with HFD. In addition, the effect of HFD on *ad libitum* water intake was also evaluated. Male Holtzman rats (290-320 g) treated with standard diet (SD, 5% calories from fat; n = 5-10/group) or HFD (45% calories from fat; n = 8-15/group) for 6-7 weeks were used. At the end of the 6^{th} week, a group of rats received a stainless steel cannula in the lateral ventricle (LV). A week later, ANG II (25 ng/1 µl) was injected in the LV and water intake was measured for 1 h and expressed in ml/100 g of body weight (b.wt.). Two days later, a catheter was implanted in the femoral artery and in the following day, mean arterial pressure (MAP) was recorded in conscious, freely moving rats, before (baseline period for 20 min) and after injections of saline (1 µl) and ANG II (25 ng/1 µl) into the LV. In another group of rats treated with SD or HFD for 6 weeks, daily water intake was measured and averaged for the week. The peak of the pressor response induced by ANG II injected into the LV was comparable in HFD and SD rats (20 ± 4,

vs SD: 21 ± 3 mmHg), however 20 min after the injection of ANG II into the LV, MAP was still increased in HFD compared to the SD group (19 ± 3, vs SD: 9 ± 3 mmHg, $p < 0.05$). Rats that ingested HFD had a lower daily water intake for the 6 week-period analyzed (5.1 ± 0.3, vs. SD: 8.3 ± 0.7 ml/100 g of body weight at the 6^{th} week, $p < 0.05$), whereas ANG II injected into the LV induced similar intake of water in HFD and SD (3.6 ± 0.4, vs. SD: 3.1 ± 0.4 ml/100 g b.wt.). These results suggest that rats treated with HFD have a sensitization for the pressor response to central ANG II, without changing central ANG II-induced water intake.

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Poster

501. Water and Salt Balance and Thirst

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 501.13/XX1

Topic: F.09. Thirst and Water Balance

Support: FAPESP
CNPq

Title: Involvement of the medial septal area in the control of sodium intake

Authors: S. P. BARBOSA, L. A. DE LUCA, Jr, P. M. DE PAULA, D. S. A. COLOMBARI, E. COLOMBARI, C. A. F. ANDRADE, D. B. ZOCCAL, *J. MENANI
UNESP, Araraquara, Brazil

Abstract: Angiotensin II (ANG II) and aldosterone are typical facilitatory mechanisms involved in the control of water and/or sodium intake. The deactivation of the inhibitory mechanisms with moxonidine (α_2 adrenergic/imidazoline agonist) into the lateral parabrachial nucleus (LPBN) not only strongly increases 1.8% NaCl intake in sodium depleted rats, but also surprisingly drives hyperosmotic rats to ingest 1.8% NaCl. In the present study, water and 1.8% NaCl intake was investigated in rats treated with intragastric load of 2 M NaCl that received losartan (AT1 antagonist) into the medial septal area (MSA) combined with injections of moxonidine into the LPBN. In addition, it was also investigated water and 1.8% NaCl intake in satiated and normovolemic rats treated with injection of ANG II into the MSA combined with moxonidine into the LPBN. Male Holtzman rats (290-310 g, n= 7-8) with guide-cannulas implanted toward the MSA and the LPBN were used. Rats treated with intragastric 2 M NaCl (2 ml/rat) combined with moxonidine (0.5 nmol/0.2 µl) into the LPBN and saline into the MSA ingested water (11.1 ± 1.8, vs. vehicle: 2.6 ± 1.0 ml/2 h) and 1.8% NaCl (27.0 ± 8.1, vs. vehicle: 0.6 ± 0.3 ml/2 h). The injection of losartan (20 µg/0.5 µl) into the MSA reduced water (6.4 ± 3.2 ml/2 h) and 1.8% NaCl intake (5.3 ± 3.3 ml/2 h) in hyperosmotic rats treated with moxonidine into the LPBN. The

injection of ANGII (10 ng/0.5 µl) into the MSA combined with moxonidine into the LPBN also induced 1.8% NaCl intake (15.7 ± 5.8 ml/2 h) compared to saline + vehicle (0.6 ± 0.4 ml/2 h) or ANG II into the MSA + vehicle (0.6 ± 0.2 ml/2 h). The ingestion of water also increased in rats were treated with ANG II into the MSA + moxonidine into the LPBN (5.1 ± 2.2 ml/2 h) compared to ANG II into the MSA + vehicle (1.5 ± 1.1 ml/2 h) or saline + vehicle (1.0 ± 0.5 ml/2 h). The results suggest that the LPBN strongly inhibits the facilitatory mechanisms for sodium intake activated by ANG II acting in the MSA. In addition, the results suggest that the activation of AT1 receptors in the MSA is an important step to drive hyperosmotic rats to ingest sodium when the inhibitory mechanisms are deactivated with moxonidine into the LPBN.

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Poster

501. Water and Salt Balance and Thirst

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Program #/Poster #: 501.14/XX2

Topic: F.09. Thirst and Water Balance

Support: FAPESP - 2015/20500-3
CNPq

Title: Central MAPK-Erk1/2 inhibition reduces sodium appetite in spontaneously hypertensive rats

Authors: G. M. F. ANDRADE-FRANZÉ, E. D. PEREIRA, Jr., L. A. DE LUCA, Jr., J. V. MENANI, *C. A. ANDRADE
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Abstract: Excessive salt intake has been associated with the development or worsening of chronic diseases such as hypertension. Spontaneously hypertensive rats (SHR) have a typical increased sodium preference when compared to normotensive strains. In normotensive rats, angiotensin II (ANG II)-induced water intake can be selectively blocked by protein kinase C inhibitors, while ANG II-induced sodium intake is dependent on MAPK-Erk1/2 activation (Exp Physiol 94:130, 2009). However, the effects of MAPK-Erk1/2 inhibition on sodium and water intake in SHR are not clear. Therefore, in the present study, we investigated if selective inhibition MAPK-Erk1/2 pathway would change sodium appetite and water intake in SHR. Spontaneously hypertensive rats (280 - 330 g, 24 weeks old, n = 09) and normotensive Holtzman rats (HTZ, 280 - 330 g, 16 weeks old, n = 07) with stainless steel guide cannulas implanted in the lateral ventricle (LV) were used. Rats with 24 h of water deprivation (WD) had access to only

water during 2 h for partial rehydration (PR) (WD-PR protocol) before receiving LV injections of U0126 (p44/42 MAPK inhibitor, 2 mM; 2 μl) or vehicle (0.9% NaCl:DMSO 20%). Then, the animals had 2 h access to 0.3 M NaCl and water (sodium appetite test). SHR treated with intracerebroventricular (icv) injections of vehicle ingested more 0.3 M NaCl than vehicle-treated HTZ rats (10.4 ± 1.4, vs. 5.3 ± 1.8 ml/120 min, respectively). The icv injections of U0126 in HTZ produced no change in 0.3 M NaCl intake (3.5 ± 1.8, vs. vehicle: 5.3 ± 1.8 ml/120 min) or water intake (1.8 ± 0.7, vs. vehicle: 3.8 ± 2.0 ml/120 min). However, icv injections of U0126 in SHR reduced 0.3 M NaCl intake induced by WD-PR (4.6 ± 1.3, vs. vehicle: 10.3 ± 1.4 ml/120 min) and water intake (2.1 ± 0.9, vs. vehicle: 6.4 ± 1.1 ml/120 min). In addition, the icv injection of U0126 produced no change in basal mean arterial pressure and heart rate, however, reduced the pressor response induced by icv ANG II (25 ρmol/1 μl) in both SHR and HTZ rats. The present results suggest that the inhibition of central MAPK-Erk1/2 ANG II receptor signaling pathway decreases sodium appetite in SHR and the pressor response to icv ANG II in HTZ and SHR rats. **Financial Support:** FAPESP and CNPq.

Disclosures: G.M.F. Andrade-Franzé: None. **E.D. Pereira:** None. **L.A. De Luca:** None. **J.V. Menani:** None. **C.A. Andrade:** None.

Poster

501. Water and Salt Balance and Thirst

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Program #/Poster #: 501.15/XX3

Topic: F.03. Neuroendocrine Processes

Support: NRF 2016R1D1A1B03932771
NRF 2014R1A2A1A11049900
NRF 2017R1A2B2002277

Title: Perinatal exposure of the rat to high levels of NaCl via mother induces salt sensitivity in later life that depends on enhanced vasopressin secretion

Authors: W. JUNG, Y.-B. KIM, S. LEE, X. JIN, H. KANG, *Y. I. KIM
Dept. of Physiology, Korea Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Salt sensitivity (SS) is a trait of clinical importance because it carries strong prognostic implication for various cardiovascular disorders including hypertension. Whether perinatal exposure to high levels of NaCl via mother induces SS in adulthood has been a subject of several studies, with little evidence for this hypothesis. This study sought to determine whether, in rats, excessive maternal salt intake during gestation and lactation would induce SS in the offspring in later life, and if so, the mechanisms underlying its expression. The 7~8weeks-old male-offspring of dams (Sprague-Dawley rats) provided with 1.5% saline as drinking water

during these reproductive periods (experimental group) had higher systolic blood pressures (SBP) after high-salt challenge, which was given by providing 2% saline as drinking water for 3 days or 8% NaCl-containing chow as the diet for 4 weeks, than the age- and sex-matched rats, the mothers of which were supplied with tap water, instead of 1.5% saline, as drinking water (control group). Furthermore, after the high-salt challenge, experimental rats had greater increases in plasma arginine-vasopression (AVP) level and greater depressor responses to intravenously injected V1a receptor antagonist. In experimental and control rats prazosin lowered SBP to a similar extent both before and after the high-salt challenge. Meanwhile, Na^+-rich ACSF ([Na^+]: 300 mmole/L or 450 mmole/L) injection into the lateral ventricle increased the SBP and heart rate to similar degrees in control and experimental rats. Lastly, after the high-salt challenge, GABA functioned as an excitatory, instead of inhibitory, neurotransmitter in most AVP neurons of experimental rats. These results indicate that perinatal exposure to high levels of NaCl via mother induces SS in adulthood, the expression of which may not depend on enhanced sympathetic outflow, but on increased AVP secretion, which in turn is aided by the inhibitory-to-excitatory transition of GABAergic transmission in AVP neurons. We speculate that, by examining the AVP system, one may be able to detect SS and decipher its nature.

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Poster

501. Water and Salt Balance and Thirst

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Program #/Poster #: 501.16/XX4

Topic: F.10. Food Intake and Energy Balance

Support: K08 NS099425 (JCG)
Aging, Mind, and Brain Institute, University of Iowa (JCG)
F32 DK103387 (JMR)

Title: Aldosterone-sensitive HSD2 neurons in the nucleus of the solitary tract: Gene expression and axonal projections in mice

Authors: *S. GASPARINI[1], J. M. RESCH[2], S. V. NARAYAN[1], L. PELTEKIAN[1], G. N. IVERSON[1], J. C. GEERLING[1]
[1]Neurol., Univ. of Iowa, Iowa City, IA; [2]Dept. of Med., Beth Israel Deaconess Med. Ctr., Boston, MA

Abstract: Hyperaldosteronism is linked to increased rates of mood disorders including anxiety and depression and to other broadly dysphoric symptoms, but the neural circuit basis for aldosterone affecting mood remains obscure. Aldosterone boosts the activity of neurons in the

brainstem that contain the enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (HSD2), a hallmark of aldosterone-sensitive cells. To better understand these aldosterone-sensitive neurons and their output projections, we performed immunolabeling, fate-mapping, and Cre-dependent axon tracing in mice. Fate-mapping identified cells throughout the brain with a developmental history of *Hsd11b2* expression, yet in adults expression is limited to neurons in a region of the nucleus of the solitary tract with a leaky blood-brain barrier. Their axons project first to the parabrachial nucleus (PB) and pre-locus coeruleus (pLC), intermingling with AgRP-immunoreactive axons and forming dense terminal fields among FoxP2-immunoreactive neurons. Their axons also extend into the forebrain, intermingling with AgRP- and CGRP-immunoreactive axons and forming a compact terminal field amid GABAergic neurons in the ventrolateral bed nucleus of the stria terminalis (BSTvL). En route to BSTvL, they form sparse branches and boutons in the parasubthalamic nucleus, suprafornical lateral hypothalamic area, central nucleus of the amygdala, and paraventricular hypothalamic nucleus. Dual retrograde tracing revealed that projections to PB or BSTvL originate from largely separate HSD2 neurons. In addition to promoting sodium appetite in BSTvL, we predict from their pattern of output connections that HSD2 neurons promote dysphoric symptoms linked to sodium deficiency and hyperaldosteronism.

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Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 502.01/XX5

Topic: G.01. Appetitive and Aversive Learning

Support: CONACyT (CB176639 and PN2463)
DGAPA-UNAM (IA200313, IA200715 and IN205417)
CONACyT (736773) to EI-H

Title: Prelimbic prefrontal cortex is necessary to face threats during a motivational conflict guided by learned, but not innate, stimuli

Authors: E. ILLESCAS-HUERTA, *L. RAMÌREZ-LUGO, R. ORDOÑEZ-SIERRA, F. SOTRES-BAYÓN
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Abstract: When animals forage for food they are often challenged with a conflict based on opposing signals such as facing threat to obtain food. In such motivational conflict, selecting the appropriate behavioral response to execute is critical for survival. The prelimbic prefrontal

cortex (PL) is implicated in signaling fear-related responses and reward-seeking. It is not clear, however, if PL is necessary when opposing signals compete during motivational conflict. To address this issue, we performed pharmacological inactivations of PL in rats that learned to face a threat (crossing an electrified grid floor signaled by white noise) to obtain a reward (press a bar to receive food signaled by light). We found that PL inactivation decreased the latency of rats to cross the signaled threat to obtain food, suggesting PL is necessary to promote fear-related responses when competing with reward-seeking responses. Interestingly, we found that PL inactivation did not affect the latency to obtain food in the absence of threat (no-conflict trials) and did not affect the retrieval of a threat memory in the absence of reward-seeking responses during fear conditioning. Together, these results suggest that PL is crucial to signal fear-related responses when competing with reward-seeking behavior and not when each response is signaled separately. But not all motivational conflicts are guided by learned stimuli. To test if PL is necessary in motivational conflict responses guided by innate motivations, we inactivated PL in rats where both motivations were innate (simultaneous presence of food and intense light in the center of an open field) or where one motivation was learned (step-down to a grid associated with an electric shock) but the other was innate (sweet water). We found that PL inactivation does not affect motivational conflict responses when competing motivations are both innate. Yet, if one of the two competing motivations is learned, PL inactivation decreased latency to cross during conflict trials. Thus, our results suggest that PL is necessary to execute the appropriate behavioral response (face threat to obtain reward) when animals are challenged with a motivational conflict guided by at least one previous experience but not for those guided by innate motivations.

Disclosures: E. Illescas-Huerta: None. **L. Ramìrez-Lugo:** None. **R. Ordoñez-Sierra:** None. **F. Sotres-Bayón:** None.

Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

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Program #/Poster #: 502.02/XX6

Topic: G.01. Appetitive and Aversive Learning

Support: CONACyT CB176639
CONACyT PN2463
DGAPA-UNAM IA200313
DGAPA-UNAM IA200313
DGAPA-UNAM IA200313
CONACyT 614528

Title: Opposing roles of the anterior and posterior ventral striatum in choice behavior guided by taste aversion memory

Authors: A. P. PEÑAS-RINCÓN, L. RAMÍREZ-LUGO, *F. SOTRES-BAYON
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Abstract: Although much is known about brain mechanisms underlying associations with dangerous taste stimuli, very little is known about how these stored emotional associations guide choice behavior. The ventral striatum (VS) is implicated in taste aversion processing and in mediating choice between goal-directed actions. It is not clear, however, if VS, along its anterior-posterior axis, is necessary for choice behavior guided by taste preferences. To address this, we used GABA agonists (muscimol and baclofen) to perform pharmacological inactivations of anterior (aVS) and posterior (pVS) VS before retrieval of an aversive memory in choice or no-choice-based conditioned taste aversion (CTA) tasks in rats. In CTA, rats acquire aversion to a novel taste (saccharin) when followed by digestive malaise induced with lithium chloride. During standard CTA task, rats avoid a single bottle containing saccharin solution without choice (no-choice CTA). To evaluate choice behavior, we developed a choice CTA task that involves actively choosing between bottles with aversive saccharin or safe water (choice CTA). We found that aVS inactivation blocked retrieval of choice CTA, but had no effect on no-choice CTA. This suggests that aVS plays a key role in guiding choice by facilitating the use of CTA memory without being necessary for its retrieval. Notably, aVS inactivation did not affect choice behavior when guided by innate taste stimuli, highlighting its role in choice guided by learned but not unlearned stimuli. In contrast to aVS inactivation, we found that pVS inactivation facilitated retrieval of choice CTA memory without affecting retrieval of no-choice CTA memory nor choice behavior guided by innate taste. These results suggest that pVS plays an opposing role to aVS, as it is necessary to suppress the retrieval of taste aversion memory when facing a choice. Yet, like aVS, pVS is not necessary to process choice guided by innate taste stimuli. Together, these findings provide novel evidence for the role of VS in choice behavior guided by taste aversion memory by revealing opposing roles of this brain structure along its anterior-posterior axis.

Disclosures: A.P. Peñas-Rincón: None. **L. Ramírez-Lugo:** None. **F. Sotres-Bayon:** None.

Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 502.03/XX7

Topic: G.01. Appetitive and Aversive Learning

Support: CONACyT Grant CB176639 and PN2463
DGAPA-UNAM Grant IA200313, IA200715 and IN205417

CONACyT Grant 705417

Title: Basolateral amygdala, but not the orbitofrontal cortex, is necessary for motivational conflict responses guided by previous experiences

Authors: *A. HERNANDEZ-JARAMILLO, F. SOTRES-BAYON
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Abstract: Animals foraging for food are often challenged with a conflict between opposing motivations driven by previous experiences, such as facing a cue that predicts threat to approach another cue that predicts food. Selecting the appropriate behavioral response to execute in such motivational conflict guided by biologically significant memories is critical for survival. The basolateral amygdala (BLA) has been implicated in the regulation of defensive responses to threats (fear) as well as reward-seeking signaling. The orbitofrontal cortex (OFC) has been involved in action selection based on the relative value of cues learned by positive and negative experiences. It is not clear, however, whether these structures are necessary when opposing cues compete during a motivational conflict. To address this issue, we performed pharmacological inactivations of BLA or OFC in rats trained to face a threat (crossing an electrified grid floor signaled by withe noise) to obtain a reward (press a bar to receive food signaled by light). We found that BLA inactivation (with a high but not low dose of GABA agonists muscimol and baclofen) decreased the time it takes (latency) for rats to cross the predicted threat to obtain food. This result suggests that BLA is necessary to promote fear-related responses when competing with reward-seeking behaviors. Consistent with previous studies, we found that BLA inactivation impaired the retrieval of a threat memory in the absence of available reward in fear conditioning, but did not affect the latency to obtain food in the absence of threat during no-conflict trials. These results support the predominant notion that BLA is key to execute behavioral responses triggered by cues associated with threats, but not by cues associated with rewards. Surprisingly, we found that OFC inactivation did not affect any of the motivational conflict responses including fear-related responses and reward-seeking behaviors. Together, our findings suggest that BLA, but not OFC, is necessary to promote fear-related behaviors when an animal is challenged to face potential threats to approach a reward guided by previous experiences.

Disclosures: A. Hernandez-Jaramillo: None. **F. Sotres-Bayon:** None.

Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 502.04/XX8

Topic: G.01. Appetitive and Aversive Learning

Support: CONACyT (CB176639 and PN2463)
DGAPA-UNAM (IA200313, IA200715 and IN205417)
CONACyT (658352) to V-H G,

Title: Habenula is necessary to promote expression of fear memory when it competes against a safety memory

Authors: *G. VELAZQUEZ-HERNANDEZ, F. SOTRES-BAYON
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Abstract: Although the habenula has been implicated in the regulation of emotional behaviors, it is not clear *when* it is necessary to regulate defensive responses to a threat (fear). During auditory fear conditioning, animals learn the tone-shock association, which leads to the formation of a fear memory. During extinction training, animals learn that the tone no longer predicts shock, which forms a "safety memory". Thereby, it has been suggested that after extinction training, fear memory and safety memory coexist in the brain and compete for control of behavior. To evaluate the contribution of the habenula in the different phases of learned fear regulation, we performed pharmacological inactivations of the habenula at specific time points. On day 1, rats associated the presence of tones with foot shock delivery (fear learning). On day 2, rats learned to extinguish fear responses by presenting tones in the absence of foot shocks (safety learning). On day 3, rats were presented with tones alone to test for fear against safety memory retrieval. We found that habenula inactivation before fear acquisition or before extinction acquisition had no effect, indicating that this structure is not necessary for: fear learning, fear memory expression nor extinction learning. Surprisingly, however, we found that habenula inactivation before the memory retrieval test decreased fear responses, suggesting its role in regulating competing fear and safety memories. To further test the idea that habenula is necessary when fear and safety memories compete, we switched the order of fear and safety learning by using a latent inhibition protocol. Thus, on day 1, rats acquired safety learning (tones, no shocks). On day 2, rats acquired fear learning (tones paired with foot shocks). On day 3, rats were presented with tones alone to test for safety memory vs fear memory retrieval. Indeed, we found again that habenula inactivation before retrieval test of safety memory against fear memory decreased fear responses. Together our findings suggest that the habenula is necessary to promote the expression of fear memory when it competes against a safety memory.

Disclosures: G. Velazquez-Hernandez: None. **F. Sotres-Bayon:** None.

Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 502.05/XX9

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant R37-MH058883
NIH Grant P50-MH086400
NSF Grant #3003851464
MARC# 5T34GM007821-38

Title: Approach/avoidance conflict training reveals distinct behavioral phenotypes for conflict resolution

Authors: *H. BRAVO-RIVERA, P. A. RUBIO-ARZOLA, A. J. CABAN-MURILLO, G. J. QUIRK
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Abstract: We recently introduced an approach/avoidance conflict task in which rats must choose between stepping onto a nearby platform to avoid a 2s shock predicted by a 30s tone, or pressing a lever for sucrose pellets (Bravo-Rivera et. al., GRC amygdala, 2017). Unlike our previous avoidance task where rats could obtain food between the shock-associated tones, here food was only available during a 30s light, which was co-presented with the tone. When presented with this light-tone conflict, 26% (19/70) of male rats spent all the tone on the platform and did not press for food (avoidance-preferring subgroup), 30% (21/70) engaged in excessive food-seeking showing little to no avoidance (food-preferring subgroup), and 44% (30/70) were able to accommodate both food seeking and avoidance by shifting their avoidance later in the tone (timer subgroup). Female rats showed similar percentages. We used the neural activity marker c-fos to assess activity profiles for each subgroup. The food-preferring subgroup showed decreased prefrontal c-fos density compared to the other two groups. This agrees with previous work showing a correlation between low prefrontal activity and increased reward sensitivity, impulsivity, and low anxiety levels (Rivalan et. al., 2010). Decreased PFC activity has also been correlated with decreased social interactions in rats (Hamilton et.al., 2010). Consistent with this, rats in the food-preferring subgroup showed decreased anxiety in the EPM ($F_{2,41}=7.65$, $p=0.002$) and impaired social interactions ($F_{2,40}=5.50$, $p=0.007$) relative to the other subgroups. Interestingly, the timer subgroup showed the highest PFC/Amygdala ratio of cFos density, consistent with prefrontal control of both foraging and avoidance. Next, we examined the factor of age. Developmental studies show that prefrontal pruning and myelination continues through P240 (Sturrock, R.R., 1980). Consistent with this, the food-preferring phenotype was less prevalent in older rats (5%, P180-P200, n=59) compared to younger rats (30%, P125-P140, n=70) (Chi sq= 15.77, $P<0.001$). This is consistent with a shift in older rats from ventrostriatal- to prefrontal-based decision making (Worthy et. al., 2012, Kolb et. al., 2012). Taken together, the approach of focusing on naturally occurring differences in approach/avoidance conflict, along with age and social factors, may provide insight into the circuitry of conflict resolution and its potential dysfunction in anxiety and addiction.

Disclosures: H. Bravo-Rivera: None. **P.A. Rubio-Arzola:** None. **A.J. Caban-Murillo:** None. **G.J. Quirk:** None.

Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

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Program #/Poster #: 502.06/XX10

Topic: G.01. Appetitive and Aversive Learning

Support: NIH grant P50-MH086400
NIH grant R37-MH058883
NSF grant 3003851464

Title: The role of orbital/insular outputs in a rodent model of persistent avoidance

Authors: *F. J. MARTINEZ, J. E. PÉREZ-TORRES, C. I. HUERTAS-PÉREZ, M. J. SÁNCHEZ-NAVARRO, C. D. VELÁZQUEZ-DÍAZ, G. J. QUIRK
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Abstract: Avoidance compulsions are commonly treated with exposure-with-response-prevention (ERP) therapy, in which patients are prevented from carrying out avoidant actions in response to triggers. To model excessive avoidance and ERP in rodents, we used a platform-mediated avoidance task in which rats learn to avoid a tone-signaled shock by stepping onto a nearby platform. This is followed by extinction with response prevention (Ext-RP) training, where the tone-shock association is extinguished over four days while access to the platform is blocked with a barrier (Rodriguez-Romaguera, et al., 2016). The barrier is then removed to test the transfer of extinction learning to avoidance behavior. We previously reported that pharmacological inactivation of the lateral orbitofrontal/agranular insular area (LO/AI) during the post Ext-RP test induced persistent avoidance in rats that would have otherwise not avoided (Rodriguez-Romaguera, et al., 2016). This suggests that projections of LO/AI are needed for the transfer of extinction to avoidance, but the targets of these projections are not known. To address this, we photo-inhibited LO/AI terminals in prelimbic cortex (PL), ventral striatum (VS), or basolateral amygdala (BLA) with halorhodopsin. Photo-inhibiting LO/AI-PL projections had no effect on the expression of avoidance, but induced persistent avoidance during the post-Ext-RP test ($F_{(1,14)} = 6.02$, $p= 0.03$), an effect that was maintained seven days later ($F_{(1,4)} = 13.20$, $p= 0.02$). There was no immediate effect of photo-inhibiting LO/AI projections to VS or BLA on avoidance, however seven days later, the LO/AI-BLA rats showed persistent avoidance without any additional laser exposure ($F_{(1,24)} = 6.85$, $p= 0.01$). Together, our findings suggest that activity in the projection from LO/AI to PL facilitates the execution of the appropriate avoidance decision at test, and induces plasticity in PL and BLA to maintain low levels of avoidance. Given that excessive harm-avoidant compulsions in OCD are associated with poor decision-making (Pushkarskaya et al., 2015), hypoactivity in the human homologue to rat LO/AI (vlPFC?) may promote these maladaptive behaviors.

Disclosures: F.J. Martinez: None. **J.E. Pérez-Torres:** None. **C.I. Huertas-Pérez:** None. **M.J. Sánchez-Navarro:** None. **C.D. Velázquez-Díaz:** None. **G.J. Quirk:** None.

Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 502.07/XX11

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NIH Grant R25-NS080687
NIH Grant R25-GM061151
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Title: Interrogating the projections of rostral prelimbic cortex that drive active avoidance

Authors: *M. M. DIEHL[1], J. IRAVEDRA-GARCIA[1], F. N. GONZALEZ-DIAZ[1], G. J. QUIRK[2]
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Abstract: Active avoidance has recently garnered much interest; however, little is known about the neural circuits that drive avoidance. Using an avoidance task in which a rat can avoid a tone-signaled footshock by stepping onto a nearby platform (Bravo-Rivera, et al., 2014), we observed that pharmacological inactivation of the prelimbic prefrontal cortex (PL) delayed avoidance (Diehl et al., eLife, in press). Additionally, excitatory responses in rostral PL neurons (rPL) were correlated with platform entry. PL projections that drive avoidance remain largely unknown. Here, we assessed the role of rPL projections to ventral striatum (VS) or basolateral amygdala (BLA), two known targets of rPL (Sesack et al., 1989; Vertes, 2004), by either photoactivating with Channelrhodopsin (ChR2; 15-20Hz, 30 sec,) or photosilencing PL terminals with Halorhodopsin (Halo; 30 sec). Photoactivation of rPL-VS projections impaired the expression of avoidance (ChR2: 42.7% time on platform (n=11), eYFP-control: 77.6% (n=9), p=0.033). Photosilencing PL-BLA projections showed a trend toward impaired avoidance expression (Halo: 16% time on platform (n=5), eYFP-control: 26% (n=5), p=0.074). Moreover, photoactivation of rPL-BLA projections reinstated avoidance following extinction (ChR2: 25% time on platform (n=3), eYFP-control: 3% (n=3), p=0.005). These findings suggest that rPL projections to VS and BLA have opposing effects on avoidance and are consistent with recent cFos findings that avoidance retrieval activates PL-BLA projections but not PL-VS projections (Martinez-Rivera et al., Psychopharm., submitted). Additional experiments will determine

whether photoactivating PL-BLA or silencing PL-VS projections impair or promote platform-mediated avoidance, respectively. Together, these findings suggest that distinct rPL projections exert bidirectional control over avoidance behavior.

Disclosures: M.M. Diehl: None. **J. Iravedra-Garcia:** None. **F.N. Gonzalez-Diaz:** None. **G.J. Quirk:** None.

Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 502.08/XX12

Topic: G.01. Appetitive and Aversive Learning

Support: MH099073

Title: Neural correlates of risky decision-making in rats encountering a 'predatory' threat

Authors: *E. KIM[1], H. DING[2], M.-S. KONG[1], J. J. KIM[1,3]
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Abstract: Fear alters foraging behavior in animals to decrease exposure to threats and thus increase their survival while searching for resources in their environment. Previously, we have investigated rats' foraging behavior in an ecologically-relevant setting and found that rats can discern conditional predatory (Robogator) threats and adjust their foraging strategy (Kim et al., 2016), which was abolished by amygdala lesions. Here, we investigated the neural basis for animals to discriminate the conditional threat and to switch their foraging preference by simultaneously recording single-units in the basolateral amygdala (BLA) and the prelimbic area of the medial prefrontal cortex (PL), two structures implicated in fear and decision-making processes (Mobbs and Kim, 2015). To do so, male Long-Evans rats, implanted with tetrode arrays in the BLA and PL ipsilaterally, underwent successive stages of nest habituation, foraging preference baseline, and robot testing. Tetrodes were gradually advanced towards their target structures, and neural activity was recorded as the rats exited their nest in search of food pellets placed in a large open field. During the preference baseline trials, rats were allowed to forage for chocolate and normal pellets placed equidistance from the nest but on opposite sides of the foraging arena. In general, rats exhibited preferences of choosing chocolate pellets over normal pellets. When the Robogator was placed on the opposite end of the foraging area and programmed to surge each time the animal approached chocolate (but not normal) pellet, consistent with our previous findings, all animals shifted their foraging behaviors toward normal pellets. By performing a cross-correlation analysis, we found that a subset of simultaneously recorded BLA and PL cell pairs showed increased spike synchrony prior to foraging preference shift during the robot session, where comparable proportions of the significant cell pairs

indicated BLA-leading and PL-leading cross-correlations. Moreover, a greater number of BLA cells that displayed correlated firing with PL cells responded to the robot surge while a greater number of PL cells that displayed correlated firing with BLA cells responded to the food pellets. These results suggest that BLA neurons encoding imminent threats actively interact with PL units signaling food pellets to alter foraging behavior in the face of conditional threat.

Disclosures: E. Kim: None. **H. Ding:** None. **M. Kong:** None. **J.J. Kim:** None.

Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 502.09/XX13

Topic: G.01. Appetitive and Aversive Learning

Support: R01 MH099073

Title: The amygdala influences spatial information processing in the hippocampus in risky foraging situations

Authors: *M.-S. KONG[1], H. DING[2], E. KIM[1], J. J. KIM[1,3]
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Abstract: In nature, animals seeking resources are vulnerable to predation and thus must be able to discern safe-versus-dangerous boundaries of their habitat, but how the brain integrates threat and spatial information is poorly understood. Our previous work revealed that a surging 'predator' robot induced transient remapping of hippocampal place fields near the source of threat (i.e., distal to the nest), whereas those fields adjacent to or inside of the safe area (i.e., nest) were relatively stable; amygdalar lesions prevented both fear of the robot and place cell remapping (Kim et al., 2015). More recently, we found that distinct populations of amygdala neurons transiently increased spiking as rats either advanced or fled the robot predator, which suggests that the amygdala signals the occurrence of real threats (Kim et al., 2018). To further understand these findings, we examined the functions of basal amygdala (BA) and dorsal hippocampus (dHPC) as rats exited a safe nest to procure food in a large open space before, during and after encountering the robot predator programmed to surge from distant. Male Long-Evans rats were implanted with tetrodes into the BA and the dHPC to record neural activities simultaneously. After the postoperative recovery, all rats maintained ~85% normal body weight to motivate foraging behavior during the experiment. Unit activities and local field potentials were recorded during the pre-robot (~ 10 trials of procuring the pellet without the robot predator), robot (~ 10 times of attempts to acquire the food with a presence of the robot predator), and post-robot (same as the pre-robot session) sessions. Simultaneous recordings revealed that BA neuronal activity increased while dHPC place fields became unstable as

animals advanced and fled from the predatory robot. These results suggest that fear signals from the BA influence spatial information processing in the dHPC to protect animals traversing safe and dangerous areas.

Disclosures: M. Kong: None. **H. Ding:** None. **E. Kim:** None. **J.J. Kim:** None.

Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 502.10/XX14

Topic: G.01. Appetitive and Aversive Learning

Support: SUNY Start Up Funds

Title: The role of neonatal gonadal hormones in organizing juvenile and adult contextual fear conditioning

Authors: *L. M. COLON[1], D. G. ZULOAGA[2], A. M. POULOS[3]
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Abstract: Our previous research highlights a sex-dependent, developmentally divergent pattern of context fear mediated freezing. Context fear expression in male Long Evans rats increases from pre-adolescence to adulthood, while in female rats an opposite pattern of fear emerges (Colon et al., 2018). This unique developmental pattern initiated prior to puberty suggests that neonatal gonadal hormones may play a role in organizing the differentiation of neural systems underlying contextual fear conditioning. In this study, we sought to determine whether neonatal gonadal hormone exposure mitigates an organizational role in the sex-specific development of context fear conditioning by removing the presence of testicular hormones at birth in Long Evans male rats. This was accomplished by neonatal orchiectomy, and the examination of conditioning at 24 and 60 days postnatal. Our preliminary findings indicate that orchiectomy alters the expression of contextual fear compared to control subjects, suggesting that gonadal hormones have an organizational influence on the neural systems underlying contextual fear conditioning.

Disclosures: L.M. Colon: None. **D.G. Zuloaga:** None. **A.M. Poulos:** None.

Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 502.11/YY1

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant R03MH93781
NIH Grant SC3GM109817
SUNY Start-up Funds
SUNY FRAP 2018

Title: Organization and functional recruitment of neuronal populations in rat prefrontal cortex that project to the basolateral amygdalar nuclei: A combined retrograde tracing and Fos activation study of context fear conditioning across development

Authors: *A. J. SANTARELLI[1], A. M. KHAN[2], A. M. POULOS[3]
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Abstract: A growing body of research suggests an important function for prefrontal cortical (PFC) regions in contextual-spatial mediated learning. Several of these cortical areas, including the rostral anterior cingulate (ACA), infralimbic (ILA) and prelimbic (PL) areas, undergo a protracted period of development and innervate directly the anterior and posterior portions of the basolateral amygdalar nuclei (BLAa & BLAp; respectively). These BLA afferents undergo a relatively extended period of cellular proliferation, which culminates in large-scale synaptic pruning. Recently, we proposed that the degree of PFC involvement in context fear conditioning may depend on the developmental status of ILA-BLAp and PL-BLAp projections. Here, we sought to investigate the extended anatomical development of PFC-BLA projections and their activation during contextual fear retrieval. We hypothesized that the afferent projections from certain PFC areas will exhibit a unique pattern of anatomical development in juvenile rats compared to the adult and that contextual fear conditioning in juveniles may bias the activation of these projections. We tested these predictions by combining Fluorogold (FG) tract-tracing of BLA afferents - to retrogradely label PFC neurons - with detection of Fos immunoreactivity (Fos+) induced by the retrieval of context fear memory in infant (P19), juvenile (P24, P35), and adult (P90) rats. Nissl stained coronal sections were aligned to a reference atlas extending across 1.4mm of the PFC and within proximity to the injection site. All regions and subnuclei were parcellated according to previously established definitions. We identified FG+ neurons in the PL, ILA, medial orbital (ORBm), posterior-ventral anterior olfactory nucleus (AONpv), dorsal ACA, endopiriform (EPd), tenia tecta (TTd) and agranular insular area (Aid). We then mapped the

observed FG+, Fos+, and FG+/Fos+ double-labeled neurons to a reference atlas (Swanson, 2004) through the rostrocaudal extent of these regions. Quantification of FG+ neurons across development revealed BLA afferents peaked at either P24 (ILA, ACA, AONpv) or P35 (PL, Aid) with ILA, ACA and AONpv undergoing significant pruning towards adulthood. Moreover, in P24 rats both BLA projecting, PL and ILA regions displayed increased FG+/Fos+ neurons following contextual fear retrieval. These results demonstrate that PFC-to-BLA projections in juvenile rats are quantitatively distinct from the adult and may provide vital insight into the development of fear-related neural circuitry.

Disclosures: A.J. Santarelli: None. **A.M. Khan:** None. **A.M. Poulos:** None.

Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 502.12/YY2

Topic: G.01. Appetitive and Aversive Learning

Support: SUNY Startup Funds

Title: A neuroanatomical and functional characterization of bidirectional trans-hemispheric projections between the left and right BLA complexes in the rat

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Abstract: The basolateral complex of the amygdala, which consists of the anterior and posterior portions of the basolateral amygdalar (BLAa, BLAp) and lateral amygdalar (LA) nuclei, is a crucial component of the neural circuitry underlying Pavlovian fear conditioning. Despite evidence in humans and rodents suggesting a left versus right BLA complex bias in the expression of fear, relatively little is known about what contributes to this asymmetrical pattern of activation. One possible source of this variation is the bidirectional trans-hemispheric projections previously identified between the left and right BLA complexes. Here, we characterize and explore the importance of this connectivity by employing double co-injections of anterograde and retrograde tracers targeting the left and right BLA as well as inactivation of these trans-hemispheric afferents during the retrieval of contextual fear memories.

Disclosures: N. Odynocki: None. **A.J. Santarelli:** None. **A.M. Poulos:** None.

Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 502.13/DP12/YY3

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant MH107238

Title: Synaptic rearrangement in the zebrafish pallium after fear learning

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Abstract: Synaptic connections are considered to be the functional elements that make up an engram, the structural representation of a memory in the brain. However, the nature of the synaptic changes that occur when a memory is formed remain poorly understood, in part because of the difficulty of visualizing a large collection of synapses in the brain before and after learning. In an effort to visualize the formation of a memory in a living organism in four dimensions (x, y, z, t) at the synaptic level, we have established a novel experimental pipeline using the larval zebrafish brain as a model for vertebrate learning. Combining FingR (Fibronectin Intrabodies Generated with mRNA display) labeling, a novel classical fear conditioning paradigm, optimized non-invasive and sub-micron-level (0.3 x 0.3 x 1.0 µm voxel size) selective plane illumination microscopy (SPIM) imaging, and a semi-automated synapse segmentation and analysis program, we monitor changes in the zebrafish pallium as a lasting fear memory is formed. After behavioral training, we found striking differences in the synaptic changes in highly circumscribed anatomical areas within the pallium, suggesting that one population of cells receives a dramatically diminished projection from sensory areas while a second region receives dramatically strengthened input.

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Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 502.14/YY4

Topic: G.01. Appetitive and Aversive Learning

Support: University of Scranton Grant for Research as a High Impact Practice

Title: Involvement of caffeine cAMP signaling on neural activity and aggression in crayfish, Procambarus clarkii

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Abstract: Caffeine is a known phosphodiesterase (PDE) inhibitor with an affinity for interacting with dopaminergic pathways in vertebrates and invertebrates (Mustard 2014). PDE inhibitors have been suspected to increase the activity of cAMP cascades producing greater exocytosis of calcium ions by blocking the breakdown of cAMP (Beaumont et. al 2001). Studies have shown that caffeine exposure also decreases action potential threshold in crayfish neuromuscular junctions (Araki et. al 2005; Chiarandini et. al 1970). Behaviorally, crayfish demonstrate a heightened submissive response in conspecific encounters through cAMP signaling on dopaminergic pathways (Momohara et. al 2014, 2016). Our study aims to observe how the physiological effects of caffeine translate behaviorally. Conspecific fights were run using adult, male, *Procambarus clarkii* to measure the aggression before and after the administration of caffeine or 3-Isobutyl-1-methylxanthine (IBMX), a sole PDE inhibitor. Losing crayfish received doses via water bath solution (10 mg/L caffeine or IBMX), while winners were submerged in vehicle. Results for IBMX and caffeine trials indicated enhanced submissive responses in losers, including a decrease in approaches (Two sample T-test; t= -2.479, p= 0.038171, = .05) and an increase in retreats as opposed to tail-flips (F-test, = 4.0205, p=0.0262, .05), when compared to vehicle in IBMX trials. In caffeine trials, control to experimental fights demonstrated a significant increase between the winner and loser mean score differences (Two sample t-test: t = -2.4522, df = 6, p-value = 0.02482). To further investigate the increase in submissive behaviors, we exposed the abdominal nerve chain for extracellular recording on nerve I of the third abdominal ganglion while dripping IBMX (15 mg/ 100 mL), caffeine (15 mg/100 mL), or vehicle (crayfish saline) solutions. When compared to vehicle, IBMX and caffeine application resulted in a mean increase of two to four events per stimulation, a three-fold rise in the magnitude of the amplitude of the peaks, and an increase in their sharpness by slope measurement. These similarities of effects could suggest that caffeine leads to synaptic enhancement through PDE inhibition which increases submission in losing crayfish.

Disclosures: C.C. Horchos: None. **R.F. Waldeck:** None.

Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 502.15/YY5

Topic: G.01. Appetitive and Aversive Learning

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Title: Supramammillary nucleus modulates dentate gyrus activity and hippocampus-dependent behavior

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Abstract: The dentate gyrus (DG) is critical for memory acquisition and retrieval and modulates stress- and anxiety-related behaviors. Activity in DG is strongly modulated by novelty, but the sources of this modulation are not well understood. The Supramammillary Nucleus (SuM) of the ventromedial hypothalamus sends a pronounced projection to the DG. Previous studies demonstrate that SuM is strongly activated by contextual novelty and that lesions or inactivation of SuM impair performance in a variety of hippocampus-dependent tasks. These findings suggest that SuM may be an important modulator of DG function. However, because previous studies of SuM lacked anatomical precision, it is unknown whether these behavioral effects reflect SuM-DG interactions specifically. Here we examine the role of SuM in DG functioning by isolating and manipulating DG-specific SuM projections. We first examined novelty-evoked activity in SuM using the immediate-early gene cfos. Exposure to a novel environment or fear conditioning in a novel context evoked elevated levels of cfos expression in SuM, whereas exposure to a familiar environment did not. To confirm the role of SuM in hippocampus-dependent behavior, adeno-associated virus was used to express Gi-coupled (inhibitory) or Gs-coupled (excitatory) DREADDs in SuM. Excitation of SuM increased exploration of an open field while inhibition decreased exploration. Excitation of SuM also produced a deficit in context fear retrieval. We next explored anatomical projections of SuM to the hippocampus. Injection of AAV-GFP into

SuM confirmed strong projections of SuM along the full dorsal-ventral axis of DG, terminating within the inner molecular layer. Dorsal DG-projecting SuM cells were previously reported to be distributed more laterally than ventral DG-projecting SuM cells. To confirm this distribution, retrograde tracers (Cholera Toxin B and retrograde AAVs) were injected into dorsal and ventral DG and labeled cells in SuM were examined. Results confirm that dorsal and ventral DG receive projections from separate populations of SuM cells. To evaluate whether these projections have unique functions, retrograde AAV-Cre was injected into dorsal or ventral DG, while Cre-dependent AAVs were injected into SuM. This produced expression of excitatory or inhibitory DREADDs in cells projecting from SuM to either dorsal or ventral DG. Experiments in progress evaluate the role of DG-projecting SuM cells in spatial and emotional learning. We predict that dorsal DG-projecting SuM neurons modulate novelty-evoked learning and behavior, whereas ventral DG-projecting neurons modulate stress-dependent learning and anxiety-like behavior.

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Poster

502. Fear and Aversive Learning and Memory: Neural Circuitry I

Location: SDCC Halls B-H

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Program #/Poster #: 502.16/YY6

Topic: G.01. Appetitive and Aversive Learning

Support: SNSF 31003A_176332 / 1

Title: Insular cortex processes aversive information and is crucial for threat learning

Authors: *E. BERRET, M. KINTSCHER, S. PALCHAUDHURI, W. TANG, O. KOCHUBEY, R. SCHNEGGENBURGER
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Abstract: During threat learning, an emotionally innocuous sensory percept like a tone (the conditioned stimulus or CS), acquires emotional meaning when paired with an aversive stimulus (the unconditioned stimulus or US). The amygdala, and especially the lateral amygdala (LA) is a brain structure critical for the integration of CS (tone) and US (footshock) information in the formation of treat memories. Nevertheless, little is known about upstream CNS circuits which process aversive events and relay them to LA. We used *in-vivo* optogenetic silencing experiments with Halorhodopsin, combined with *ex-vivo* functional mapping of synapses, to investigate these questions. Optogenetic silencing of the ventroposterolateral thalamus (VPL), or of the posterior Insular cortex (pInsCx) temporally selectively at the time of footshock presentation strongly suppressed acute fear behavior, and one-day threat memory. Viral tracer experiments show that largely segregated neuronal populations in the pInsCx make output

projections with the LA, and with the central amygdala (CeA). *Ex-vivo* optogenetic mapping approaches with expression of Chronos in the pInsCx followed by slice recordings of neurons in the LA and CeA showed robust optically-evoked glutamatergic EPSCs in both amygdalar substructures. To investigate the role of each pathway in fear behavior and threat memory, we expressed Halorhodopsin bilaterally in each pInsCx, and placed optic fibers bilaterally over either the LA or the CeA. This showed that the pInsCx - LA pathway contributes to one-day threat memory but is not involved in acute fear behavior, whereas the pInsCx - CeA pathway strongly contributes to acute fear behavior, but is less relevant for one-day threat memory. Thus, the posterior Insular Cortex processes US information relevant for threat learning, and routes this information to various amygdala substructures to cause specific phases of fear behavior and threat memory.

Disclosures: E. Berret: None. **M. Kintscher:** None. **S. Palchaudhuri:** None. **W. Tang:** None. **O. Kochubey:** None. **R. Schneggenburger:** None.

Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 503.01/YY7

Topic: G.01. Appetitive and Aversive Learning

Support: National Natural Science Foundation of China (91432306)

Title: Amygdala GABAergic inputs to nucleus accumbens modulate fear memory

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Abstract: Fear is a central motive state that is critical for survival. The nucleus accumbens (NAc) , located in the ventral striatum, is an emotional valence center, but whether and how NAc is involved in fear have not been identified. Here, we showed that chemogenetic inhibition adenosine A2A receptor-expressing indirect pathway neurons in the core region of the NAc impaired fear learning in Pavlovian fear condition. Furthermore, we demonstrated anatomically, behaviorally and electrophysiologically that amygdala GABA-input to NAc mechanisms underlie these behaviors. Our results illustrate how defined NAc circuits regulate fear bilaterally.

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Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

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Program #/Poster #: 503.02/YY8

Topic: G.01. Appetitive and Aversive Learning

Support: NSF Graduate Research Fellowship DGE-1553798
NIH R01 NS095311
NIH R01 DC000566

Title: Cell type specific control of plasticity in the basolateral amygdala via feedforward inhibition

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Abstract: The basolateral amygdala (BLA) plays a vital role in associating specific sensory stimuli with salient valence information. Excitatory principal neurons (PNs) undergo plastic changes to encode this integrated sensory-valence information; however, local BLA inhibitory interneurons (INs) gate the plasticity of the PNs via feedforward inhibition (FFI). One major source of FFI to the BLA is the lateral entorhinal cortex. Despite extensive literature implicating parvalbumin expressing (PV^+) INs in FFI in cortex and hippocampus, prior experiments in the BLA and our own work implicates somatostatin expressing (Sst^+) INs in BLA FFI. To test the hypothesis that entorhinal afferents target Sst^+ INs in the BLA to mediate FFI and gate the plasticity of PNs, we performed whole-cell electrophysiology experiments in horizontal slices of adult mice. We recorded from BLA neurons in response to stimulation of the lateral entorhinal cortex and show that these afferents synapse onto a subset of Sst^+ INs that displayed a fast spiking phenotype, PV^+ INs, and BLA PNs. However, only the fast spiking Sst^+ INs but not PV^+ INs fired action potentials in response to the stimulation. To determine the role of the different INs in FFI, we expressed the inhibitory chemogenetic protein $hM4D_i$ in Sst^+ and PV^+ INs and found that inactivation of Sst^+ but not PV^+ INs decreased FFI onto BLA PNs. Finally, we tested the role of Sst^+ and PV^+ INs in gating plasticity. To do this, we chemogenetically inactivated these cell types while attempting to induce plasticity at the entorhinal to amygdala synapse and found that inactivation of Sst^+ but not PV^+ INs allows the PNs to undergo both LTP and LTD. In the BLA, Sst^+ INs provide FFI to PNs via putative dendritic targeting inhibition in marked contrast to other brain regions, where somatic targeting PV^+ INs provide this function. Additionally, these Sst^+ INs gate the plasticity of cortical inputs to BLA PNs, consistent with the

role of dendritic inhibition across the brain in gating calcium dynamics and with BLA FFI gating plasticity.

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Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

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Program #/Poster #: 503.03/YY9

Topic: G.01. Appetitive and Aversive Learning

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Title: Amygdala CRF promotes fear learning with a touch of periaqueductal gray

Authors: *M. B. POMRENZE[1,2], R. MAIYA[1,2], S. M. GIOVANETTI[1,2], G. A. DILLY[1,2], A. G. GORDON[1,2], Y. SHAH[1,2], M. MARINELLI[1,2], R. O. MESSING[1,2,3]
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Abstract: Canonical models of fear circuitry involve sensory and cortical inputs to the lateral and basolateral amygdala, which activate neurons of the central nucleus of the amygdala (CeA) that target the midbrain periaqueductal gray (PAG). Recruitment of the PAG then orchestrates rapid defensive behavioral responses, such as freezing, to a fearful stimulus. Neurons in the medial subdivision of the CeA, whose activity is regulated by neurons in the lateral CeA, are thought to be the preferential population targeting the PAG to promote defensive behavior. However recent data show that lateral CeA neurons also give rise to long-range projections, some of which target the ventrolateral PAG (vlPAG) and express stress neuropeptides such as corticotropin releasing factor (CRF). Despite the existence of these projections, their contribution to fear learning is unexplored. We investigated the role of CeA CRF neurons in fear learning using *Crh*-Cre rats. We found that chemogenetic inhibition of CeA CRF neurons interferes with the acquisition, but not expression, of contextual and cued fear, similar to previous reports. Genetic knockdown of *Crh* expression in the CeA recapitulated this effect. Chemogenetic silencing of CRF neurons in the dorsal bed nucleus of the stria terminalis (BNST), a limbic structure strongly connected to the CeA, had little effect on fear acquisition. Anterograde and retrograde viral tracing confirmed a sizeable subpopulation of CeA CRF neurons that project their axons to the vlPAG. Inhibition of these axon terminals in the vlPAG using chemogenetics and targeted CNO microinjections disrupted contextual, but not cued, fear acquisition. Ongoing

experiments are employing fiber photometry to measure activity patterns of CeA CRF neurons during fear conditioning. We are also using retrograde AAV constructs to selectively record calcium dynamics and chemogenetically silence vlPAG-projecting CeA CRF neurons. These data demonstrate a dissociable role for subpopulations of CeA CRF neurons in contextual versus cued fear learning.

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Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

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Topic: G.01. Appetitive and Aversive Learning

Support: ERC Grant StG 335587
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Minna James Heineman Foundation

Title: Learning-related plasticity of dendritic inhibition in neocortical layer 1

Authors: *E. ABS[1], R. B. POORTHUIS[1], K. MUHAMMAD[1], B. PARDI[1], L. ENKE[1], I. SPIEGEL[2], J. J. LETZKUS[1]
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Abstract: Layer 1 (L1) of sensory cortex receives top-down information from higher cortical areas, thalamic nuclei and neuromodulatory systems, which converges with bottom-up input entering in deeper cortical layers. While top-down signaling has been suggested to contribute to learning and memory expression, we know little about how this information is integrated in the apical tuft dendrites of L2/3 and L5 pyramidal cells in behaving animals. One well-studied inhibitory modulator of apical tuft dendrites are deeper layer somatostatin-positive Matinotti cells. In this study we investigate a second source for dendritic inhibition, the sparse population of L1 interneurons. Using a novel genetic marker for a subpopulation of L1 interneurons, Neuron Derived Neurotrophic Factor (NDNF) in combination with *in vitro* electrophysiology, viral tracing, optogenetics and *in vivo* 2-photon calcium imaging, we find that NDNF neurons target their output mainly within L1, connecting to distal dendrites of L2/3 and L5 pyramidal cells as well as deeper layer interneurons. These connections control the initiation of dendritic spikes in pyramidal cells through recruitment of a strong component of $Gaba_B$ receptor signalling. To address whether Ndnf positive layer 1 interneurons show learning-related plasticity, we combined *in vivo* calcium imaging with a form of cortex-dependent auditory fear learning. These

results reveal that sensory responses of Ndnf positive layer 1 interneurons are potentiated in response to learning in proportionality to the strength of the memory. In contrast, dendritic inhibition derived from somatostatin-positive Martinotti cells remains unchanged after learning, but in turn tightly controls sensory responses in Ndnf interneurons. These data indicates a differential role of these two interneuron types in dendritic inhibition. Matching these findings, results of dendritic imaging of L5 pyramidal neurons show a learning-induced increase in post-stimulus inhibition. In summary, the results indicate that, in addition to perisomatic disinhibition, memory retrieval is associated with elevated levels of a specialized form of dendritic inhibition.

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Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

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Title: Amygdala neuronal ensembles dynamically encode behavioral states

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Abstract: Learning and memory shape our daily life, social interactions and mental well-being. Mapping state-dependent large-scale network activity on identified neuronal circuits will be essential to understand the neurophysiological and pathophysiological basis of behaviour and memory formation. Here we follow the activity patterns of large populations of amygdala neurons across paradigms of anxiety and learned fear behaviors with the help of genetically encoded calcium indicators and a deep brain imaging miniature microscope approach in freely moving animals. We demonstrate that changes in the relative activity levels of two major, non-

overlapping populations of principal neurons in the basal nucleus of the amygdala (BA) predict switches between exploratory and anxiety-like or defensive behavioral states across different environments. Moreover, we found that the amygdala widely broadcasts internal state information via several output pathways to larger brain networks, and that sensory responses in the BA were not correlated with behavioral states. Our data indicate that the brain processes external stimuli and internal states in an orthogonal manner, which may facilitate rapid and flexible selection of appropriate, state-dependent behavioral responses.

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Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

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Novartis Research Foundation

Title: Low dimensional Amygdala network dynamics generalize across behavioral paradigms

Authors: *Y. BITTERMAN[1], J. GRÜNDEMANN[2], J. COURTIN[1], S. KRABBE[1], M. FUSTIÑANA[1], A. LUTHI[1]
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Abstract: The field of classical conditioning highlights the role of the amygdala in learning associations between sensory stimuli and behavioral output. In parallel, the basal amygdala has long been implicated in the regulation of persistent states, such as anxiety and drive. We use deep brain calcium imaging of genetically identified neurons in the basal amygdala while mice engage in a range of self- paced behaviors. By tracking large neuronal populations across days and paradigms, we identify a hierarchy of activity patterns that emerges in the network dynamics during learning and corresponds to behavior on multiple timescales. We further describe the response of the network dynamics to perturbations along different dimensions and the interplay

between state-like representation and the processing of specific events and actions. Our findings suggest a general principle of network dynamics that could underlie the involvement of the amygdala in such different functions as sensory associative learning, action selection and emotional processing.

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Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

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Program #/Poster #: 503.07/YY13

Topic: G.01. Appetitive and Aversive Learning

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Title: Neuronal correlates of social interactions in amygdala circuits

Authors: *M. FUSTIÑANA, Y. BITTERMAN, A. LUTHI
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Abstract: Social behaviors encompass a complex set of conducts, which are impaired in several psychiatric disorders including autism spectrum disorder (ASD) and social anxiety disorder. In humans, the amygdala has been implicated in the regulation of social interactions and ASD patients exhibit abnormal amygdala activity upon exposure to social stimuli. In rodents, the amygdala has mainly been studied in the context of fear and anxiety-like behaviors. However, the role of the amygdala during social behavior in freely-interacting rodents has not been addressed. We established a naturalistic paradigm in which two mice freely interact while recording neuronal activity. To make this complex behavior tractable, we developed a set of algorithms to automatically score active and passive behaviors, including initiated interactions, approach, avoidance and aggression. To record neuronal activity, we combined cell-type specific targeting and deep brain calcium imaging in the basal nucleus of the amygdala (BA) using a head-mounted miniature microscope. At the single cell level, our data revealed neuronal responses time-locked to social interactions. At the population level, amygdala neurons can be robustly divided into anti-correlated clusters which exhibit slow dynamics and predict the animal's active engagement in social interactions. Taken together, our results indicate that the BA is part of the brain's circuitry engaged during social interactions.

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Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

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Program #/Poster #: 503.08/YY14

Topic: G.01. Appetitive and Aversive Learning

Support: VA #I01RX002705
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NIH #R01NS101108

Title: Changes in limbic circuitry underlying fear related behaviors following TBI: Small and large, translational animal models

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Abstract: Traumatic Brain Injury (TBI) is considered the signature injury of recent US military conflicts and has been implicated in memory deficits and anxiety disorders such as Post-Traumatic Stress Disorder (PTSD). Previous studies investigating changes in circuitry underlying these deficits suggest that TBI disrupts theta, an oscillation known to organize ensembles of neurons within and between brain regions in a behaviorally relevant manner. In order to understand how TBI disrupts theta and investigate how this disruption may lead to anxious behaviors, we subjected rats to a lateral fluid percussion injury (FPI) or sham injury, chronically implanted them with high-density silicon electrodes in basolateral amygdala (BLA) and bipolar electrodes in medial prefrontal cortex (mPFC) and ventral hippocampus (vHC), then ran them through anxiety testing consisting of plus maze (PM), open field (OF), and fear conditioning (FC). Our FC paradigm consisted of acquisition, in which rats learned to associate white noise (CS+) with a footshock, followed by 2 days of extinction, in which rats were presented with the CS+ and a novel tone (CS-) without getting footshocks, then reinstatement, in which rats were repeatedly presented the CS+ but only received a footshock with the first presentation. We found that compared to sham injured rats, FPI rats acquired fear responses (freezing) faster, extinguished fear responses to both CS+ and CS- slower, and did not consolidate extinction as well. Preliminary results have also shown FPI rats had decreased vHC-mPFC and vHC-BLA theta coherence during anxiety testing compared to sham, and BLA single-unit entrainment to vHC theta was altered between the two groups. In parallel with the above work, we have developed a method to wirelessly record from chronically implanted electrodes in pigs, and are assessing behavioral and electrophysiological changes induced by a more

translational rotational inertial TBI model in swine. In addition, we have successfully developed a FC paradigm in swine similar to the one described above for rats, and have determined that heartrate can be used as an outcome measure as it closely mirrors freezing rates in rodent FC models and is not correlated with movement. Importantly, we found that heartrate values follow typical extinction curves both within and between extinction sessions indicating that our swine FC paradigm could be a translational model of extinction therapy following PTSD. Future recordings from BLA and HC of injured pigs as they go through FC will allow us to assess how TBI induced changes in limbic circuitry may affect extinction, which is relevant to therapy for comorbid TBI/PTSD patients.

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Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

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Program #/Poster #: 503.09/YY15

Topic: G.01. Appetitive and Aversive Learning

Support: NS22061

Title: Influence of nicotine exposure on the development profile of cholinergic circuits engaged in fear/threat memory

Authors: *J. A. WILKING[1], D. A. TALMAGE[2], L. W. ROLE[3]
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Abstract: Smoking during pregnancy is the most preventable risk factor associated with many adverse fetal outcomes including cognitive deficits and later increased substance abuse. Additionally, approximately 80% of smokers initiate tobacco use during adolescence. This suggests that age of nicotine exposure may play a critical role in the developing brain and the cholinergic system. The cholinergic system has been implicated in attention, learning, and memory processes. One key brain region that is highly involved in fear/threat learning is the amygdala. Part of the amygdala, the basolateral amygdala (BLA) receives abundant cholinergic innervation and is critical for establishing emotionally salient memories. Our laboratory has demonstrated that cholinergic input from the basal forebrain is critical for BLA dependent learning and memory as well as endogenous acetylcholine (ACh) increases synaptic plasticity in the BLA and this requires ACh and nicotinic acetylcholine receptors (nAChRs). Now, in order to examine the effect of chronic nicotine administration during development, pregnant C57BL/6J dams are administered 200 µg/ml nicotine plus Splenda or only Splenda in drinking water from

embryonic day 14 (E14) to postnatal day 21 (P21). Additionally, naive adolescent C57BL/6J animals (P21) are administered either 200 µg/ml nicotine plus Splenda or Splenda alone in their drinking water for 3 weeks to span most of the adolescent period as well as to correspond to length of treatment in the prenatal group. Following chronic nicotine administration animals receive paired tone and foot shock to examine freezing in this cued fear conditioning paradigm. The following day (recall), the animal receives the same tone and the freezing response is recorded to investigate nicotine and age related changes in fear response. Further, to determine cholinergic circuity modifications and developmental differences following chronic nicotine administration, changes in cFos and vesicular acetylcholine transporter (VAChT) immunohistochemistry have been measured in BLA.

Disclosures: J.A. Wilking: None. **D.A. Talmage:** None. **L.W. Role:** None.

Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

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Topic: G.01. Appetitive and Aversive Learning

Support: NIMH R01 MH069558

Title: Contextual novelty encoded by the dorsal hippocampus regulates synaptic destabilization and memory lability in the amygdala

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Abstract: During Pavlovian fear conditioning, a neutral auditory conditional stimulus (CS) is paired with an aversive unconditional stimulus (UCS). The CS acquires aversive value and can elicit a fear response during a retrieval session. Fear memory retrieval has been associated with synaptic destabilization in the amygdala, which is thought to be a primary factor allowing for modification of the original memory. The internalization of calcium impermeable AMPA receptors (CI-AMPAR) following retrieval allows for the calcium-dependent plasticity necessary to destabilize, and the protein synthesis-dependent plasticity to restabilize, amygdala synapses. Thus CI-AMPAR internalization may be critical for memory updating. Recent work from our lab shows that pre-exposure to the retrieval context is sufficient to prevent amygdala AMPAR internalization and prevent memory disruption as a result of protein synthesis inhibition (e.g., Jarome et al 2015). The dorsal hippocampus (DH) encodes information about context and shows

increased synchrony with the amygdala following auditory fear memory formation and retrieval (e.g., Narayanan et al 2007; Seidenbecher et al 2003). Additionally, strong fear memories that are resistant to disruption with protein synthesis inhibition can be made susceptible with DH lesions, suggesting DH mediated processes may contribute to memory lability and synaptic destabilization in the amygdala. The goal of these experiments was to determine how DH neural activity contributes to memory lability and synaptic destabilization in the amygdala during retrieval when contextual novelty is removed. When the training and retrieval contexts were the same, we were unable to disrupt the auditory memory with local infusions of anisomycin into the amygdala. However, DH inactivation during auditory fear conditioning was sufficient to allow for disruption of the auditory fear with protein synthesis inhibition in the amygdala after retrieval. We also found DH inactivation was associated with AMPAR internalization in amygdala synapses after retrieval regardless of contextual novelty, while removal of contextual novelty prevented AMPAR internalization, as measured by expression of AMPAR in synaptic fractions from the amygdala. Collectively, these results suggest that the DH encodes contextual information during auditory fear formation that in turn regulates retrieval-dependent memory modification. Ongoing experiments will determine whether DH activity is also necessary during retrieval when contextual novelty is removed to render the memory susceptible to disruption with protein synthesis inhibition and how this impacts AMPAR trafficking.

Disclosures: N. Ferrara: None. **S.E. Pullins:** None. **M. Shin:** None. **F.J. Helmstetter:** None.

Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 503.11/YY17

Topic: G.01. Appetitive and Aversive Learning

Title: A hypothalamus-habenula circuit controls aversion

Authors: *I. LAZARIDIS[1], O. TZORTZI[1], M. WEGLAGE[1], A. MÄRTIN[1], Y. XUAN[1], M. PARENT[1], Y. JOHANSSON[1], L. FENNO[2], J. FUZIK[1], D. FÜRTH[1], C. RAMAKRISHNAN[2], G. SILBERBERG[1], K. DEISSEROTH[1,3], M. CARLÉN[1], K. MELETIS[1]
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Abstract: Encoding and predicting aversive events is a critical function of basal ganglia and limbic circuits that support survival and emotional well-being. Maladaptive circuit changes in aversive signal processing can underlie the pathophysiology of affective disorders. The lateral habenula (LHb) has been linked to aversion and mood regulation through modulation of the dopamine and serotonin systems. We have defined the identity and function of glutamatergic (Vglut2+) control of LHb, comparing the role of inputs originating from the globus pallidus

internal segment (GPi) and lateral hypothalamus (LHA). We found that the LHb-projecting LHA neurons induced a negative bias in the probabilistic switching task and demonstrate that the aversive signals in LHb originate from glutamatergic LHA neurons and not the GABA/glutamate co-releasing GPi neurons. In addition, tracing of the presynaptic connectivity organization supported a predominant limbic input to LHA neurons, in contrast to the sensorimotor input to GPi. We further recorded the activity of Vglut2+ LHA neurons, by imaging calcium dynamics in response to appetitive versus aversive stimuli in conditioning paradigms. Vglut2+ LHA neurons displayed heterogeneous neural signals representing reward and punishment signals, including a candidate population that encoded and predicted future aversive events. We found that the LHb-projecting Vglut2+ LHA neurons signal the aversive event and rapidly acquire a prediction signal for future punishments. In summary, these findings establish the glutamatergic LHA-LHb circuit as a critical node in signaling and learning about the negative value of events.

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Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 503.12/YY18

Topic: G.01. Appetitive and Aversive Learning

Title: Comparisons of vlPAG cell body and midline/intralaminar thalamus terminal inhibition in positive prediction error signaling

Authors: *R. A. ZACHARIAS, S.-H. PARK, R. SUTHARD, T. PERISON, M. A. MCDANNALD
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Abstract: Recent evidence has shown that the ventrolateral periaqueductal grey (vlPAG) is necessary for generating positive aversive prediction errors (+PEs), which are learning signals that function to increase future fear. It remains unknown, however, where the vlPAG sends these signals to update expectancies. The midline/intralaminar thalamus (MIT) has been implicated in fear conditioning and receives direct projections from the vlPAG, making it a likely candidate for +PE circuitry. In this study we trained male and female Long-Evans rats in a fear discrimination paradigm in which three cues were associated with different probabilities of foot shock: safety p=0.00, uncertainty p=0.38, and danger p=1.00. This task was designed such that it requires the use of +PEs to demonstrate appropriate fear, specifically for the uncertainty cue. To causally link the vlPAG-MIT pathway to +PE signaling, we bilaterally transfected the vlPAG

with halorhodopsin under control of the human synapsin promoter or with control YFP only virus. An optical ferrule was implanted over the MIT and 532 nm light was delivered precisely during the time of shock receipt on reinforced uncertainty trials, or exactly when +PEs would be generated, and on danger trials as a control. These experimental procedures allowed us to inhibit vlPAG terminals in the MIT in a temporally precise manner. Results indicated that inhibition of the vlPAG-MIT pathway did not alter fear to uncertainty, unlike cell body inhibition, suggesting another pathway or multiple pathways may carry out vlPAG +PE signaling. Ongoing experiments seek to establish if an alternate pathway, such as vlPAG-lateral hypothalamus (LH), is responsible for this signaling.

Disclosures: R.A. Zacharias: None. **S. Park:** None. **R. Suthard:** None. **T. Perison:** None. **M.A. McDannald:** None.

Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

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Program #/Poster #: 503.13/YY19

Topic: G.01. Appetitive and Aversive Learning

Support: University of Michigan Grant #U032826
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Title: Neural correlates of contextual fear expression in sign- and goal-trackers

Authors: *C. J. FITZPATRICK, J. D. MORROW
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Abstract: Pavlovian conditioned approach behavior has been previously used to identify rats that preferentially approach reward-related cues (sign-trackers; STs) or the location of the rewards that those cues predict (goal-trackers; GTs). STs are more susceptible to cue-induced "relapse," or reinstatement of cocaine self-administration, but less susceptible to context-induced reinstatement. In addition, STs are more fearful of discrete cues that predict aversive stimuli, but less fearful of contexts. This indicates that STs have a decreased capacity for contextual learning as compared to GTs, but the neural substrates underlying these behavioral differences are unknown. To test for differences in neural activity induced by contextual learning, we characterized rats as STs and GTs prior to contextual fear conditioning or a control procedure (context exposure with no shocks), followed by a contextual fear expression test twenty-four hours later. We then measured regional expression of c-Fos mRNA, a marker of neural activity, using radioactive in situ hybridization. Replicating our previous findings, GTs showed increased

contextual fear expression compared to STs during the test. Quantification of c-Fos mRNA is ongoing, but we hypothesize that GTs compared to STs will have increased expression of c-Fos mRNA in a contextual fear circuit that includes: the prefrontal cortex (prelimbic and anterior cingulate cortices), lateral septum, hypothalamus (lateral and paraventricular nuclei), thalamus (anterior and ventral posteromedial nuclei), amygdala (basolateral and central nuclei), hippocampus (dorsal and ventral), and periaqueductal gray. These findings could enhance our understanding of individual differences in contextual learning that may contribute to the development of addiction, posttraumatic stress disorder, and related neuropsychiatric disorders.

Disclosures: C.J. Fitzpatrick: None. **J.D. Morrow:** None.

Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 503.14/YY20

Topic: G.01. Appetitive and Aversive Learning

Support: CAPES (Grant: Proex 1966/2016)
CNPq [grant number 141918/2013-6 to FPBack, 305711/2014-8 to APCarobrez]
FAPESP [grant number 2012/17626-7]

Title: Aversive learning from periaqueductal gray stimulation: Glutamatergic, endocannabinoid and vanilloid modulation

Authors: *A. P. CAROBREZ, F. BACK
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Abstract: Glutamatergic stimulation of the dorsolateral periaqueductal gray matter (dlPAG) by N-Methyl-D-Aspartate (NMDA) elicited an immediate defensive response (IDR). Moreover, this experience was capable to support an olfactory fear conditioning (OFC) retrieved and expressed as defensive behavior 48h later in the presence of the olfactory stimulus (CS). Therefore, a suggestion that dlPAG-NMDA stimulation provoked IDR as well as ascending negative valence instruction, serving as unconditioned stimulus (US) facilitating aversive memory formation, was proposed. IDR can be elicited or modified by glutamatergic, endocannabinoid and vanilloid receptors systems, however, it is not clear whether dlPAG activation by these modulators also promotes learning. Considering this, we sought to investigate the interplay of these systems post dlPAG activation in both the IDR and further aversive learning. Male Wistar rats implanted with guide cannulas aimed at the dlPAG were used throughout the experiments. The OFC protocol was performed during four consecutive days divided in two stages: 1) conditioning (two days; Box A); and 2) retrieval/expression (two days; Box B). Experiment 1: twenty-four hours after being familiarized in Box A, rats received microinjections (0.2 µl) of NMDA (25-200 pmol) and

were replaced in the same box now saturated with amyl acetate odor (CS). OFC retrieval was performed in Box B (familiarization and CS-exposure). DB was scored on days 2 (Box A), 3 and 4 (Box B). Experiment 2: rats received microinjections of CB1 receptor antagonist, AM251 (50-200 pmol) or the TRPV1 agonist capsaicin (0.1-10 nmol) followed by NMDA (25 pmol) before being paired with the CS. Experiment 3: AP5, a NMDA receptor antagonist (6 nmol), DNQX, an AMPA blocker (2-4 nmol) or AIDA, an mGlu I antagonist (30 nmol) were microinjected before NMDA stimulation. Experiment 1: Rats that received NMDA 50, 100 or 200 pmol expressed higher levels of IDR than those treated with PBS or NMDA 25 pmol during CS association. However, only rats from the 50 and 100 pmol groups showed aversive learning during CS re-exposure. Experiment 2: AM251 and capsaicin potentiated learning from NMDA 25 pmol, with little influence over IDR. Experiment 3 indicated that immediate defensive responses were blocked by AP5, whereas aversive learning was blocked by DNQX or AIDA. Altogether, the results indicated that activation of dlPAG provokes IDR as well as subsequent aversive learning. IDR relies mostly on NMDA receptor activation whereas further aversive learning depends on the modulatory CB1, TRPV1, AMPA and mGlu I receptors into the dlPAG.

Disclosures: A.P. Carobrez: None. **F. Back:** None.

Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

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Topic: G.01. Appetitive and Aversive Learning

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Title: Ventral Pallidum neurons control aversive learning

Authors: *T. MACPHERSON[1], H. MIZOGUCHI[2], A. YAMANAKA[2], T. HIKIDA[1]
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Abstract: The ventral pallidum (VP) is a critical component of the basal ganglia neurocircuitry, and has been implicated in controlling hedonic responses to rewards. However, its possible role in controlling Pavlovian conditioning of cues associated with rewarding or aversive outcomes is unclear. Our group has previously demonstrated that nucleus accumbens (NAc) dopamine D1- or

D2-receptor-expressing neurons are known to control reward and aversive learning, respectively (Hikida et al, 2010, Neuron). While classically it was thought that only NAc D2-neurons project to the VP, recent evidence has shown that a subpopulation of D1-neurons also projects to the VP, suggesting that VP neurons may play a role in either/both types of learning (Kupchik et al, 2015, Nature Neuroscience). Here we used a Tet-Tag AAV virus system, in which designer receptors exclusively activated by designer drugs (DREADDs) were expressed in a population of VP neurons containing the peptide enkephalin, to investigate the possible role of the VP in reward and aversive learning. During acquisition of an autoshaping task, hM3Dq DREADDs were activated by administration of CNO, leading to increased activity in enkephalin-expressing VP neurons. Both CNO-treated and saline-treated (control) mice showed an equal ability to acquire the task, as indicated by an increase in Pavlovian approach behavior to a reward-associated cue over the course of 6 daily sessions. Whereas, in a passive avoidance task, administration of CNO during conditioning of an aversive foot-shock upon entering a dark chamber resulted in a decreased latency, in comparison to saline-treated controls, to enter the foot-shock-associated chamber when tested 24 hours later. These findings indicate that activity in enkephalin-expressing VP neurons disrupts aversive, but does not alter appetitive, Pavlovian conditioning. Thus, decreased activity in enkephalin-expressing VP neurons appears to be necessary for aversive learning, which supports previous evidence from our group that neurotransmission blocking in NAc D2-neurons, likely leading to disinhibition of downstream VP neurons, similarly inhibits passive avoidance learning.

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Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 503.16/YY22

Topic: G.01. Appetitive and Aversive Learning

Support: Grant from the Région de Franche-Comté

Title: Direct and indirect connections from the insular cortex into the parasubthalamic nucleus in the rat

Authors: M. BARBIER, *P.-Y. J. RISOLD
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Abstract: The parasubthalamic nucleus (PSTN) is formed by a small cell condensation adjacent to the subthalamic nucleus (STN) in the lateral hypothalamic area (LHA). The network in which it is involved and its functions are still poorly investigated. The object of this study was to

analyze with some details the organization of its connections with the insular cortex (INS). Twelve injections of the anterograde tract tracer *Phaseolus vulgaris* leucoagglutinin (PHAL) were obtained in granular and agranular areas of the INS. Axons were traced with various densities into the PSTN from each injection sites. The INS did not provide any innervation of the STN, in contrary to projections from areas of the isocortex. Interestingly, most insular areas also innervated the capsular or lateral parts of the central nucleus of the amygdala (CEA). As the PSTN receives abundant projections from the medial part of the CEA, we performed additional experiments with injections of the retrograde tracer fluorogold (FG) into the PSTN and PHAL into the lateral CEA. PHAL axons from the capsular and lateral parts of the CEA made apparent contact on retrogradely labeled neurons in the medial CEA as well as in neighboring regions of the substantia innominata, suggesting that the INS may also influence the PSTN through this indirect route. INS, CEA are involved in responses such as neophobia and visceral pain. We then exposed rats in experimental conditions related to these responses and observed that c-Fos expression increased in the PSTN with regard to these conditions. To conclude, the PSTN is involved in a complex network with the INS and CEA. The organization of this network is reminiscent of the hyperdirect and indirect pathways connecting the isocortex with the STN. These data as well as their functional significances are actually completed by investigations in mouse models using genetic tools and the DREADD technology.

Disclosures: M. Barbier: None. **P.J. Risold:** None.

Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 503.17/YY23

Topic: G.01. Appetitive and Aversive Learning

Support: NIMH R01 MH069558

Title: Inhibition of thalamic terminals in the amygdala may facilitate extinction learning

Authors: *N. FERRARA, P. K. CULLEN, S. E. PULLINS, M. W. GRUTZA, F. J. HELMSTETTER
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Abstract: Fear memory formation is characterized by increased excitatory synaptic strength between primary auditory areas (i.e., the auditory thalamus (MgN) and auditory cortex) and the amygdala. The strength of these connections is increased as a result of learning, and the retention of auditory fear is dependent on the maintenance of potentiated cortico- and thalamo-amygdala synapses. Extinction has been viewed as an inhibitory learning process that results in a context-specific decrease in fear responding due to increased inhibition in the amygdala. Input from the

medial prefrontal cortex is thought to be a primary factor driving elevated inhibition through strengthened connections with local interneurons. This increased inhibition is associated with several plasticity related events in the amygdala, such as maintained potentiation of cortico- and thalamo-amygdala connections and decreased phosphorylation of cAMP response element-binding protein (CREB), that may provide molecular correlates for extinction. Here we study the role of the thalamo-amygdala pathway during fear recall. We silenced input from the MgN to the amygdala using the light driven proton pump, ArchT (AAV9-CAG-ArchT-GFP). We found that MgN driven activity in the amygdala is critical during auditory fear retrieval and when silenced during retrieval, impairs fear assessed during a long-term test. This suggests activity in the thalamo-amygdala pathway is necessary to maintain fear responding at remote time points. Additionally, fear renewed in the training context, demonstrating a context-specific reduction in fear independent of thalamo-amygdala silencing. Groups that did not receive contiguous CS presentations with optogenetic inhibition during retrieval did not show reductions in fear during retrieval or test, suggesting inhibition of MgN-amygdala terminals is specifically required during memory reactivation. Phosphorylation of CREB was measured and quantified following initial retrieval, LTM test, and renewal. Groups that received MgN-LA terminal silencing during retrieval showed reduced phosphorylated CREB after retrieval and test, but not following renewal. We next measured the synaptic expression of AMPA receptors in the amygdala after MgN-amygdala inhibition and did not find differences in the expression of GluR1 or GluR2 subunits, suggesting the decrease in fear responding was not due to a loss of potentiated amygdala synapses. Together, these results suggest inhibition of MgN activity in the amygdala during recall can facilitate extinction learning.

Disclosures: N. Ferrara: None. **P.K. Cullen:** None. **S.E. Pullins:** None. **M.W. Grutza:** None. **F.J. Helmstetter:** None.

Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 503.18/YY24

Topic: G.01. Appetitive and Aversive Learning

Support: KTIA_NAP_13-2-2015-0010
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NKFIH-PD124034
EFOP-3.6.2-16-2017-00008

Title: Nucleus-specific interrogation of the mouse thalamus in aversive cue processing

Authors: *K. KOCSIS[1,2], A. MAGYAR[1,3], B. BARSY[1], Á. BABICZKY[1], V. KANTI[1,3], L. TRUKA[1], M. SZABÓ-HÁRY[1], F. JÁRTÓ[1], M. VÁNCSODI[1], A. BERÉNYI[4], F. MÁTYÁS[1,5]

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Abstract: Sensory information relayed by thalamic inputs to the amygdala is essential in cue-associated behaviors. However, the network elements and exact function of this thalamo-amygdala route have remained to be elucidated. We have recently shown that the majority of thalamic inputs to the amygdala is sent by calretinin-positive (CR+) cells which relay essential information in auditory fear learning.
We hereby investigated the connectivity of CR+ thalamic neurons and their spontaneous, unimodal and multimodal sensory-elicited electrophysiological firing characteristics as well as their effect on the amygdalar subnuclei. The collicular and cortical innervation of these neurons are cell type-specific and strikingly different from those of the neighboring CR- cells. In anesthetised animals, sound(CS)- and shock(US)-evoked as well as paired cue driven firing patterns were examined in CR+ and CR- auditory-related thalamic neurons. In freely behaving tetrode-implanted animals, CR+ and CR- thalamic cued responses were tested in fear conditioning and extinction. In both acute and chronic conditions, CR+ cells were more likely responsive to multimodal or associated cues and they exhibited distinct frequency tuning. Optogenetic stimulation of nucleus-specific thalamo-amygdala pathways led to different outcomes in the amygdalar circuits which underlies the presented anatomical organization and behavioral data.
According to our findings, the connectivity and firing characteristics emphasize the role of CR+ thalamic cell populations in aversive sensory processing and associative learning.

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Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 503.19/ZZ1

Topic: G.01. Appetitive and Aversive Learning

Support: MOST 106-2320-B-007 -006 -MY3

Title: Activation of nucleus reuniens is necessary for acquisition of trace fear conditioning

Authors: *Y.-J. LIN, C.-H. CHANG
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Abstract: The Nucleus Reuniens (RE) of the midline thalamus is reciprocally connected to the hippocampus (HPC) and the medial prefrontal cortex (mPFC). Neuronal tracing studies suggested that there is direct projection from the HPC to mPFC, and RE may serve as a return route. In Pavlovian fear conditioning, a conditioned stimulus (CS), such as a tone, is paired with an unconditioned stimulus (US), such as a footshock. Fear conditioning is robust that animals can learn the CS-US association after a few pairings. In our study, we used two different conditioning paradigms: delay conditioning, which consisted pairings of co-terminating CSs and USs, and trace conditioning, which consisted pairings of CS and US that are separated in time by a stimulus-free trace interval. Earlier studies have suggested that the recruitment of HPC and mPFC is necessary in trace, but not delay, fear conditioning; however, the role of RE in this process remains unknown. In this study, we first used 48 male Long-Evans rats, repeated by three cohorts with 16 rats, to establish that both trace and delay fear conditioning group could achieve equivalent learning and performance. Next, we used 32 Long-Evan rats, repeated by two cohorts with 16 rats, with behavioral pharmacology approach to examine the effects of the pre-conditioning RE inactivation. We hypothesized that RE inactivation would lead to a learning deficit only in trace fear conditioning. Supporting our hypothesis, trace animals demonstrated a down-shift of fear level during retrieval test, indicating that inactivation of RE before conditioning impaired the acquisition of trace fear memory. The results pointed out that RE is recruited and played a critical role in the encoding phase of trace fear conditioning at the behavioral level. Our preliminary data suggested that inactivation of RE before memory retrieval did not interfere with the expression of learned fear in either trace or delay animals, and we are replicating this experiment. Assuming our results hold true, together our data would suggest a "learning phase" specific role of RE and only in trace, but not delayed, fear conditioning.

Disclosures: C. Chang: None.

Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 503.20/ZZ2

Topic: G.01. Appetitive and Aversive Learning

Support: MOST 106-2320-B-007-006-MY3

Title: Midline thalamic nuclei in fear renewal

Authors: *C.-W. SHIH[1], R.-J. CHIOU[2], C.-H. CHANG[1]
[1]Inst. of Systems Neurosci., Natl. Tsing Hua Univ., Hsinchu, Taiwan; [2]Anat. and Cell Biol., Taipei Med. Univ., Taipei, Taiwan

Abstract: In recent years, more and more attention has been paid to explore the pathophysiology of the anxiety disorders, like post-traumatic stress disorder (PTSD), phobia, panic disorder, and obsessive-compulsive disorder (OCD). Pavlovian fear conditioning and extinction is a widely used animal model to study the mechanisms of negative emotion control. In laboratory settings, after the rats acquire the fear response to tones with tone-footshock pairings during conditioning, fear level decreases with repeated presentation of tones alone during extinction. However, extinction does not erase the original conditioned behavior but acts as an active process to modulate learned memory, because extinguished behavior spontaneously recovers with the passage of time and renews outside the extinction context. Earlier literature suggested that context-mediated renewal requires the coordination of the medial prefrontal cortex (mPFC), the hippocampus, and the amygdala. In this study, we used cfos immunoreactivity (IR) to explore whether the midline thalamic nuclei, such as nucleus reuniens (RE) and paraventricular nucleus (PVT), were recruited during fear renewal because of their dense connections with the fear/extinction circuit. We used ABA renewal paradigm, in which the rats were conditioned (5 tone-footshock pairings) in context A, extinguished (45 tones alone) in context B for two days, and then tested (10 tones alone) in context A (DIFF, different from extinction context; n = 10) or context B (SAME, same as extinction context; n = 10). Two control groups were included for comparisons. For no-conditioning controls (NoCOND, n = 6), the animals were presented with the tones but no footshocks during “conditioning”, and for no-extinction controls (NoEXT, n = 6), the rats were placed into chambers for equivalent amount of time without tones during “extinction”. Ninety minutes after the first tone presentation during test, rats were perfused to grasp the peak of cfos expression, followed by tissue processing using standard immunohistochemical procedures to visualize the signals. Our behaviroal results suggested that fear response renewed when the tones were presented outside the extinction context (i.e., in context A). The general cfos expression level in RE was very low in all behavioral conditions (n < 5). Thus, we did not find evidence that RE was recruited during fear renewal. There has been studies pointed out that PVT is recruited in renewal of appetitive behavioral tasks, and we are currently analyzing whether the PVT is also involved in negative emotion control.

Disclosures: C. Shih: None. **R. Chiou:** None. **C. Chang:** None.

Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

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Topic: G.01. Appetitive and Aversive Learning

Support: “MOST 106-2320-B-007-006-MY3” (Taiwan)

Title: Functional lateralization of lateral orbitofrontal cortex on acquisition and expression of fear extinction in rats

Authors: *Y.-H. CHANG, C.-H. CHANG
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Abstract: Our earlier study suggested that the lateral orbitofrontal cortex (lOFC) acts to interfere expression of fear and to impair acquisition of fear extinction when it is activated bilaterally prior to fear extinction training. To investigate the mechanism underlying this effect, we tested whether the lOFC effect is mediated through the projection onto the basolateral amygdala (BLA) using functional disconnection procedure. However, unilateral activation of the lOFC-BLA pathway did not show the behavioral interference of bilateral lOFC activation in fear extinction. To rule out the possibility that the null result is because unilateral activation of the lOFC is not sufficient to induce the effect, we systemically examined unilateral lOFC activation on fear extinction learning in this study. Unilateral left or right, as well as bilateral lOFC, was activated with N-methyl-D-aspartate receptor (NMDA) before fear extinction session, while saline was infused (extinction and no-extinction) as controls. To our surprise, our preliminary data showed distinct differences between animals with left or right lOFC activation. Unilateral activation of the left lOFC, but not the right lOFC, interfered fear expression during extinction session, an effect similar to bilateral lOFC activation. Nonetheless, unilateral activation (left or right), as well as bilateral activation of the lOFC, all abolished the encoding of extinction, in that during retrieval test, all animals displayed equivalently high freezing levels comparable to no-extinction saline controls and were significantly higher than extinction saline animals. We are currently replicating this experiment. Assuming the results hold true, it will suggest a functional dissociation between the left and right lOFC on acquisition and expression of fear extinction.

Disclosures: Y. Chang: None. **C. Chang:** None.

Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 503.22/ZZ4

Topic: G.01. Appetitive and Aversive Learning

Support: MOST 106-2320-B-007-006-MY3

Title: Activation of medial orbital frontal cortex interferes with fear extinction acquisition and fear expression in rats

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Abstract: The medial orbital frontal cortex (mOFC) has been studied for its role in reward-based decision-making in rodents. The similarity between its anatomical projection and that of the medial prefrontal cortex raises the question of whether the mOFC plays a role in memory extinction process. In our previous studies, we reported that activation of the lateral orbital frontal cortex (lOFC) interferes with memory extinction. Therefore, in this study, we sought out to explore the role of mOFC in extinction learning process.
We used a 3-Day Pavlovian fear conditioning and extinction protocol. On Day 1, all rats were conditioned with 5 trials of tone (CS)-footshock (US) pairings. On Day 2, half of the rats underwent extinction procedure (EXT; 45 trials of tones alone), while the other half was placed into the chambers for the equivalent amount of time without tones, serving as no-extinction controls (NoEXT). On Day 3, all rats were tested with 45 trials of tones. The mOFC was activated either immediately before the extinction (pre-extinction) on Day 2 or immediately before the test (pre-test) on Day 3 with N-methyl-D-acidic acid (NMDA) injection through pre-planted cannula or saline as controls. After histology check, a total of 57 male LE rats (31 in pre-extinction and 26 in pre-test), aged from 6 to 7 weeks, were included for final data analyses.
We found that activation of the mOFC resulted in generally low freezing levels in the early trials that developed in amplitude over time regardless of the behavioral stages of interventions (pre-extinction or pre-test) nor the presentation of tones or not (EXT and NoEXT). We also found that activation of the mOFC before extinction on Day 2 abolished the acquisition of extinction learning, for that there was no statistical difference in freezing levels between EXT and NoEXT groups when tested on Day 3, which were equivalently high compared to NoEXT saline controls. Together, these results suggested that activation of the mOFC interfered with the encoding of extinction and fear expression in general.

Disclosures: H. Hsieh: None. **C. Chang:** None.

Poster

503. Fear and Aversive Learning and Memory: Neural Circuitry II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 503.23/ZZ5

Topic: G.01. Appetitive and Aversive Learning

Support: MOST 106-2320-B-007 -006 -MY3

Title: Collateral projections from lateral orbitofrontal cortex to nucleus accumbens and basolateral amygdala

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Abstract: Earlier neuronal tracing studies have shown that lateral orbitofrontal cortex (lOFC) projects to the nucleus accumbens (NAcc) and also projects to the basolateral amygdala (BLA). The lOFC to NAcc pathway and lOFC to BLA pathway each regulates different behaviors, such as compulsive drug seeking and reward-outcome encoding. However, whether the lOFC neurons modulate different downstream targets simultaneously remains unknown. In this study, we examined the connections between lOFC to NAcc and BLA, respectively, and also if there are collateral projections from the lOFC to both the NAcc and BLA. We used in vivo extracellular single unit recordings in anaesthetized rats. The stimulation electrodes were placed in the NAcc and BLA in search of antidromic or orthodromic responsive neurons in the lOFC. A total of 14 neurons were recorded from 9 rats. Among our sampled units, eight neurons projected from lOFC to NAcc with a latency of 8.34 ± 0.97 ms (range 4.49 to 12.01 ms), while five neurons projected from NAcc to lOFC with a latency 6.85 ± 2.22 (range 1.36 to 11.72 ms). We only found one neuron projected from BLA to lOFC with a latency of 26.17 ms, and failed to sample any neurons projected from the lOFC to BLA. Under our filter settings (bandpass 300-10K Hz), two of the sampled neurons (from NAcc to lOFC) have high firing rate (4.75 and 8.53 Hz) with short spike duration (0.80 to 0.78 ms), presumably are interneurons. The spontaneous firing rates of the rest 12 neurons are low (0.32 ± 0.16 Hz, range 0 to 1.8 Hz) with relative long spike duration (2.40 ± 0.25 ms, range 0.38 to 3.60 ms), suggesting the majority of these units are putative projections neurons. To confirm our methodology, we found two neurons adjacent to lOFC during our sampling but excluded from analysis because of histological misplacement, projected to the BLA. Of these two, one (in dorsal endopiriform nucleus) projected to the BLA, and the other (in lateral olfactory tract) had collateral projections to both the NAcc and BLA. Because of the low sampling rate of BLA responsive neurons in the lOFC, we will collect more neurons and further examine whether there is difference in responsive threshold of these two pathways. We will also combine tracer study to examine if there is topographic segregation of NAcc and BLA projections from lOFC.

Disclosures: C. Lai: None. **C. Chang:** None.

Poster

504. Reward Neuropharmacology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 504.01/ZZ6

Topic: G.02. Motivation

Support: NIH DA016285-4

Title: Sex differences in sucrose reinforcement in Long-Evans rats

Authors: *J. W. GRIMM, K. NORTH, M. HOPKINS, K. JIGANTI, P. JOHNSON, A. MCCOY, J. SULC, D. HOVANDER, D. MACDOUGALL, F. SAUTER
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Abstract: Background: There are sex differences in addiction behaviors including consumption and relapse. The present study examined sex differences in these behaviors using a rat model.
Methods: Subjects were adult male and female Long-Evans rats. Rats first self-administered 10% sucrose on a FR1 schedule of reinforcement (40 sec timeout to availability of next reinforcer) in 10 daily 2 hr sessions. Sucrose was paired with a 5 sec tone+light cue. Rats were then tested with different concentrations of sucrose (0, 3.75, 7.5 or 7.5, 15, 30%; counterbalanced) with 3 days of 10% sucrose in between each test. Rats next trained with 10% sucrose on a PR schedule for 7 days and then tested on the PR, with the different concentrations as before, with 3 days of 10% sucrose (PR) in between each test. Finally, rats trained again on a FR1 for 3 days and then had 3 extinction tests with 3 FR1 re-training sessions in between each test. Prior to each extinction test, rats were pre-treated with the dopamine D1 antagonist SCH23390 (0, 1, 10 micrograms/kg, 15 min pretreatment, IP; counterbalanced). In separate cohorts of rats, saccharin preference (2-bottle choice; 4 alternating concentrations of saccharin v. water) and sucrose preference (10% sucrose v. water) were assessed. A final study was conducted with rats responding for water on a FR1 schedule (10 days) and then PR (7 days).
Results: Females responded for more sucrose on both FR and PR schedules of reinforcement, even when not accounting for body weight. Females also responded at a higher rate in extinction. ANCOVA analysis revealed that the extinction sex difference was not accounted for by the higher rate of responding during training. The 10 microgram/kg dose of SCH23390 significantly reduced responding of both males and females. In bottle preference tests, males consumed more saccharin across a range of concentrations (0.075, 0.15, 0.3, 0.6%), but there was no sex difference when considering body weight. Males also consumed more 10% sucrose, although females consumed more when accounting for body weight. In both preference test studies, water consumption was similar between males and females. However, females responded more for water on both FR1 and PR schedules of reinforcement.
Discussion: Female Long-Evans rats are more motivated to respond for sucrose and sucrose-paired cues than males. Their increased avidity for sucrose is not explained by sweet taste preference, or a generally higher rate of operant responding (e.g. Day 10 FR1 active lever training for water for males was 17.8% of sucrose-maintained responding; 14.0% for females). These results provide a robust model for further exploring sex differences in sucrose reinforcement in rats.

Disclosures: J.W. Grimm: None. **K. North:** None. **M. Hopkins:** None. **K. Jiganti:** None. **P. Johnson:** None. **A. McCoy:** None. **J. Sulc:** None. **D. Hovander:** None. **D. MacDougall:** None. **F. Sauter:** None.

Poster

504. Reward Neuropharmacology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 504.02/ZZ7

Topic: G.02. Motivation

Support: Alfred P Sloan Foundation

Title: Serotonin modulates impulse control and motivated action

Authors: *H. B. WEINBERG-WOLF[1], N. A. FAGAN[1], O. DAL MONTE[1], S. W. C. CHANG[2,1]
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Abstract: Serotonergic function is impaired in individuals suffering from disorders with seemingly opposing symptomologies - depression and impulse control disorders. We posit that depression and impulsive aggression are marked by impairments in cognitive effort but that this impairment may result in divergent effects due to individual differences. In some cases, when individuals have a family history or risk of impulsivity, an impairment in cognitive effort can manifest as impulsive action (Carver et. al, 2008). In other cases, like where individuals are at risk of depression, impaired cognitive effort can cause a drive towards inaction that is difficult to overcome, as well as low motivation and the development of clinical depression. However, no study has directly tested this hypothesis by examining how modulating central serotonin impacts impulse control and motivation under varying cognitive effort.
This study attempts to rectify this and examine the role of increasing central serotonin concentrations on impulse control and motivated action in rhesus macaques. We do this by examining performance on a saccade-based go/no-go task, allowing us to investigate not only impulse control, via typically analyzed performance on no-go trials, but also motivated action, by analyzing performance on go trials. We have previously shown that i.m. injections of the serotonin precursor l-5-hydroxytryptophan (5-HTP) effectively increases central concentrations of serotonin in CSF and modulates cognition and behavior in rhesus macaques (Weinberg-Wolf et. al 2018). We now examine how increasing 5-HTP modulates impulse control and motivated action with a repeated, within-subject, go/no-go study design.
Applying the signal detection theory, we observed that 5-HTP impacted both the sensitivity and criterion of responses. Furthermore, 5-HTP impacted both impulse control and motivated action. Critically, these effects were particularly pronounced for trials that required more cognitive effort - trials with longer delays between the onset of the go/no-go cue and the target. These results indicate that increasing central concentrations of serotonin impacts impulse control and motivation. Both of these processes are impacted by differences in cognitive effort, supporting the hypothesis that impaired serotonergic function is linked to depression and impulse control

disorders via a common impairment in cognitive effort.
Carver, C. S., Johnson, S. L., & Joormann, J. (2008). Psychological Bulletin, 134(6), 912-943.
Weinberg-Wolf H, Fagan NA, Anderson GM, Tringides M, Dal Monte O and Chang SWC (2018). Neuropsychopharmacology, DOI: 10.1038/s41386-017-0003-7

Disclosures: H.B. Weinberg-Wolf: None. **N.A. Fagan:** None. **O. Dal Monte:** None. **S.W.C. Chang:** None.

Poster

504. Reward Neuropharmacology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 504.03/ZZ8

Topic: G.02. Motivation

Title: Effects of modafinil on impulsivity, hyperactivity and attention in prepubertal male wistar rats prenatally treated with alcohol

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Abstract: It has been reported that exposure to alcohol in specific stages of prenatal development produces persistent reduction in spontaneous activity of dopamine neurons in the ventral tegmental area, which is normalized with both amphetamines and methylphenidate. Changes in the dopamine system are related with several behavioral disorders, such as the attention deficit hyperactivity disorder (ADHD), which is usually accompanied by high impulsivity. The usual pharmacologic therapy for this symptomatology includes methylphenidate and Atomoxetine. Due to the relative efficiency of these drugs, it has raised the need for the use of other drugs for alleviate that symptomatology; such is the case of modafinil that recently has been used experimentally for the treatment of symptoms of some diseases, which include ADHD, with positive results. However, there are no sufficient studies that support their efficacy. The mechanism of action of modafinil is not clear; however, it has been described that its effects on CNS and behavior are similar to those of methylphenidate; therefore, modafinil has been proposed as an alternative for ADHD treatment. Therefore, the present study sought to identify the effect of different doses of modafinil (0.0, 10, 30 and 60 mg/kg) on the reactive impulsivity in rats treated with prenatal alcohol. Animals were exposed to a “wait to go signal task” and it was observed that animals treated prenatally with sucrose (isocaloric control) show higher number of correct responses than the alcohol treated, and a dose of 30 mg/kg of modafinil reverses significantly this phenomenon during the course of the test. Animals treated prenatally with alcohol and postnatal vehicle, showed higher frequency of commissions (impulsive responses) than their sucrose controls, and the dose of 30 mg/kg, inverted this effect, i.e.,

impulsivity decreased in prenatal alcohol treated rats and it increased in control animals. This phenomenon does not occur with other doses. Additionally, the number of omissions (inattention measure) was increased significantly only in rats treated prenatally with sucrose when 30 mg/kg was administered. These results support that some symptoms of the ADHD are due to an imbalance in the dopamine mediated by other neurotransmission systems and that modafinil action contributes to the normalization of such imbalance. However, the dose-response effect of modafinil, is apparently not linear, since the low and high doses did not produce the beneficial effects of the intermediate dose.

Disclosures: D.M. Gomez-Ordoñez: None. **J. Juarez:** None.

Poster

504. Reward Neuropharmacology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 504.04/ZZ9

Topic: G.02. Motivation

Support: NIH Grant T32 AA007583
NIH Grant R21 DA043190
State University of New York BRAIN Network of Excellence Postdoctoral Fellow program
Whitehall Foundation 2017-12-98

Title: Exendin-4 dose dependently attenuates responding to reward predictive cues in rats

Authors: *K. T. WAKABAYASHI[1], A. N. BAINDUR[2], K. CHEN[2], M. FEJA[2], K. BERNOSKY-SMITH[3], C. E. BASS[2,1]
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Abstract: Exendin-4 (EX4) is a GLP-1 receptor (GLP-1R) agonist used to control blood sugar levels in type-2 diabetes. EX4 has been shown to induce weight loss, which can be attributed to both its peripheral and central effects, most notably in mesolimbic dopamine pathways that mediate cue-induced reward seeking. Behaviorally, GLP-1R agonists influence palatable food preference (e.g. sweet vs. fat) as well as the motivation to obtain different types of food. Recent evidence suggests that GLP-1 receptor activity can attenuate cue-induced reward seeking behaviors, including those that do not involve food. Here we have tested EX4 (0.6, 1.2, and 2.4 μg/kg i.p.) in a sophisticated rat model of incentive cue (IC) responding, in which a rat must emit a nosepoke response into a port during an intermittent audiovisual cue in order to obtain a reward (10% sucrose solution) delivered in an adjacent receptacle. Thus in this task, we interpret the

choice to enter the active nosepoke port or enter the reward cup as quantifiable elements of *response choice*, while the latency to nosepoke in response to an IC, and the latency to enter the reward cup after a reward has been delivered, are reflective of *response vigor*. Therefore, metrics centered on the motivational properties of the IC include response ratio and nosepoke latency, while metrics focused on the sucrose reward include reward cup entries and reward cup entry latencies. We found that EX4 dose-dependently attenuates responding to reward predictive cues, and increases both the latencies to respond to these cues and to enter the reward cup to consume the sucrose reward. EX4 also dose-dependently decreased the number of nosepokes compared to the number of cues presented during the session. However, the number of reward cup entries per reward earned during the session, a related reward-seeking behavior with similar locomotor demand, was not attenuated by EX4. EX4 had different effects on IC responding and nosepoke response latency at the beginning of the session versus the end, depending on the dose, so that the overarching response to 2.4 μg/kg EX4 appeared to be a delay in responding to the first IC in the session. Our findings using a free-operant task heavily reliant on ICs suggest that EX4 agonism, and by extension GLP-1 signaling can directly modulate the incentive properties of cues attributed with motivational significance.

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Poster

504. Reward Neuropharmacology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 504.05/ZZ10

Topic: G.02. Motivation

Support: University of Missouri Life Sciences Fellowship

Title: Influence of physical activity and sex on nucleus accumbens opioid mediated feeding

Authors: *J. R. LEE[1,2], M. A. TAPIA[3], V. N. WEISE[3], J. R. NELSON[3], A. M. TAMASI[3], K. R. FODOR[3], K. L. MASON[3], L. L. RIVERA[3], F. W. BOOTH[4], M. J. WILL[2]
[2]Interdisciplinary Neurosci., [3]Psychology, [4]Biomed. Sci., [1]Univ. of Missouri, Columbia, MO

Abstract: Palatability driven feeding and voluntary physical activity are both regulated via the mesolimbic reward pathway which includes the nucleus accumbens. Like other rewarding behavior, these behaviors are dependent on opioid signaling and are altered following nucleus accumbens opioid administration. In addition, physical activity and palatable diet intake both produce changes in reward related transcription factors within the nucleus accumbens. Recent studies suggest sex dependent effects on both behavioral and physiological adaptations in response to voluntary physical activity. To explore the influence of physical activity on nucleus

accumbens opioid mediated feeding, both male and female Wistar rats were provided access to a voluntary running wheel (RUN group) or no access to a wheel (SED group) and assessed for intake of 2 unique diets. After 2 weeks of RUN or SED treatment, rats were acclimated to testing chambers that contained the 2 diets presented simultaneously, a high-carbohydrate diet and a high-fat diet. After acclimation, intake of both diets were measured with various doses of a mu opioid receptor agonist (DAMGO) (0.025, 0.25 and 2.5 μg/0.25 μl/side) or opioid receptor antagonist (naltrexone) (20/.25ul/side) injected into the nucleus accumbens. Results demonstrate that all groups expressed a slight preference for the high-carbohydrate diet under control treatment. There was an effect of intra-accumbens DAMGO to increase feeding of both the high-carbohydrate and high-fat diet. This effect was greater in females compared to males. In males, the stimulatory effects of feeding were not influenced by physical activity condition for either high-carbohydrate or high-fat diet. In females, there was an interaction between dose of DAMGO and physical activity condition on intake of high-carbohydrate diet, as the there was a difference in intake between RUN and SED in only the 0.025 μg dose. Naltrexone did not alter baseline intake, but did block the increased diet intake induced by the high dose of DAMGO in all groups.

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Poster

504. Reward Neuropharmacology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 504.06/ZZ11

Topic: G.02. Motivation

Support: MH 074723

Title: Feeding elicited by mu-opioid receptor stimulation in the prefrontal cortex and nucleus accumbens: An exploration of sex differences and estradiol regulation

Authors: *B. A. BALDO[1], J. DIAZ[2], K. DUNAWAY[3], K. SADEGHIAN[1], A. AUGER[4]
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Abstract: Infusion of the mu-opioid agonist DAMGO ([D-Ala2, N-Me-Phe4, Gly5-ol]-enkephalin) in the ventromedial prefrontal cortex (vmPFC) and the nucleus accumbens (Acb) induces food impulsivity and abnormally high food motivation, two features of binge eating disorder. In animal models, vmPFC or Acb mu-opioid-driven feeding has been studied primarily in males, but has received little attention in the context of sex differences. We hypothesized that

mu-opioid driven feeding could be sexually dimorphic because (1) women are more vulnerable to eating disorders, (2) in animal self-administration studies, estrogen facilitates opiate self-administration at an early post-estrogen time point, and (3) estrogen inhibits food intake (although effects on telencephalic opioid-driven feeding are not well understood). Hence, we evaluated feeding induced by mu-opioid stimulation in the vmPFC and Acb across gender and estradiol status in *ad-libitum*, chow fed rats. First, we assessed sex differences independent of estradiol by obtaining DAMGO dose-response curves in the vmPFC and Acb for ovariectomized (OVX) females without estrogen replacement and compared these effects to those seen in males. Next, we explored the effects of intra-vmPFC and intra-Acb DAMGO in OVX females given 5μg estradiol benzoate (EB) subcutaneously to evaluate acute (cell-surface receptor-mediated) and delayed (canonical genomic-mediated) effects of EB. To assess acute and delayed estrogenic effects, DAMGO-induced food intake was measured in 2-hour testing sessions both immediately post-EB administration and 24 hours post-EB. Males and females had similar DAMGO-induced dose-dependent increases in food intake; however, OVX females consumed significantly more chow when a high 2.5μg DAMGO dose was infused in the Acb. In OVX females treated with EB, both intra-vmPFC and intra-Acb DAMGO-induced feeding was inhibited 24-26 hours post-EB, but was unchanged directly after EB administration. These data suggest a slight intrinsic sex difference in intra-Acb mu-opioid sensitivity independent of the activational properties of estradiol. Additionally, our studies revealed a modulatory role of systemic EB at the delayed post-EB time-point, suggesting that genomic-mediated effects of EB exert regulatory control over telencephalic mu-opioid-responsive feeding circuits.

Disclosures: J. Diaz: None. **K. Dunaway:** None. **K. Sadeghian:** None. **A. Auger:** None.

Poster

504. Reward Neuropharmacology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 504.07/ZZ12

Topic: G.02. Motivation

Support: Psi Chi Undergraduate Research Grant (to CD)

Title: Examining the impact of orexin A and GLP-1 receptor manipulation on feeding induced by nucleus accumbens μ-opioid receptor stimulation of the rat

Authors: *Z. PIERCE-MESSICK[1], C. DO[2], M. C. NIGRO[2], R. VACA-TRICERRI[2], W. E. PRATT[2]
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Abstract: Recent work has shown that neuropeptides and peptide hormones that regulate homeostasis may additionally impact food intake by directly acting on brain regions that process

the palatable and rewarding nature of a diet. For instance, Orexin A and GLP-1 receptors are both found within the nucleus accumbens (NAcc), a brain region involved in promoting the consumption of palatable diets. Our laboratory and others have reported that stimulation of μ-opioid receptors in the NAcc with DAMGO potently increases feeding on palatable, fatty diets, but it is not known if or how this feeding effect might be impacted by orexin or GLP-1 signaling. To examine this directly, these experiments assessed the effects of stimulating or blocking NAcc Orexin A or GLP-1 receptors in rats co-treated with DAMGO. Male Sprague-Dawley rats (n = 8/group) were surgically implanted with bilateral guide cannulas targeting the NAcc. Upon recovery, they were acclimated to 2-hr daily feeding sessions during which they had free access to a sweetened fat diet and water. On subsequent drug testing days, four groups of rats received NAcc saline or DAMGO infusions (0.025 μg/side) in a cocktail with either Orexin A (0, 1.78, or 3.56 microg/side), the Orexin A antagonist SB3348670 (at 0, 0.16, or .32 μg/side), the GLP-1 agonist Exendin-4 (at 0, 0.05, or .10 μg/side), or the GLP-1 antagonist Exendin-9 (at 0, 2.5, or 5.0 μg/side). Each rat randomly received all possible combinations of their DAMGO/drug injections across 6 treatment days. Food and water intake, rearing, and ambulatory behavior were monitored throughout each session. Consistent with previous reports, stimulation of NAcc μ-opioid receptors significantly increased consumption of the high-fat diet. Although Orexin A tended to increase feeding when given on its own, co-injecting DAMGO with Orexin A transiently inhibited DAMGO-induced feeding, but had no impact on total diet eaten by the end of the 2-hr session. Blocking Orexin A receptors did not impact food intake in the presence of μ-opioid receptor stimulation. In contrast, stimulation of NAcc GLP-1 receptors inhibited DAMGO-elicited feeding, and reduced ambulatory activity. Blockade of the GLP-1 receptor resulted in a significant three-way interaction of the two drugs and time across the feeding session. Preliminary analyses suggest that GLP-1 receptor blockade did not affect feeding when given alone, but may have enhanced food intake in response to μ-opioid receptor stimulation. These studies suggest that food intake that is directed by opioid receptors in the nucleus accumbens may, in some cases, be co-modulated by peptides associated with the regulation of homeostasis and energy balance.

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Poster

504. Reward Neuropharmacology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 504.08/ZZ13

Topic: G.02. Motivation

Title: Inactivation of the lateral habenula increases locomotion and differentially impacts feeding on palatable or pabulum diets

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Abstract: Overconsumption, or eating beyond the point of homeostasis, is a key feature in the development of obesity. Although people are consuming beyond the point of homeostasis, they are not consuming constantly or indefinitely. Thus, there is likely a mechanism that acts to terminate periods of food intake at some point beyond satiation and prior to aversion, or the negative effects of extreme excess (nausea, bloating, etc.). The purpose of the present study was to assess the lateral habenula as a candidate region for such a mechanism, due to its connectivity to midbrain reward circuitry, sensitivity to metabolic signaling, and pronounced role in drug-related motivated behaviors. Two groups of male Sprague-Dawley rats were surgically implanted with bilateral guide cannula targeting the LHb. Rats were then habituated to feeding chambers, wherein locomotion and food intake were monitored throughout a two-hour session. One experimental group was tested in the presence of rat chow; the second group was instead given access to a sweetened fat diet. Across four injection days, each individual rat separately received a 0.2 µl vehicle (0.9% saline solution) and baclofen-muscimol (50ng/0.2µL of each drug dissolved in 0.9% saline) injection, first in an *ad libitum* state, and then following 22 hours of food deprivation. Additionally, on a fifth injection day, each rat received an injection of mu-opioid agonist DAMGO (0.1 µg/0.2 µl) prior to placement in the chamber. In the first experiment (N = 6), inactivation of the LHb attenuated feeding of deprived animals on a sweetened-fat diet, but had no significant impact on the feeding behavior of sated animals. Specifically, inactivation of the LHb appeared to enhance feeding early in the session when the animals were offered the sweetened-fat diet in a sated condition, but reduced feeding compared to the vehicle injections when subjects were deprived for 22 hours prior to entering the feeding chamber. Interestingly, subjects consumed less of the sweetened-fat diet following 22 hour deprivation, regardless of inactivation. In the second experiment (N = 8), inactivation did not alter feeding of the standard chow diet in deprived or sated conditions. LHb inactivation also produced a consistent increase in locomotor activity across all conditions and in both experimental groups. Furthermore, mu-opioid stimulation increased feeding on standard chow, but decreased intake of the sweetened-fat diet. Although LHb inactivation did not increase feeding as predicted, these are the first data to suggest a possible role for the LHb in directing food intake on palatable foods when rats are food restricted.

Disclosures: H.N. Carlson: None. **B. Christensen:** None. **K. Cowie:** None. **W.E. Pratt:** None.

Poster

504. Reward Neuropharmacology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 504.09/ZZ14

Topic: G.02. Motivation

Support: Center of Molecular Signaling Grant, Wake Forest Univerity

Title: Stimulation of nucleus accumbens mu-, delta-, or kappa-opioid receptors differentially affect effort-based choice in the rat

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Abstract: The nucleus accumbens (NAcc) is critical for regulating appetitive and consummatory phases of motivated behavior. Stimulation of nucleus accumbens μ- and δ-opioid receptors increases food consumption, particularly in the presence of highly palatable foods. Previous experiments in our laboratory have suggested that stimulation of NAcc μ-opioid receptors may shift the motivational state of the rat from appetitive food-seeking to an emphasis on consummatory processes. To test this formally, rats were trained to lever press for sucrose pellets on a progressive-ratio 2 (PR2) schedule, and then offered the choice to work for sugar pellets or to eat freely available rat chow following stimulation of μ-, δ-, or κ receptors of the NAcc. Male Sprague-Dawley rats (n = 12/group) were food restricted to 90% *ad libitum* weight and trained on a PR2 schedule to earn sugar pellets. Following training, food was returned, and rats were surgically implanted with bilateral guide cannulas targeting the NAcc core. Rats were then retrained on the PR-2 task, with rat chow also freely available in the operant chamber. Access to the sugar-associated lever and the food was continuous throughout each 1-hr session. Separate groups were tested following μ-opioid receptor stimulation (with 0, 0.025, and 0.25 μg DAMGO/side), δ-opioid receptor stimulation (with 0.31, 3.1 D-Pen/side), or κ-receptor stimulation (with 0.0, 0.186, and 1.86 μg/side U-50488 hydrochloride; doses were equimolar across the separate drugs). Individual rats in each drug group were tested on all doses of a single drug across three test days, and then again following 24-hr food restriction (for a total of six drug testing days). 23-hrs of food deprivation increased feeding on the available rat chow but did not reliably alter breakpoint across these experiments. Stimulation of NAcc μ-opioid receptors shifted rats' behavior away from sugar-seeking by reducing break point for the sucrose, and increased the consumption of the freely available rat chow. In contrast, stimulation of δ opioid receptors increased both feeding on the rat chow and the effort expended to earn sugar pellets; this effect appeared to be driven by increases when the animals were not food restricted during testing. Stimulation of NAcc κ receptors had no significant overall effects on food intake or lever-pressing, though there was a trend for an increased breakpoint across drug doses on days when the animals were not food-restricted. These data confirm prior reports indicating that μ- and δ-receptors of the nucleus accumbens facilitate consummatory behavior, and suggest that δ receptors may also impact appetitive motivation by impacting NAcc circuitry.

Disclosures: W.E. Pratt: None. **H.N. Carlson:** None. **C. Murphy:** None.

Poster

504. Reward Neuropharmacology

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Program #/Poster #: 504.10/ZZ15

Topic: G.02. Motivation

Support: R01-DA-038599
NSF GRFP

Title: Elucidating the interaction between glucocorticoids and dopamine in an animal model of individual variation in cue-motivated behaviors

Authors: *S. A. LOPEZ[1], A. VALENTA[2], P. CAMPUS[4], R. T. KENNEDY[2], S. B. FLAGEL[3]
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Abstract: Learning to associate cues in the environment with appetitive and/or aversive stimuli allows organisms to develop a behavioral repertoire fit to obtain valuable resources or avoid danger. Cues, however, can also gain inordinate control and elicit maladaptive behaviors. For example, addicts often relapse upon exposure to cues previously associated with the drug-taking experience. Using an animal model that captures individual variation in response to reward-cues, we are able to examine the neurobiological processes that contribute to such cue-driven psychopathologies. Rats that undergo Pavlovian training, consisting of cue presentation followed by delivery of a food reward, will often develop either a sign- or goal-tracking conditioned response. For both sign-trackers (STs) and goal-trackers (GTs) the cue attains predictive value, but for STs the cue also attains incentive value. The attribution of incentive value to the cue transforms it into a "motivational magnet", rendering it attractive and desirable for STs, but not GTs. It has been shown that different brain circuits are engaged in response to the cue in STs vs. GTs, and that dopamine (DA) is necessary for incentive (i.e. sign-tracking), but not predictive (i.e. goal-tracking) learning processes. DA has long been known to interact with corticosterone (CORT), the main glucocorticoid in rodents, to mediate motivated behaviors; yet little research has been done to directly investigate the interaction between these two molecules in the context of sign- and goal-tracking behaviors. Here we assessed the relationship between peripheral and brain CORT levels and the mesocorticolimbic DA system in male and female STs and GTs. To do so, samples were obtained via tail nick (CORT) and *in vivo* microdialysis (CORT, DA) within the nucleus accumbens before and after sessions 1 and 6 of Pavlovian training. This experimental design allowed us to assess CORT/DA interactions prior to acquiring a conditioned response and following the development of sign- and goal-tracking behavior. We found that female rats tend to have greater peripheral CORT levels, but there do not appear to be sex differences in brain CORT levels. There were no apparent sex differences in brain DA levels, but STs of both sexes

show greater CORT and DA during Pavlovian conditioning relative to GTs. Ongoing studies are assessing whether differential expression of glucocorticoid receptors throughout the mesocorticolimbic system may be contributing to these results. These data contribute to our understanding of the role of glucocorticoids in DA-dependent learning processes that are relevant to cue-motivated psychopathologies.

Disclosures: S.A. Lopez: None. **A. Valenta:** None. **P. Campus:** None. **R.T. Kennedy:** None. **S.B. Flagel:** None.

Poster

504. Reward Neuropharmacology

Location: SDCC Halls B-H

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Program #/Poster #: 504.11/ZZ16

Topic: G.02. Motivation

Support: NIDA Grant R01 DA038599

Title: Elucidating the role of cortico-thalamic-striatal circuitry in cue-reward learning

Authors: *P. CAMPUS[1], Y. KIM[2], B. N. KUHN[3], S. A. LOPEZ[3], I. RIVERO-COVELO[1], S. M. FERGUSON[5], M. SARTER[2], S. B. FLAGEL[4,1]
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Abstract: When cues in the environment are repeatedly associated with rewards, they acquire predictive value and become conditioned stimuli (CS), eliciting a conditioned response. However, such cues can also acquire incentive value, gaining the ability to trigger motivational states that can lead to dysfunctional behaviors. Individuals vary considerably in the extent to which they attribute motivational value to reward-cues. In a Pavlovian Conditioned Approach (PCA) task, in which the presentation of a lever-cue is immediately followed by the delivery of a food reward, some rats approach the lever-cue (sign-trackers, ST) while others approach the food cup (goal-trackers, GT). Importantly, while the lever-cue is a predictor for both ST and GT, it only becomes an incentive stimulus for ST. It has been previously shown that the sign-tracking response is dopamine (DA) dependent, but the goal-tracking response is not. Further, presentation of the lever-cue engages different neural circuitry in sign-trackers vs. goal-trackers. The sign-tracking response appears to be mediated primarily by subcortical mechanisms; whereas goal-tracking behavior appears to depend on “top-down” cortical engagement. We recently demonstrated that the paraventricular nucleus of the thalamus (PVT) represents a key node that integrates subcortical and cortical input differentially in ST and GT. Together, these data led us to hypothesize that in GT, the prelimbic cortex (PrL) to PVT pathway may serve to

suppress subcortical processes critical for the expression of sign-tracking. In support of this view, activation of the PrL-PVT circuit in ST, using Designer Receptors Exclusively Activated by Designer Drugs (DREADD) decreases sign-tracking behavior. In contrast, inhibition of PrL-PVT pathway in GT increases sign-tracking behavior. Here, we investigated the effects of selective manipulation of the PrL-PVT pathway on extracellular levels of DA in the NAc of ST and GT. To this end, we used a dual viral vector approach to selectively express stimulatory Gq- or inhibitory Gi/o- DREADD in PrL to PVT projecting neurons. Clozapine-N-oxide (CNO) (3 mg/kg) was administered (i.p.) to activate DREADD during Pavlovian conditioning while levels of DA and other neurotransmitters in the NAc were assessed using in vivo microdialysis. In agreement with the behavioral effects mentioned above, "turning on" the PrL-PVT pathway reduced DA in the NAc of ST while, "turning off" the PrL-PVT pathway in GT increased DA levels. Therefore, the cortico-thalamic-striatal pathway seems to be differentially "tuned" to mediate individual variation in cue-motivated behaviors.

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Poster

504. Reward Neuropharmacology

Location: SDCC Halls B-H

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Program #/Poster #: 504.12/ZZ17

Topic: G.02. Motivation

Support: NIDA Grant R01DA038599
NIDA T32DA007821

Title: The effects of chemogenetic inhibition of a "top-down" cortico-thalamic circuit on individual variation in cue- and cocaine-induced drug-seeking behavior

Authors: *B. N. KUHN[1], P. CAMPUS[2], M. S. KLUMPNER[3], S. B. FLAGEL[4]
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Abstract: Relapse remains the biggest problem in the treatment of addiction, and is often triggered by stimuli (e.g. drug paraphernalia) that have been previously associated with the drug-taking experience. Such cues become powerful motivators and gain the ability to elicit drug-seeking behaviors when attributed with incentive salience, a process that occurs via Pavlovian learning. Importantly, however, only for some individuals are such cues transformed into incentive stimuli and attain inordinate control over behavior. We are able to capture individual variation in the propensity to attribute incentive salience to reward-paired cues using an animal model. In this model, sign-trackers (STs) are rats that attribute incentive salience to a reward-

predicting cue, and approach and manipulate the cue upon its presentation; whereas goal-trackers (GTs) assign only predictive value to the cue and go to the location of reward delivery upon cue presentation. Intermediate rats (INs) vacillate between these two conditioned responses. Relative to GTs, STs are more impulsive, more motivated to take cocaine and more susceptible to cue- and cocaine-induced reinstatement. These phenotypes also engage distinct neural mechanisms in response to reward-associated cues. The paraventricular nucleus of the thalamus (PVT) has been recognized as a central node that mediates both sign- and goal-tracking behavior, but via different circuit dynamics. Data from our lab support a role for projections from the prelimbic cortex (PrL) to the PVT in differentially mediating sign- and goal-tracking behaviors. Here we investigated the role of this pathway in regulating individual differences in cue- and drug-induced drug-seeking behavior. To do so we used a dual-vector approach to selectively express inhibitory (G_i) DREADD (Designer Receptors Exclusively Activated by Designer Drugs) in the PrL-PVT pathway. Rats were characterized as STs, INs or GTs based on their behavior during a Pavlovian conditioned approach task and then underwent 2 weeks of cocaine self-administration followed by 4 weeks of abstinence and then extinction training. Prior to the tests for reinstatement, rats received either vehicle or clozapine-N-oxide (5 mg/kg) to activate the DREADD. Inhibition of the PrL-PVT pathway causes an increase in drug-induced reinstatement, independent of phenotype. In contrast, only INs show an increase in cue-induced reinstatement, such that "turning-off" this top-down circuit renders them comparable to STs. The PrL-PVT circuit, therefore, appears to inhibit drug-seeking behavior, but does so to a different degree depending on the stimulus (drug vs. cue) and phenotype (STs, GTs, INs).

Disclosures: B.N. Kuhn: None. **P. Campus:** None. **M.S. Klumpner:** None. **S.B. Flagel:** None.

Poster

505. Post-Traumatic Stress Disorder: Human Studies

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 505.01/ZZ18

Topic: G.06. Post-traumatic Stress Disorder

Title: Instructed extinction learning: Neurocircuity of additive effects of instruction on emotional learning of safety

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Abstract: $$MISSING OR BAD TABLE SPECIFICATION {62C59324-9250-40B9-8829-019AA1199AF2}$$

One-sample t-test comparing functional activity CS+I v. CS+U ($\alpha < 0.005$).

Region	**Area**	**Z Score**	**P Value**	**ClusterSize**	**x**	**y**	**z**
Insula	Right Insular	3.4417	0.0001	345	39	-4	-1
Hippocampus	Left Hippocampus	3.0119	0.0013	37	-38	-27	-15
Hippocampus	Right Hippocampus	3.3985	0.0001	63	38	-33	-13
Cingulate Cortex	Right AnteriorCingulate	2.8196	0.0024	10	5	29	-7
Superior Frontal Gyrus	Left Superior Frontal Gyrus	3.56	0.002	15	-17	10	53
Ventral Medial Prefrontal Cortex	Left vmPFC	2.8284	0.0023	20	-9	58	4
Middle Frontal Gyrus	Right Mid Frontal Gyrus	2.9271	0.0017	27	29	7	55
Inferior Frontal Gyrus	Right Operculus	2.9931	0.0014	17	60	14	8
Parahippocampus	Right Parahippocampus	3.27	0.001	47	36	34	-12
Dorsal Medial Prefrontal Cortex	Left dmPFC	3.0741	0.0011	730	-41	10	52
Dorsal Medial Prefrontal Cortex	Right dmPFC	3.0323	0.0012	730	-6	47	47
Dorsal Lateral Prefrontal Cortex	Left dlPFC	3.0741	0.0011	311	-41	10	52
Middle Frontal Gyrus	Left Middle Frontal Gyrus	3.1017	0.001	730	-27	29	52

Mask applied for areas involved in extinction learning (hippocampus, parahippocampus, frontal cortex

Extinction learning is laboratory model for exposure therapy. Safety learning can happen through instruction, observation, or experience. Our knowledge of combined effects of instruction and experience in extinction learning is limited. This is one of the first functional neuroimaging studies to examine combined effects of instruction with experiential learning of safety in a within subject design. We hypothesized that instruction would recruit areas involved in emotion regulation.14 healthy participants (m = 7; mean age = 20; 3T Siemens Verio) underwent two consecutive days of scanning. Habituation, conditioning, and extinction learning took place on

day 1; recall on day 2. Participants were conditioned to two stimuli paired with a loud noise (CS+). Prior to extinction learning, absence of the noise was informed for one of the two CS+ (CS+I). fMRI data were preprocessed and analyzed using typical methods (SPM12). Here, we present preliminary extinction data. A mask for the hypothesized ROIs was applied, and a one sample t-test was used to compare brain activation between CS+I and the Uninformed CS+. Extinction data showed higher activation in areas involved in contextual processing and emotion regulation (bilateral parahippocampal gyrus, right hippocampus, bilateral insula, and Brodmann's Area 9), when instruction was combined with experiential learning. Integrating instruction with exposure-based treatment may improve extinction learning by involving additional networks. This line of research will help explore potential deficits in processing of cognitive context in PTSD and GAD, with therapeutic implications.

Disclosures: I. Liberzon: None. **S. Madaboosi:** None. **A. Chowdry:** None. **A. Javanbakht:** None.

Poster

505. Post-Traumatic Stress Disorder: Human Studies

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Program #/Poster #: 505.02/ZZ19

Topic: G.06. Post-traumatic Stress Disorder

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Clinical Trials.gov NCT number: NCT01524133

Title: Resting-state functional connectivity is associated with treatment outcome in PTSD patients

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Abstract: Resting-state functional connectivity (rsFC) magnetic resonance imaging (MRI) represents a powerful method for illuminating brain network function. Moreover, it has a particular relevance for posttraumatic stress disorder (PTSD), where abnormalities in rsFC have recently been demonstrated. The current study is part of the PROlonGed ExpoSure and Sertraline Trial (PROGrESS; Rauch et al. *Contemporary Clinical Trials*, 2018), and examined the role that rsFC abnormalities might play in therapeutic interventions in PTSD. Methods: Sixty-one military veterans with PTSD were assigned to evidence-based treatment groups: Prolonged Exposure (PE) plus placebo, Sertraline (SERT) plus enhanced medication management, or PE/SERT. Twenty-nine veterans without PTSD were recruited as a control group. Symptom assessment and MRI scanning occurred before and after treatment. Seed-based results were thresholded at p=.001 uncorrected and then subsequently, at p<.050 (FWE) at the cluster level. Results: At baseline, seed-based analyses revealed that PTSD was associated with lower connectivity between PCC, vmPFC and other default-mode network (DMN) regions, replicating prior findings of decreased within-DMN connectivity in PTSD. In contrast, PCC and vmPFC, as well as the insula (salience-network (SN) seed), had greater connectivity with regions within dorsal-attention network (DAN) in patients, which is in line with the cross-network desegregation in PTSD. Graph-theoretic analysis showed that DMN and DAN were also characterized by decreased small-worldness in patients, further suggesting these networks' decreased integration in PTSD. When testing treatment effect, we found that patients who responded to treatment had lower baseline amygdala-PCC connectivity, supporting the importance of DMN-SN segregation in PTSD. In sum, these findings confirm and extend our knowledge of network-level abnormalities in PTSD, and importantly, propose a neural biomarker to predict successful response to treatment.

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Poster

505. Post-Traumatic Stress Disorder: Human Studies

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Program #/Poster #: 505.03/ZZ20

Topic: G.06. Post-traumatic Stress Disorder

Support: W81XWH-11-2-0166
Dielmann Family Genetic and Environmental Risk Endowment

Title: Divergent astrocyte gene expression changes in post-mortem autism and PTSD cortex

Authors: *K. A. YOUNG[1,2,3], K. A. KUSTER[3,2], D. L. CORCORAN[4], D. A. CRUZ[5], D. E. WILLIAMSON[5,6]
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Abstract: Astrocytes support neurotransmission in the cortex through a variety of functional mechanisms. While their role in reactive gliosis in response to CNS damage is widely recognized, astrocytes also form the neurovascular unit, linking neurons to the circulatory system and providing trophic support and peri-neuronal maintenance. A recent study has identified up-regulated astrocyte gene expression in cortex of autistic brains, and suggests that astrocytosis, astroglial activation, or both may be occuring (Gandal et al., 2018, PMID:29439242). Using this recently published data, we compared and contrasted post-mortem gene expression changes in autism and PTSD. Differential PTSD gene expression changes in 6 PTSD cases and 8 controls was determined in the medial orbitofrontal cortex using Illumina microarrays, quantile normalization and standard data cleaning procedures. We previously reported evidence for reductions in overall and mushroom spine density in the mOFC in these 14 cases (Young et al., 2015; PMID:26844242). Using data from purified mouse brain cells (Zhang et al., 2014 PMID:25186741), we identified a set of 119 astrocyte-specific genes with at least 16X higher expression in astrocytes compared to neurons, mature oligodendrocytes, microglia and endothelial cells. Gene set enrichment analysis (GSEA) indicated that astrocyte-specific genes were highly up-regulated in both autism and PTSD (FDR q's> 0.0001). We next identified a set of gene transcripts up-regulated in rodent models of middle coronary artery occlusion and LPS-induced astrogliosis (N=199; Zamanian et al., 2012 PMID:22553043) and a set of gene transcripts found in astrocyte endfeet making contact with blood vessels (N=49; Boulay et al.. 2017, PMID:28377822). Astrocyte endfeet genes were selectively up-regulated in PTSD (FDR q> 0.0001) compared to autism (NS), while astrogliosis genes were selectively up-regulated in autism (FDR q<0.0001) compared to PTSD (NS). Although astrogliosis has been noted in several studies of autism, the robust gene expression response observed above suggests that additional studies of classical reactive astrocyte responses may be warranted. Post-mortem studies of PTSD are very limited, and this is the first observation of astrocyte responses in PTSD brain. The lack of a strong astrogliotic signal and the presence of robust up-regulation of astrocyte neurovascular unit transcripts in PTSD suggests that trophic, neuroprotective and/or maintenance functions of astrocytes are up-regulated in PTSD orbitofrontal cortex.

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Poster

505. Post-Traumatic Stress Disorder: Human Studies

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Program #/Poster #: 505.04/ZZ21

Topic: G.06. Post-traumatic Stress Disorder

Support: VAI01RX000825
NIH/NEI R01EY024554

Title: Increased PTSD severity reduces the discriminability of neutral compared to fearful face stimuli in a pharmacological fMRI study of working memory

Authors: *A. J. WESTPHAL[1,2,3], N. RODRIGUEZ[1,2,3], M. BALLARD[1,2,3], T. VEGA[1,2,3], A. S. KAYSER[1,2,3]
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Abstract: Working memory is compromised in anxiety disorders such as post-traumatic stress disorder (PTSD). This impairment is thought to result from multiple cognitive changes, including reductions in cognitive control over working memory representations and overgeneralization from fearful to neutral stimuli. We hypothesized that enhancing cortical dopamine tone through use of the COMT inhibitor tolcapone would improve mnemonic discriminability between fearful and neutral faces. In the present study, 26 participants with a range of post-traumatic stress disorder severity scores (range: 0 - 68, SD: 20.66), assessed by the CAPS PTSD scale, underwent fMRI scanning while completing an emotional working memory task after the randomized, double-blind administration of either tolcapone or placebo. The working memory task involved the presentation of three consecutive face stimuli, either all fearful or all neutral, with instructions to remember all three faces (high load condition) or only the final face (low load condition). During the intervening delay period after the cues were shown, participants indicated whether distractor stimuli were faces or scenes. Participants then rated whether the probe face stimulus, 50% of which were novel, was presented during the cue phase.
Task behavioral data specifying whether the cue period contained fearful or neutral expressions were entered into separate linear mixed models, along with drug session and CAPS and their interactions, predicting either mnemonic discriminability (d') or response bias. The model predicting d' showed an interaction between cue expression and CAPS, such that less severe PTSD severity (1 SD below mean and mean CAPS) was associated with better performance on trials with neutral expressions than with fearful expressions, while more severe PTSD (1-2 SDs above mean) was associated with non-significant d' between cue emotions. There was also a significant interaction between CAPS and administered drug, such that drug 2 did not affect d' for less severe PTSD, but did improve performance for more severe PTSD. The study currently

remains blinded. The model predicting response bias demonstrated a 3-way interaction between CAPS, cue expression, and drug session such that participants exhibited more liberal responding to fearful cues for drug 1, a finding that was exacerbated by more severe PTSD and alleviated by administration of drug 2. In contrast, participants with less severe PTSD exhibited a more conservative response tendency to neutral cues for drug 2, a result that was not shown in severe PTSD patients (2 SDs above mean CAPS). Ongoing imaging analyses will evaluate the neural correlates of these findings.

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Poster

505. Post-Traumatic Stress Disorder: Human Studies

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Topic: G.06. Post-traumatic Stress Disorder

Support: Department of Defense Research Grant (W81XWH-10-1-0925)
SD Governor's Research Center Grant

Title: Prefrontal activation during cognitive control of emotional processing in posttraumatic stress disorder is influenced by hazardous alcohol use in veterans

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Abstract: Many affective disorders including posttraumatic stress disorder (PTSD), depression, and anxiety are characterized by alterations to executive function, such as cognitive control of emotional processing. A number of prefrontal regions are implicated in such processing, including the ventrolateral (vlPFC) and dorsomedial (dmPFC) prefrontal cortices. However, there is some debate as to how these regions contribute to deficits in cognitive control of emotional processing as revealed by the emotional Stroop task. Numerous computational and neurocircuitry models predict that the Stroop effect elicited by emotional distractors would be associated with reduced prefrontal activity. This stands in contrast to a recent meta-analysis of control and clinical populations demonstrating increased activity in the vlPFC and dmPFC during negative word conditions of an emotional Stroop task. The purpose of the current study was to further examine the role of the vlPFC and dmPFC in cognitive control of emotional processing in veterans with and without current PTSD symptoms. Given that 50-85 % of individuals with PTSD exhibit hazardous alcohol use, we also sought to explore the contribution of hazardous alcohol use to prefrontal-based emotional processing. Ninety-eight male and female

right-handed veterans of Operations Enduring Freedom and Iraqi Freedom (OEF/OIF) were assessed for combat intensity, PTSD symptoms, alcohol use and alcohol dependence, and other mental and physical health indices. Participants underwent functional magnetic resonance imaging (fMRI) while performing the emotional counting Stroop task adapted for OEF/OIF veterans, with reaction time and errors recorded. A region of interest analysis was performed blind to PTSD or alcohol status and focused on changes in activity within the vlPFC and dmPFC. In line with the recent neuroimaging meta-analysis, left vlPFC and dmPFC activity increased during negative conditions across all participants. While all participants were combat-exposed, a clear Stroop effect for combat-related words was only observed for individuals with PTSD symptoms. However, greater activity of the left vlPFC and dmPFC during the combat condition was observed for participants reporting hazardous alcohol use, rather than being directly related to the presence of PTSD symptoms. Overall, findings suggest that prefrontal regions are engaged during the processing of emotional distractors. However, current results also suggest that activity of prefrontal regions during cognitive-based emotional processing in clinical populations should be interpreted in the context of the individual's alcohol use.

Disclosures: G.L. Forster: None. **R. Simons:** None. **J. Simons:** None. **L. Baugh:** None. **V. Magnotta:** None.

Poster

505. Post-Traumatic Stress Disorder: Human Studies

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 505.06/ZZ23

Topic: G.06. Post-traumatic Stress Disorder

Support: VA National Center for PTSD Brain Bank

Title: Neuroactive steroid levels in the orbital frontal cortex of subjects with posttraumatic stress disorder and controls

Authors: *D. A. CRUZ[1], K. D. MCGAUGHEY[1], G. PARKE[1], L. J. SHAMPINE[1], J. KILTS[1], J. NAYLOR[1], C. E. MARX[1,2], D. E. WILLIAMSON[1,2]
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Abstract: Neuroactive steroids mediate stress signaling pathways and have been implicated in the pathogenesis of posttraumatic stress disorder (PTSD). Measures of neuroactive steroid levels in peripheral blood and cerebrospinal fluid in subjects with PTSD show abnormal levels compared to controls. Additionally, both clinical and pre-clinical studies have shown that neuroactive steroids, particularly those that impact GABAergic neurotransmission, are decreased in PTSD with differential changes based on sex. Functional imaging studies of PTSD show hypoactivity of the ventromedial prefrontal cortex, including the medial orbital frontal cortex.

This study examines neuroactive steroid levels in the orbital frontal cortex of subjects with PTSD (n=18) and normal controls (n=40). Gray matter (80mg) was dissected from fresh-frozen medial orbital frontal cortex and the neuroactive steroids pregnenolone, pregnanolone, allopregnanolone, epiallopregnanolone, epipregnanolone, THDOC, and androsterone levels were determined by gas chromatography-mass spectrometry (GC/MS/MS) methodology with a limit of detection of 1 pg. The results identified significant interactions between sex and PTSD for pregnanolone ($F1,43 = 7.52$, $P < 0.01$) that was due to PTSD females having higher levels of pregnanolone ($F1,43 = 8.71$, $P < 0.005$) compared to control females. There was also a significant interaction between sex and PTSD for epiallopregnanolone ($F1,45 = 4.97$, $P < 0.031$) that was due to PTSD females having significantly higher levels compared to PTSD males ($F1,45 = 9.73$, $P < .003$)) but not control females ($F1,45 = 2.20$, $P < 0.145$). These data suggest that there may be sex differences in neuroactive steroids in subjects with PTSD. Future directions include expanding the number of subjects in these cohorts in order to gain better insight into sex differences in neuroactive steroid levels in subjects with PTSD. In addition, we will measure neuroactive steroids in other brain regions to determine regional distribution.

Disclosures: D.A. Cruz: None. **K.D. McGaughey:** None. **G. Parke:** None. **L.J. Shampine:** None. **J. Kilts:** None. **J. Naylor:** None. **C.E. Marx:** None. **D.E. Williamson:** None.

Poster

505. Post-Traumatic Stress Disorder: Human Studies

Location: SDCC Halls B-H

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Program #/Poster #: 505.07/ZZ24

Topic: G.06. Post-traumatic Stress Disorder

Support: Univ. of Ca. San Diego Frontiers in Innovation Scholars Program
Univ. of Ca. San Diego Chancellor's Research Excellence Scholarship
Univ. of San Diego
Veterans Affairs (VA) San Diego

Title: Using EEG neurofeedback to decrease medial frontal theta activity in patients with PTSD

Authors: A. M. RIVAS[1], M. GRAMS[2], J. VALDEZ[2], J. A. PINEDA[2], *I.-W. SHU[1]
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Abstract: The salience network (SN), includes the limbic system, insula and anterior cingulate cortex (ACC), and is responsible for monitoring threats to the organism. The SN shares brain areas and works closely with memory systems. For example, the hippocampus, ACC and prefrontal cortex exhibit increased and synchronized neural activity during consolidation and recall of negative stimuli. These events can be assessed neurophysiologically. For example, synchronous limbic-frontal activity produces greater medial frontal theta activity during

electroencephalography (EEG). Trauma-related increases in SN activity, and its effects on memory systems, can contribute to posttraumatic stress disorder (PTSD). For example, PTSD+ subjects generally exhibit excessive recall of trauma-related memories and hypervigilance of potentially-negative stimuli. In further support of this model, PTSD+ subjects also often exhibit greater medial frontal theta activity, a marker of greater limbic-frontal activation. We hypothesize that decreasing medial frontal theta activity in patients with PTSD would lower symptoms by normalizing excessive SN activity and its effects on memory systems. To validate this, as a first step, we designed a treatment study using EEG neurofeedback to inhibit frontal theta activity in PTSD patients. More specifically, by coupling a patient's theta activity to dynamic visual targets on a digital display, EEG neurofeedback allows the patient to, in real time, decrease their theta activity by manipulating the visual targets. In this study, PTSD patients were randomized to EEG neurofeedback inhibiting medial frontal theta power or, for comparison, neurofeedback enhancing posterior alpha power. Patients received 15-30 min trainings twice a week for 6 weeks (12 trainings total). Resting EEG and clinical measures were acquired before, halfway and after treatment. Theta reduction training was associated with > 35% decrease in PTSD severity. Furthermore, clinical improvements were associated with lower resting theta power. At the single-subject level, lower theta power correlated with improved PTSD symptoms, especially in the Avoidance symptom cluster. Of note, similar neurophysiologic and clinical effects were also observed in subjects completing alpha enhancement training, suggesting that learning to modulate generators of alpha activity may also be helpful for PTSD patients. These promising early results suggest that targeting medial frontal theta activity using EEG neurofeedback may lead to novel, neuroscientically-informed treatments for PTSD in the near future.

Disclosures: A.M. Rivas: None. **M. Grams:** None. **J. Valdez:** None. **J.A. Pineda:** None. **I. Shu:** None.

Poster

505. Post-Traumatic Stress Disorder: Human Studies

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 505.08/ZZ25

Topic: G.06. Post-traumatic Stress Disorder

Title: Altered maturation of emotion-regulation brain circuitry in young children with a history of Post-Traumatic Stress Disorder

Authors: *A. M. MOYETT[1], C. L. FALES[2], A. D. BARBER[2], P. DEROSSE[2], A. MALHOTRA[2], K. H. KARLSGODT[3]
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Abstract: Introduction: The experience of childhood adversity greatly increases the risk for depression and anxiety in adulthood, but the brain basis for this linkage is poorly understood. Animal studies suggest that early adversity accelerates the maturation of brain circuitry underlying emotion regulation. Likewise, human studies indicate that children who experience early adversity show emotion-regulation brain circuitry patterns that are characteristic of much older children. However these studies have most often operationalized childhood adversity as maternal deprivation or other forms of familial trauma (e.g., child abuse or neglect) likely to interfere with developing attachment systems. The current study explores the effects of trauma more generally (i.e., car accidents, natural disasters as well as familial trauma) on children's developing brains.
Methods and Materials: We examined emotion-regulation brain circuitry as a function of trauma in youth aged 9-20 (n=114) from the Philadelphia Neurodevelopmental Cohort (PNC). Three groups (PTSD, trauma-exposed controls, and no-trauma controls) underwent functional neuroimaging (fMRI) including a resting-state scan and an emotion-recognition task. Analyses examined connectivity or task activation between the right amygdala and frontal control regions.
Results: Across the age range, amygdala-prefrontal relationships were significantly different in the Post-traumatic Stress Disorder (PTSD) group relative to either control group. The youngest children in the trauma-exposed and no-trauma control groups showed a positive relationship between frontal control regions and the amygdala, a relationship that grew steadily more negative as participants aged. By contrast, the youngest PTSD group showed negative amygdala-prefrontal relationships not seen in the control groups until late adolescence. Moreover in the connectivity analyses, the prefrontal regions showing this pattern were not ventromedial, as in previous studies. Instead, when PTSD participants were compared to no-trauma controls, a right fronto-insular/orbitofrontal region (associated with salience processing and reward valuation) emerged, while when they were compared to trauma-exposed controls, two other prefrontal regions also showed this pattern (i.e., precentral/middle frontal cortex and supplementary motor area).
Discussion: These findings suggest that trauma exposure and PTSD at an early age are associated with adult-like emotion-regulation patterns in brain circuitry, providing further insight into childhood emotional resilience as well as increased risk for depression in adulthood.

Disclosures: A.M. Moyett: None. **C.L. Fales:** None. **A.D. Barber:** None. **P. DeRosse:** None. **A. Malhotra:** None. **K.H. Karlsgodt:** None.

Poster

505. Post-Traumatic Stress Disorder: Human Studies

Location: SDCC Halls B-H

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Program #/Poster #: 505.09/ZZ26

Topic: G.06. Post-traumatic Stress Disorder

Support: UC Reagents through an Academic Senate grant

Title: Chronic cannabis use effects on the extinction in post traumatic stress disorder

Authors: *B. CUCCURAZZU[1,2], D. STOUT[1,2], D. GLENN[3,2], D. ACHESON[1,2], V. B. RISBROUGH[1,2]
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Abstract: Rationale: Posttraumatic stress disorder (PTSD) lifetime prevalence is estimated to be approximately 7% in USA, with high prevalence rates in victims of interpersonal violence and combat veterans. Evidences based on pharmacological and psychological interventions shows that nonresponse rates to treatments is as high as 50%, and that a high percentage of subjects use cannabis to relieve symptoms of PTSD. However, controlled studies have not been conducted to evaluate the safety or effectiveness of marijuana for PTSD. Animal studies and studies in healthy controls suggest that fear inhibition, a core deficit in PTSD, may be enhanced by cannabinoid receptor signaling. Here we tested the hypothesis that cannabis use may modulate fear inhibition processes in PSTD. To test this hypothesis we investigated the effects of moderate to high cannabis use on laboratory-based fear extinction in PTSD patients. We recruited PTSD subjects with (N=17) and without (N=11) moderate-high cannabis use (used marijuana at least 5 times/week over the previous 90 days or not a current user). On Day 1, subjects were assessed for PTSD using the CAPS for DMS-5 and cannabis use was recorded using a modified version of the CDDR. Subjects then underwent acquisition of fear learning using the fear potentiated startle task (FPS). Shortly after acquisition subjects then underwent extinction training. On Day 2, subjects returned for assessment of recall of extinction learning. Subjects were screened for acute intoxication before testing to ensure behavioral effects were not mediated by acute cannabis use effects. Results: Analyses are ongoing and will be provided at the meeting.

Disclosures: B. Cuccurazzu: None. **D. Stout:** None. **D. Glenn:** None. **D. Acheson:** None. **V.B. Risbrough:** None.

Poster

505. Post-Traumatic Stress Disorder: Human Studies

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 505.10/AAA1

Topic: G.06. Post-traumatic Stress Disorder

Title: Elevated cortisol and alpha-amylase levels in behaviorally inhibited individuals exposed to physiologic stress: Implications for enhanced associative plasticity with anxiety vulnerability

Authors: *D. R. COOK-SNYDER[1], H. LATHAM[1], J. R. MILLER[2], P. F. MARTINO[2], D. P. MILLER[1], R. J. SERVATIUS[3]
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Abstract: A number of studies have used elevated levels of CO2 inhalation to activate physiological stress responses. While these studies reliably activate increased respiratory responding, activation of salivary stress hormones has been mixed. Our study examined stress hormone activation following exposure to 7% CO2 while controlling for stress/anxiety vulnerability. Behaviorally inhibited (BI) temperament has been identified as a key vulnerability factor for stress and anxiety disorders (e.g., Gladstone and Parker, 2005). Recently, a number of studies in both human (e.g., Allen and Miller, 2016) and non-human (e.g., Beck et. al, 2010) participants have demonstrated that organisms that are consistently inhibited across the lifespan show increased associative plasticity, especially when reinforcement of the environmental stressor is uncertain. We have hypothesized that stress vulnerable BI individuals may show enhanced stress hormone responses to environmental stressors. To test that hypothesis, we had participants perform a simple spaceship-based computer task (Sheynin et. al., 2014). Participants received 7% CO2 administration either during the first 7 min or the second 7 min of the game. A control group received air only throughout the testing. Air and CO2 were administered using a Hans Rudolph breathing apparatus. Two saliva samples from each participant were analyzed, one sample acquired 15 min prior to beginning the computer task, and a second sample taken immediately following the computer task. All samples were analyzed for alpha-amylase and cortisol levels using ELISAs. Level of BI was identified using the Adult Measure of Behavioral Inhibition (Gladstone and Parker, 2005). All participants regardless of level of BI showed increases in respiratory tidal volume immediately upon exposure to 7% CO2. Individuals who scored high in BI appeared to show increases in alpha-amylase activity shortly after exposure to 7% CO2, and increases in cortisol concentration approximately 30 min after 7% CO2 exposure. We did not see similar increases in individuals who scored low in BI. Our data indicate that, while all individuals showed physiological respiratory responses to elevated CO2, only stress vulnerable individuals appeared to show stress hormone response within our time frame. Our ongoing research examines whether sex differences may have contributed to our current

findings. Our preliminary data suggest that, given the significant consistency of enhanced associative plasticity in the human and non-human BI literature, stress hormone responding to environmental stressors may contribute to the enhanced learning that has been observed.

Disclosures: D.R. Cook-Snyder: None. **H. Latham:** None. **J.R. Miller:** None. **P.F. Martino:** None. **D.P. Miller:** None. **R.J. Servatius:** None.

Poster

505. Post-Traumatic Stress Disorder: Human Studies

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 505.11/AAA2

Topic: G.06. Post-traumatic Stress Disorder

Support: Stress and Motivated Behavior Institute, Syracuse, NY
WI Space Grant Consortium RIP-17

Title: Using enhanced CO2 (7%) exposure to examine avoidance learning reveals differences based on sex and behavioral inhibition

Authors: *D. P. MILLER[1], K. D. MUELLER[1], C. A. GRANT[1], P. F. MARTINO[2], J. R. MILLER[2], D. R. COOK-SNYDER[1], R. J. SERVATIUS[3]
[1]Neurosci., [2]Biol., Carthage Col., Kenosha, WI; [3]Stress and Motivated Behavior Inst., Syracuse VA Med. Ctr., Syracuse, NY

Abstract: Anxiety and stress disorders are prevalent diagnoses. However, the majority of individuals who experience significant aversive events do not show symptoms that endure and lead to diagnosis. The learning diathesis model suggests that individuals who are more vulnerable to these disorders show enhanced associative plasticity to environmental relationships, thus leading to symptom endurance and pathology. Numerous studies have demonstrated enhanced and persistent learning in organisms with behaviorally inhibited temperament (BI) and/or in females, two risk factors for anxiety and stress disorder. This includes rats in signaled avoidance learning (e.g., Beck, et. al, 2010) and humans in classical eyeblink conditioning (e.g., Allen, et.al., 2016). Sheynin et. al (2014) used a computer-based spaceship task to demonstrate sex and temperament differences in avoidance acquisition. However, this task is entirely cognitive, eliciting no physiological responses. We used this task to examined avoidance learning while participants breathed enhanced CO2 (7%). We tested whether stress response would alter learning acquisition and persistence in vulnerable individuals. BI was characterized using the Adult Measure of Behavioral Inhibition. Participants used a Hans Rudolph mouth piece with nose occlusion. Each session began with 15 minutes of air to allow the participant to adjust to the breathing apparatus. Avoidance training was accomplished using the spaceship task (courtesy of Sheynin and Myers). During avoidance

acquisition, participants inhaled either 7% CO2 gas (room air balance) or room air. During extinction training, participants inhaled room air. Participants receiving 7% CO2 showed rapid and consistent increases in ventilation. CO2 exposure did not appear to affect acquisition of the computer-based avoidance response, but high BI females appeared to show resistance to extinguishing the response (i.e., persistence of the response). Further, CO2 exposure appeared to significantly reduced female participant activity (i.e., a decrease in participant-controlled movement of her spaceship character and fewer shots fired). In contrast, CO2 exposure appeared to significantly increase male participant activity. Our data suggest that CO2 exposure differentially affected the performance of females and males on this task. While those performance differences did not affect acquisition of avoidance responding, it did result in a selective persistence of avoidance responding during extinction trials. We are running groups that receive air during acquisition and 7% CO2 during extinction to see if performance post-learning is similarly affected.

Disclosures: D.P. Miller: None. **K.D. Mueller:** None. **C.A. Grant:** None. **P.F. Martino:** None. **J.R. Miller:** None. **D.R. Cook-Snyder:** None. **R.J. Servatius:** None.

Poster

505. Post-Traumatic Stress Disorder: Human Studies

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 505.12/AAA3

Topic: G.06. Post-traumatic Stress Disorder

Support: Stress and Motivated Behavior Institute

Title: Alterations in acoustic startle response (asr) support a two hit hypothesis of behavioral inhibition and female gender for anxiety disorders

Authors: *T. ALLEN, M. M. GARCIA
Univ. of Northern Colorado, Greeley, CO

Abstract: Behavioral inhibition (BI), a personality temperament that is a known risk factor for anxiety disorders such as PTSD, enhances eyeblink conditioning with a tone CS and an air puff US. Female gender is also known to enhance eyeblink conditioning. Prior work has demonstrated that this enhanced associative learning with BI is not due to an increased reflexive response to the US air puff. However, this finding may be due in part to exaggerated reactivity to the tone via a startle response rather than enhanced associative learning. While BI children exhibit exaggerated acoustic startle responses (ASR) under certain conditions, ASR has not been studied in BI adults. In the current work, the Adult Measure of Behavioral Inhibition (AMBI) was used to compare ASR between BI and non-inhibited individuals based on a standard cut off score. Ninety one undergraduate students (females = 59, males = 39) completed the AMBI and

underwent ASR testing with eight trials at each of three sound intensities (82/92/102 dB) presented in a pseudorandom order. Electromyogram recordings were used to quantify peak startle response amplitudes and latencies. ASR responsivity increased as a function of intensity and habituated across repeated presentations for each intensity level as would be expected. Females exhibited exaggerated ASR as compared to males while BI individuals expressed reduced ASR. However, this BI effect was observed only with females. While BI individuals and females may be more sensitive to threatening or stressful stimuli, long term activation of the hypothalamic pituitary axis (HPA) in females expressing BI may lead to a down regulation of the stress response and associated hypervigilance resulting in depressed ASR. Since BI individuals did not exhibit exaggerated ASR, enhanced eyeblink conditioning in BI individuals appears to be due to enhanced associative learning which supports a learning diathesis model of anxiety disorders.

Disclosures: T. Allen: None. **M.M. Garcia:** None.

Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 506.01/AAA4

Topic: G.08. Drugs of Abuse and Addiction

Title: Cocaine exposure results in persisting impairment of hippocampal long-term potentiation and reduced performance in a spatial working memory task in C57BL/6J mice

Authors: *C. PRESTON[1], K. A. BROWN[2], J. J. WAGNER[3]
[1]Physiol. and Pharmacol., [3]Dept Physiol. & Pharmacol., [2]Univ. of Georgia, Athens, GA

Abstract: We investigated the effects of two different cocaine i.p. dosing schedules as well as the associated stress of vehicle (saline) injections on conditioned place preference (CPP), locomotor sensitization (LMS), long-term potentiation (LTP) in the ventral hippocampus (vH), and spatial working memory in a radial arm maze (RAM) task. CPP and LMS were established in male C57BL/6J mice using a modified conditioning protocol similar to one described by Itzhak and colleagues (2012), except that cocaine-treated mice received a double escalating-dose protocol (4,8,16,24,16,24,32,32 mg/kg; 2×4 day series). The double escalating dosing schedule produced significant CPP and LMS compared to mice that received saline vehicle. For the electrophysiology studies, a separate group of littermates were handled intermittently throughout, but not exposed to the conditioning protocol to serve as “non-behavior/naïve” controls for baseline LTP responses. Slices were prepared from the vH and fEPSPs were recorded in the CA1 region 4 weeks after the final injection day to assess persisting changes in vH function. We observed that saline conditioning results in significantly increased vH LTP (1.69 +/− 0.03) compared to behaviorally naïve mice (1.57 +/− 0.03) at this 4 week time point. A single pre-

treatment with the kappa-opioid receptor antagonist, norbinaltorphimine (norBNI; 10 mg/kg), blocks this stress-like effect associated with the conditioning protocol and results in vH LTP (1.61 +/− 0.03) that is not significantly different from the behaviorally naïve group. When norBNI is given prior to double-escalating conditioning with cocaine, we observed significantly decreased vH LTP (1.51 +/− 0.03) compared to those that received the saline vehicle ($p < .05$). Interestingly, the double-escalating/norBNI treated animals also exhibited a significant leftward shift in the stimulus-response curve of the baseline fEPSP measurements. Together, these findings are consistent with the hypothesis that a cocaine-induced enhancement of neurotransmission contributes to a partial occlusion of LTP in the vH of cocaine-exposed mice that persists 4 weeks after the final drug exposure. A separate group of norBNI/saline-treated mice showed significant improvement in a spatial working memory RAM task mice over 10 days (initial errors 1.50 +/− 0.16, final errors 0.83 +/− 0.14, $p < 0.05$) whereas norBNI/cocaine-treated mice did not show a significant improvement (initial errors 1.33 +/− 0.14, final errors 1.17 +/− 0.16). This suggests that alterations in synaptic transmission and LTP in the vH may be associated with persisting drug-induced impairments in learning and memory performance.

Disclosures: C. Preston: None. **K.A. Brown:** None. **J.J. Wagner:** None.

Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

Location: SDCC Halls B-H

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Program #/Poster #: 506.02/AAA5

Topic: G.08. Drugs of Abuse and Addiction

Support: National Basic Research Program Grants 2015CB553501
National Natural Science Foundation of China 31400880
National Natural Science Foundation of China 91332115

Title: DNMT3a in the hippocampal CA1 is critical for the acquisition of morphine self-administration in rats

Authors: *J.-J. ZHANG, F.-Z. JIANG, W. ZHENG, N. SUI
Inst. of Psychology, Chinese Acad. of Scienc, Beijing City, China

Abstract: ABSTRACT
Drug-reinforced excessive operant responding is the foundation of long-lasting addiction-like behaviors and relapse in animals. However, the unique transcriptional regulatory mechanisms responsible for the drug-specific (not natural rewards) operant behavior are not entirely clear. In this study, we established a key role for one of the *de novo* DNA methyltransferase (DNMT), DNMT3a, in the acquisition of morphine self-administration (SA) in ten weeks-old male Sprague-Dawley rats. The expression of DNMT3a in the hippocampal CA1 region but not in the

nucleus accumbens (NAc) shell was significantly up-regulated after one day and seven days morphine SA (0.3 mg/kg/infusion, n = 9-18). In contrast, saccharine SA training did not affect the expression of DNMT3a and DNMT3b (n = 6-12). DNMT inhibitor 5-aza-2-deoxycytidine (5-aza) microinjected into the CA1 region of the hippocampus significantly attenuated the acquisition of morphine SA (n = 7-12). Knockdown of DNMT3a expression impaired the ability of rats to acquire the morphine SA (n = 14-15), this manipulation also altered potential DNMT targets (*Gria2a* and *PPP1Cb*). Overall, these results suggest that DNMT3a plays an important role in the acquisition of morphine SA and may be a valid target for the treatment of morphine addiction.

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J-J Z and F-Z J contributed equally to this work.

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Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 506.03/AAA6

Topic: G.08. Drugs of Abuse and Addiction

Support: Natural Sciences and Engineering Research Council of Canada

Title: Remembering addictive behaviours: Effect of cocaine and nicotine conditioned context on memory formation

Authors: *M. WOLTER, E. HUFF, B. D. WINTERS, F. LERI
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Abstract: Cocaine and nicotine enhance memory formation and thus facilitate acquisition of behaviors leading to their consumption. These behaviors, however, are also activated and maintained by environmental stimuli that have been associated with their direct effects. Hence, it is likely that cocaine- and nicotine-associated stimuli, similarly to the acute action of these drugs, can enhance memory formation. To test this hypothesis, male Sprague-Dawley rats received 5 injections of cocaine (0 and 20 mg/kg, IP) or nicotine (0 and 0.4 mg/kg, IP) in a within-subject discriminative conditioning protocol that generated a drug-conditioned context (CS+) and a vehicle-conditioned context (CS-). Post-conditioning exposure to the CS+ context in a drug-free state induced a robust conditioned locomotor response. More importantly, exposure to the CS+,

but not CS-, immediately following the sample phase of an object recognition memory task enhanced memory on a test 72 hours later. Interestingly, the magnitude of this effect was comparable to the effects of acute cocaine (5, 10 and 20 mg/kg) or nicotine (0.1, 0.2 and 0.4 mg/kg) administration. As well, the effect of post-sample exposure to the CS+, or the drugs, was lost if exposure was delayed by 6 hours. Overall, these data identify a psychological function of cocaine- and nicotine- associated stimuli that is likely to have a critical impact on the development and maintenance of addictive behaviors.

Disclosures: M. Wolter: None. **E. Huff:** None. **B.D. Winters:** None. **F. Leri:** None.

Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

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Topic: G.08. Drugs of Abuse and Addiction

Support: R25 GM061838
NIH grant G12 RR003051
NIH grant G12 MD007600

Title: Hippocampal-accumbal BDNF and extinction of morphine place preference

Authors: *M. E. LLORET[1], J. L. BARRETO-ESTRADA[2], F. J. MARTINEZ-RIVERA[2], R. N. AYALA-PAGAN[3]
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Abstract: Excessive drug-seeking behaviors have been extensively associated with many molecular adaptions in the brain reward circuit. However, little is known about the impact of extinction learning in regulating the drug-induced synaptic plasticity on this circuit. We previously found that extinction of morphine-induced conditioned place preference (CPP) correlated with overexpression of Bdnf transcripts in the ventral striatum/nucleus accumbens (VS/Nac) (Martínez-Rivera et al., SFN 2016). Conversely, because the VS/NAc expresses low Bdnf levels (Allen brain atlas; Conner et al., 1997), it is possible that our results were due to changes in VS/NAc afferents such as the hippocampus, a brain region typically known by high levels of Bdnf expression (Allen brain atlas; Conner et al., 1997). Therefore, to determine possible contributions of the hippocampus, we performed western blots analysis of this brain region from rats showing 1) successful extinction, 2) extinction-failure, and 3) sham-extinction of morphine-CPP. While there were no significant differences in pro-BDNF, an increase of mature BDNF was observed in rats showing successful extinction. Together, our findings suggest that extinction learning increases hippocampal BDNF protein which could influence the

VS/Nac plasticity through its afferents. Future studies should expand protein expression to other brain areas associated to extinction of drug-seeking behaviors, such as the amygdala, and prefrontal cortex.

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Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

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Title: The infralimbic prefrontal cortex is involved in the blocking effect of memory retrieval-extinction procedure on methamphetamine seeking

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Abstract: It has been suggested that cue-exposure therapy in the clinic cannot usually prevent drug relapse when addicts return to the drug environment, which is a great hindrance to addiction treatment. In recent years, a memory retrieval-extinction procedure has been established to decrease reinstatement of cocaine, heroin and alcohol seeking, and to reduce cue-induced drug craving in heroin and nicotine addicts. The aim of the current study was to investigate the effect of memory retrieval-extinction procedure on methamphetamine relapse in rats and the underlying mechanisms. Firstly, rats that had learned methamphetamine self-administration were divided into three groups: no retrieval + extinction, retrieval +1h delay + extinction, and retrieval + 6h delay + extinction. We found that exposing rats to the retrieval manipulation 1h before every extinction session decreased the spontaneous recovery, renewal and methamphetamine-priming-induced reinstatement of methamphetamine seeking, although it had no effect on the extinction of methamphetamine seeking. Exposing rats to the retrieval manipulation 1h after every extinction session can also prevent the priming-induced reinstatement of methamphetamine seeking. In order to explore the brain mechanisms underlying the behavioral effects, we trained rats for methamphetamine self-administration and removed their brains 90 minutes after conditioned stimulus (CS) retrieval or no retrieval for detection of Fos and NeuN in

both prelimbic (PrL) and infralimbic (IL) prefrontal cortex, a brain area implicated in drug seeking. We observed significant activation of neurons in both PrL and IL after CS retrieval compared with the no retrieval group. Moreover, chemogenetic inactivation of IL but not PrL before CS retrieval blocked the effect of retrieval-extinction procedure on methamphetamine seeking. More specifically, selective inactivation of glutamatergic but not GABAergic IL neurons also blocked the effect of retrieval-extinction procedure on methamphetamine seeking. Taken together, these data suggest that glutamatergic neurons in the IL may contribute to the blocking effect of memory retrieval-extinction procedure on methamphetamine seeking in rats.

Disclosures: Y. Chen: None. **L. Zhang:** None. **J. Shi:** None. **Y. Xue:** None. **L. Lu:** None.

Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

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Topic: G.08. Drugs of Abuse and Addiction

Support: SCE P031S150199

Title: Methamphetamine associated memories independently go through reconsolidation, rendering the disruptive effects of memantine on drug-paired memories to be selective

Authors: *M. HANNA, A. OSBOURNE, T. TADROS, M. JESKE, T. UNDERWOOD
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Abstract: A major contributing factor to drug relapse is exposure to environmental stimuli that have been previously associated with drug administration. Exposure to such cues evokes memories of the effects of the drug and induces drug-seeking behavior. Drug associated memories go through a process of consolidation, wherein unstable memories are placed into a permanent state. When these memories are later triggered they go through reconsolidation, in which a memory becomes temporarily unstable and liable to disruption before becoming stable once again. Using the conditioned place preference (CPP) paradigm, previous research from our lab has shown that multiple injections of the NMDA receptor antagonist memantine immediately after brief exposure to a methamphetamine-paired compartment attenuated preference for the drug-associated compartment. In this study we aimed to determine the specificity of memantine in interfering with the reconsolidation of multiple drug-associated memories. We found that administration of memantine (10mg/kg) after exposure to one methamphetamine-associated compartment disrupted drug-seeking behavior for that particular compartment, but did not disrupt drug-seeking behavior for a second methamphetamine-associated compartment. Additionally, we found that exposure to a single modality, an olfactory cue, of a drug-associated memory that involved multiple modalities was sufficient to render a memory liable to

interference. Moreover, rats injected with memantine did not reinstate drug-seeking behavior when tested more than a week later, suggesting that the disrupting effects of memantine on drug-associated memories are long term.

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Poster

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Title: Escalating voluntary oral methamphetamine impairs hippocampal-dependent spatial memory and reduces synaptic stabilization through GSK3β signaling in females but not males

Authors: *N. MEMOS[1,2], J. A. AVILA[1,2], T. ANDRZEJEWSKI[1], F. TAVERNIER[1], O. SIDDIQUE[1], V. LUINE[1], P. A. SERRANO[1,2]
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Abstract: Methamphetamine (MA) is an addictive psychostimulant producing neurodegenerative processes that impair cognition. Reports indicate that females are more susceptible to the detrimental health effects and cognitive deficits associated with MA abuse. Females are also more susceptible to drug craving, relapse, and more rapidly escalate their MA abuse. We investigated the underlying mechanisms that may contribute to the increased susceptibility associated with drug abuse in female populations using a mouse model of voluntary oral MA administration (VOMA). Our VOMA paradigm involves 10d of escalating MA doses and presentations starting with one presentation/day at 0.25 mg/kg/bait over days 1-3; 4 presentations/day at 0.25 mg/kg/bait over days 4-6; 16 presentations/day at 0.25 mg/kg/bait over days 7-8; and 16 presentations/day at 0.5 mg/kg/bait over days 9-10. On days 11-28 mice receive 1mg/kg/bait for 16 presentations/day, occurring every 15 min over 4h. Our results show that the consumption rates of MA between sexes were not different. Males consumed an average total of 156 mg/kg bw/28d (7.34 mg/kg/day over last 18d). Females consumed an average total of 181 mg/kg bw/28d (8.88 mg/kg/day over last 18d). Mice were assessed for spatial working memory performance on the radial-8 arm maze two weeks into MA abstinence, followed by hippocampal tissue dissection and preparation for western blot analyses. Our results show that MA-female mice display a significant deficit in working memory performance compared to MA-male mice. Previous work from our lab has identified MA-induced spatial memory deficits

corresponding to altered AMPA receptor expression at synaptic membranes. Accordingly, we analyzed the expression of various markers within the signaling pathways associated with AMPA receptor endocytosis. Our results show that D1, Estrogen Receptor α, phospho-AKT, and phospho-GSK3β are all reduced in MA-female compared to MA-male mice. Reduced expression of these markers is known to increase GSK3β activation, promoting AMPA receptor endocytosis and the destabilization of the post-synaptic density via PSD95 phosphorylation. These results suggest that VOMA induces GSK3β activity in female mice that results in decreased proliferative signaling in the hippocampus and provides a molecular framework for female-specific susceptibility to psychostimulant-induced behavioral deficits. Current work is examining the balance of neuroprotective and neurodegenerative molecular signaling in the context of this model. Future work will determine the time course and shifts in neurodegenerative and neuroprotective signaling resulting from MA and other drugs of abuse.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

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Title: Activity changes and Perineuronal nets characterization around cerebellar Golgi cells in cocaine-induce preference memory

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Abstract: Human studies in drug addicts show that the prefrontal cortex and cerebellum might work in a competitive manner during reward tasks. Also, prefrontal impairment is accompanied by cerebellar hyperactivation. Hence, it seems that the cerebellum would acquire a higher functional relevance when the prefrontal function is compromised by disease or chronic drug use. Perineuronal nets (PNNs) are cartilage-like structures of extracellular matrix molecules (hyaluronan and hyaluronan synthases, chondroitin sulfate proteoglycans, tenascins, and link proteins) that enwrap in a net-like manner the cell-body and proximal dendrites of special subsets of neurons. PNNs stabilize their incoming connections and restrict plasticity, consequently, they have been proposed as a candidate mechanism for learning and memory storage. Indeed, PNNs

are considered to contribute to the maintenance of drug-induced conditioned memories after prolonged drug abuse. In the cerebellum, PNNs surround both inhibitory and excitatory neurons in the DCN but only inhibitory Golgi cells in the cerebellar cortex. Previous studies from the lab showed that either the deactivation of the infralimbic cortex (IL) or a lesion in the dorsal cerebellum promote preference towards cocaine-associated cues and regulates the expression of PNNs in the distal structure. Therefore, both areas seem to be part of a functional and structural network which would work on restraining goal-directed behavior when drug-cue associations are acquired.
The present research aimed to assess activity changes around Golgi PNNs in the dorsal cerebellum after an infralimbic deactivation in animals trained to acquire cocaine-induced preference conditioning. We used vGluT1, vGluT2, VGAT, and calretinin expression to estimate changes in neural activity. Also, we used synapsin I and PSD-95 to assess active synaptic contacts. Moreover, we phenotyped Golgi cells expressing PNNs using WFA, mGluR2, GlyT2, and neurogranin to determine whether there is a special population of Golgi cells that express PNNs. Our results showed that the IL deactivation increased selectively vGlut2-but not vGlut1-mediated activity around cerebellar Golgi cells' PNNs in the dorsal cerebellum. Neither VGAT nor calretinin activity seemed to be mediated by the IL deactivation. In this manner, the IL impairment would increase cerebellar activity throughout vGlut2 activity. These findings suggest that the IL has the capacity to regulate activity in the dorsal cerebellar cortex.

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Poster

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T32AA007456 (M.T.)

Title: Relapse-suppression by drug omission cues: Anti-relapse neurons in the infralimbic cortex

Authors: *N. SUTO[1], G. DE NESS[2], A. LAQUE[2], G. E. WAGNER[2], H. NEDELESCU[2], A. CARROLL[2], J. WANG[2], S. ZHANG[2], T. KERR[2], D. WATRY[2], E. KOYA[4], B. T. HOPE[5], G. I.

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Abstract: Drug addiction is a chronic relapsing disorder characterized by compulsive drug use. While significant resources have been dedicated to reveal neurobehavioral factors that promote drug relapse, this strategy has yet produced an effective treatment against relapse. Here we employed a different strategy by examining factors that suppress - rather than promote - relapse. Adapting Pavlovian procedures to suppress operant drug response, we determined the anti-relapse action of environmental cues signaling drug omission (*un*availability) in rats. Under conditions linked to compulsive drug use and heightened relapse risk, omission cues suppressed all three major modes of relapse-promotion (drug-predictive cues, stress, and drug exposure) across two major classes of abused drugs (cocaine and alcohol), thus establishing the translational relevance of the present approach. This relapse-suppression is, in part, driven by a functional unit of omission cue-reactive neurons (neural ensemble) in the infralimbic cortex comprised of distinct cellular phenotypes. Further studies of such anti-relapse neural ensembles, as well as ensemble-specific brain processes, may improve addiction medicine through functional characterization of druggable targets for relapse prevention.

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Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

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Title: Extended access to methamphetamine self-administration-induced greater propensity for relapse in male Long Evans rats is predicted by neuroadaptations in the dentate gyrus

Authors: J. TSENG[1], M. J. FANNON[2], M. J. TERRANOVA[1], D. PUROHIT[1], L. W. QUACH[1], K. K. KHARIDA[1], R. OLIVER[2], C. D. MANDYAM[1,2], *Y. TAKASHIMA[1]
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Abstract: The present study examined gender differences in methamphetamine (Meth; 0.05 mg/kg, i.v.) self-administration in adult Long Evans male and female rats during distinct phases of Meth addiction. Our findings demonstrate that females responded more than males during self-administration in an extended access paradigm. However, males and females demonstrated escalation in Meth intake with significant differences in latency to escalate. Following protracted abstinence, females show reduced spontaneous reinstatement during extinction, and have greater latency to extinguish compared with males. After extinction, females demonstrated lower context-driven reinstatement compared to males. Our findings demonstrate that Meth-addicted phenotype can be modeled in rats based on gender differences in preferred levels of Meth intake and a propensity for relapse in withdrawal. Moreover, using whole-cell patch-clamp recordings, intrinsic excitability of dentate gyrus (DG) granule cell neurons (GCNs) were recorded in acute brain slices from Meth naïve (controls) and Meth experienced male and female rats. Reinstatement of Meth seeking reduced spiking capability in GCNs compared to controls in males, an effect that was not evident in females, demonstrating distinct functional neuroadaptations in males and females GCNs. In male rats that reinstated Meth seeking, these altered electrophysiological properties of GCNs were associated with enhanced expression of plasticity-related proteins including GluN2A, CaMKII, and PSD95 and reduced expression of pGluN2B and GABAA subunits in the DG. In females, reduced reinstatement of Meth seeking correlated with reduced expression of pGluN2A and enhanced expression of pCaMKII. The alterations in functional properties of GCNs and plasticity related proteins in the DG paralleled with no significant changes in structure of microglial cells in the DG and mossy fiber projections in the DG. Taken together, our results demonstrate that enhanced reinstatement of Meth seeking results in alterations in intrinsic spiking in the GCNs and concomitant increases in expression of GluNs and decreases in GABAA subunits that may contribute to the altered synaptic connectivity-neuronal circuitry-and activity in the hippocampus, and enhance propensity for relapse in male rats. The present results highlight the importance of including sex as biological variables in exploring individual differences in Meth addiction-like behavior.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

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Title: The effect of nonmuscle myosin II inhibition on polydrug memories and reconsolidation

Authors: *M. HAFENBREIDEL[1], S. B. BRIGGS[1], E. J. YOUNG[1], G. RUMBAUGH[2], C. A. MILLER[1]
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Abstract: Substance use disorder (SUD) is maintained by long-lasting drug-cue memories, which can promote relapse. Persistent drug-associated memories are maintained, at least in part, by learning-induced, actin-dependent changes to the structure and stabilization of dendritic spines. We previously reported that depolymerizing actin with the nonmuscle myosin II inhibitor Blebbistatin (Blebb) disrupts methamphetamine (METH)- and amphetamine-associated memories. This disruption is immediate, retrieval-independent, specific to the basolateral amygdala (BLA), and selective, as Blebb does not have an immediate effect on fear-, food-, cocaine (COC)-, or morphine-associated memories. However, it was unclear if Blebb treatment would disrupt memories of other amphetamine class drugs. Thus, we first examined if Blebb could disrupt mephedrone (bath salts)-associated memories, as well as those associated with nicotine (NIC), as that had yet to be established. Using the CPP paradigm, we found that Blebb failed to disrupt NIC- or mephedrone-associated memories during the first test. However, similar to our findings with COC, reconsolidation of both drug memories was disrupted. To further examine this possibility, we are currently determining Blebb's ability to disrupt reconsolidation of a contextual COC-associated memory in the self-administration paradigm. Moreover, many individuals abuse multiple drugs (e.g., METH and NIC), but it was unknown if Blebb could disrupt polydrug memories, or if the inclusion of another substance would render Blebb no longer able to disrupt METH-associated memories. We found that NIC/METH- or morphine/METH-associated memories were rendered susceptible to Blebb disruption. Finally, we determined the effect of Blebb on drug/fear memories to assess dual memories composed of positive and negative valence. Interestingly, we found that METH or COC administration before fear conditioning resulted in attenuate freezing during a subsequent retention test. However, this affect was reversed in Blebb-treated mice given METH, but not COC. These results demonstrate that the inclusion of fear conditioning with METH administration did not render the fear memory susceptible to Blebb disruption, but did reinforce previous findings that Blebb treatment is selective for METH-associated memories. Substances are rarely used in isolation, and the recent resurgence of METH use in combination with other substances like opioids, indicates an important need to determine the mechanisms underlying polydrug memories for the development of novel therapeutics, in addition to developing further application of Blebb's therapeutic potential.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Title: Cue-elicited approach is associated with sensitivity to D1- and D2-like receptor agonists

Authors: *J. A. TRIPI, P. J. MEYER
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Abstract: There are substantial individual differences in the ability of reward-associated stimuli ("cues") to elicit approach and control motivated behavior. For example, we have shown that rats trained in a Pavlovian conditioned approach paradigm approach either the cue itself ("sign-tracking") or the reward delivery location ("goal-tracking"). Others have shown that learning to sign-track, but not learning to goal-track, is dependent on dopamine neurotransmission (Flagel et al. 2011), and that "sign-tracker" rats (STs), compared to "goal-trackers" (GTs), have differences in D1-like and D2-like dopamine receptors before and after conditioning (Flagel et al. 2007). Furthermore, we have shown that sign-trackers emit more cocaine-induced ultrasonic vocalizations (USVs) than goal-trackers, but do not differ in cocaine-induced locomotion (Tripi et al., 2017). The objective of this study was to determine whether sensitivity to dopamine receptor stimulation is associated with sign- and goal-tracking. To test this, we measured locomotor sensitivity to the D1- and D2-like receptor agonists quinpirole (0, 0.1, 0.3, 1 mg/kg; *s.c.*) and SKF-82958 (0, 0.1, 1mg/kg *i.p.*) in STs, GTs, and intermediate rats (n=48 total). We also measured cocaine-induced (10 mg/kg, *i.p.)* USVs and locomotion in these same animals. Results indicated that STs were more sensitive to SKF-82958-induced locomotion at the 1 mg/kg dose ($p < 0.01$), but not to quinpirole. However, when sensitivity to both agonists were considered together, rats that were highly sensitive to both quinpirole and SKF-82958 (as determined by median splits) sign-tracked more and goal-tracked less than rats that were sensitive to only one or neither agonist ($ps < 0.05$). Finally, while quinpirole sensitivity was positively associated with cocaine-induced locomotion, sensitivity to either agonist was unrelated to cocaine-induced USVs. These data suggest that D1- and D2-like receptors promote sign- and goal-tracking in an additive fashion. In contrast, cocaine-induced USVs, while strongly associated with sign-tracking, are not related to sensitivity to the agonists used in this study.

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Poster

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Title: mRNA expression of immediate early genes in the rat hippocampus during compulsive methamphetamine self-administration in the presence of punishment

Authors: *S. JAYANTHI[1], J. A. HERNANDEZ[2], L. CONTU[2], M. T. MCCOY[2], B. LADENHEIM[2], M. JOB[2], J. L. CADET[3]
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Abstract: Methamphetamine (METH) addiction is a serious problem with 24.7 million abusers worldwide. METH addicts experience complex psychological symptoms that are accompanied by cycles of abstinence and relapses. Maintenance of METH addiction may depend on epigenetic and transcriptional adaptations in various brain regions including the hippocampus that plays integral roles in memory formation. Nevertheless, because investigations of drug-induced neuroadaptations have focused on the nucleus accumbens, very little is known about the consequences of METH intake in the hippocampus. As a first step towards to elucidate potential involvement of the hippocampus in METH self-administration, we have quantified the mRNA expression of immediate -early genes (IEGs) in that structure. To mimic METH addiction, we used a rat model of METH self-administration (SA) wherein animals were initially divided in three groups: control (CT), saline yoked-shock (YS), and METH groups. Rats were trained to self-administer METH or saline during three 3-h sessions/day with a 30 min off interval between sessions for a total of 21 days. METH-trained rats escalated their intake of the drug during self-administration. Thereafter, lever presses for METH were punished by mild foot-shocks for 8 days (0.18-0.36 mA). The shocks led to the segregation of the METH-trained animals into two phenotypes: one METH group continued to compulsively press the lever for METH (shock-resistant, SR), whereas the other group progressively decreased their intake (shock-sensitive, SS) because of the footshocks. Groups of saline SA rats were also yoked to the METH groups so that they received footshocks at the same time as METH SA rats received shocks. Rats were euthanized 2 hours after the last METH plus shock session and quantitative PCR was used to measure mRNA in the rat hippocampus. We found that, in comparison to control and sensitive rats, resistant rats exhibited increased mRNA expression of members of *fos* (*c-Fos, fosB,* and *Fra2*), *jun* (*JunB*), *egr* family (*Egr1* and *Egr2*) and (*Nr4a1* and *Nr4a3*) families of IEGs as

compared to control and SS rats. Altered mRNA expression in the hippocampus suggests their involvement in memory mechanisms that may, in part, be responsible for the neuroadaptive changes that mediate some aspects of repeated relapses. Acknowledgement: This work is supported Department of Health and Human Services/ National Institutes of Health/ National Institute on Drug Abuse/ Intramural Research Program.

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Poster

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Title: Escalating voluntary oral methamphetamine administration induces resilience in male mice through GSK3beta signaling

Authors: *A. ASLAN[1], J. A. AVILA[1,2], T. ANDREJEWSKI[1], F. TAVERNIER[1], A. TANG[1], P. A. SERRANO[1,2]
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Abstract: Methamphetamine (MA) is a neurotoxic psychostimulant of abuse that produces neurodegenerative processes that impair cognition. We previously characterized a novel voluntary oral methamphetamine administration (VOMA) model that produced neurotoxic effects in the hippocampi of male mice and learning and memory deficits on the radial arm maze (Avila et. al, 2018). Subsequently, we aimed to characterize the higher limits of voluntary consumption through an escalating dose model of VOMA (E-VOMA). We hypothesized initial restriction to MA access would offer neuroprotection to chronic administration of the drug. Our previous work revealed that male mice on static dose VOMA (S-VOMA), who received 1 mg/kg/bait for 16 presentations/day over 28d, consumed 5.23 mg/kg bw/day, with an average total of 146 mg/kg bw. Male mice that received 10d of E-VOMA started with one presentation/day at 0.25 mg/kg/bait over days 1-3; 4 presentations/day at 0.25 mg/kg/bait over days 4-6; 16 presentations/day at 0.25 mg/kg/bait over days 7-8; and 16 presentations/day at 0.5 mg/kg/bait over days 9-10. On days 11-28 these mice received 1mg/kg/bait for 16 presentations/day. E-VOMA male mice consumed 7.34 mg/kg/day over days 11-28, with an average total of 156 mg/kg bw. Despite a shift in consumption rates, total MA consumed was not

statistically different between groups. Two weeks into MA abstinence, spatial memory assessments on the RAM revealed a significant working memory deficit for male mice on S-VOMA. However, E-VOMA did not produce a working memory deficit in male mice. Western blot analyses of hippocampi collected following radial arm maze assessments revealed that S-VOMA produces a lasting neuroinflammatory response via COX-2 and GFAP, a result not present in E-VOMA mice. Furthermore, GSK3β-phosphorylation was increased in E-VOMA mice, suggesting increases in proliferative and pro-plasticity signaling. The inactivation of GSK3β via ser9 phosphorylation is essential to the expression of pro-growth activity and the inhibition of pro-apoptotic signaling involving COX-2 and GFAP. Finally, D1 receptor and Estrogen Receptor α expression are both increased in E-VOMA mice, revealing the upstream mechanisms underlying E-VOMA induced neuroprotection via GSK3β phosphorylation. Our data have revealed a role for gradual escalation of psychostimulant exposure in priming neuroprotective pathways in the brain. Current work is examining AMPA receptor trafficking and stabilization regulated by GSK3β signaling in the context of different VOMA models.

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Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 506.15/AAA18

Topic: G.08. Drugs of Abuse and Addiction

Support: DA025922

Title: HDAC3 regulation of cocaine-induced plasticity and cocaine-associated learning in nucleus accumbens cell subtypes

Authors: *R. R. CAMPBELL[1], E. A. KRAMAR[2], A. J. LOPEZ[2], D. P. MATHEOS[2], T. J. HEMSTEDT[2], M. A. WOOD[2]
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Abstract: Cocaine exposure alters molecular and cellular mechanisms within the nucleus accumbens (NAc) that leads to the formation of context-drug associations that are critical for drug-seeking. Although the activity of the two major cell subtypes within the NAc, cells expressing dopamine D1- (D1R) vs D2-receptors (D2R), exert opposing effects on cocaine-related behaviors, the molecular mechanisms underlying these differences are unclear. Prior work from our lab demonstrates that the histone deacetylase HDAC3 within total NAc regulates cocaine-induced enhancements in gene expression and cocaine-associated memory formation. Additionally, we have shown that deletion of HDAC3 within the NAc increases gene expression

of the transcription factor Nr4a2 following the acquisition of cocaine-associated memory. NR4A2 is essential for dopaminergic neuronal differentiation and survival during development, and necessary for long-term memory in the adult brain. Although there is evidence to suggest that Nr4a2 is differentially regulated following exposure to chronic cocaine, how it may act to promote drug-seeking behaviors in these cell types remains unknown. Here, we have examined HDAC3-regulation of Nr4a2 expression within D1R- vs D2R-containing cells of the NAc following cocaine-conditioning. In addition, we have investigated the role of HDAC3 within D1R vs D2R containing cells in cocaine-induced synaptic plasticity. Lastly, we have examined the role of HDAC3 role within D1- and D2-containing cells of the NAc in cocaine-associated memory formation. Together, these results elucidate a mechanism by which HDAC3 may be regulating key downstream target genes, like Nr4a2, during cocaine exposure that leads to persistent changes in neuronal function and ultimately behavior.

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Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 506.16/AAA19

Topic: G.08. Drugs of Abuse and Addiction

Support: DA025922
MH101491
DA043998

Title: CREST in the nucleus accumbens core regulates cocaine-associated memory formation and synaptic plasticity

Authors: *Y. ALAGHBAND[1], E. KRAMAR[1], J. L. KWAPIS[1], E. S. KIM[2], T. J. HEMSTEDT[1], A. J. LOPEZ[1], A. O. WHITE[3], A. AL-KACHAK[4], O. V. AIMIUWU[5], K. K. BODINAYAKE[1], N. C. OPARAUGO[1], J. HAN[1], K. M. LATTAL[2], M. A. WOOD[1]
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Abstract: Epigenetic mechanisms lead to persistent changes at the cellular level that can ultimately result in long-lasting behavioral adaptations. Nucleosome remodeling is a major epigenetic mechanism that has not been well explored with regards to drug-associated memories. Nucleosome remodeling is carried out by multi-subunit complexes that interact with DNA or

chromatin structure and possess an ATP-dependent enzyme to disrupt nucleosome-DNA contacts and ultimately regulate gene transcription. Calcium RESponsive Transactivator (CREST) is a transcriptional activator that interacts with enzymes involved in both histone acetylation and nucleosome remodeling. In these experiments, we investigated the effects of knocking down CREST in the nucleus accumbens (NAc) core on drug-associated memory and synaptic plasticity. To examine the role of CREST in the NAc core, C57BL/6J mice or Long Evans rats received infusions of either Morpholino or small interfering RNAs (siRNA) targeted against CREST. Conditioned place preference (CPP) was used to study cue-elicited context preference. Knocking down CREST in the NAc core resulted in impaired cocaine-associated CPP memory and deficits in theta-induced long-term potentiation (LTP) in the NAc core. Further, similar to the CPP findings, using a self-administration paradigm, we found that CREST knockdown in the NAc core of rats had no effect on instrumental responding for cocaine itself on a first-order schedule, but did significantly attenuate responding on a second-order chain schedule, in which responding has a weaker association with cocaine. Together, these results suggest that CREST in the NAc core is required for cocaine-associated memories as well as synaptic plasticity.

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Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 506.17/AAA20

Topic: G.08. Drugs of Abuse and Addiction

Title: Place-conditioning phenotype predicts methamphetamine self-administration behavior in male, but not in female, C57BL/6J mice

Authors: *C. N. BROWN, A. PAGE, E. K. FULTZ, J. SHAHIN, A. F. HEALY, T. E. KIPPIN, K. K. SZUMLINSKI
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Abstract: Understanding the genetic, molecular and cellular mechanisms underpinning individual variance in drug-taking behavior and addiction vulnerability requires the development of validated, high throughput screens that are amenable to the study of large numbers of animals. To this end, our laboratory demonstrated previously that the direction and magnitude of methamphetamine (MA)-induced place-conditioning predicts the propensity to acquire oral MA self-administration, as well as the efficacy of MA to serve as a reinforcer in male C57BL/6J mice. To date, it is not known whether or not behavior manifested under simple MA-induced

place-conditioning procedures predicts subsequent MA self-administration in female mice. To examine this issue, adult female C57BL/6J mice were underwent a 4-day MA conditioning procedure in which they were injected with saline and confined to one compartment of a 2-compartment apparatus in the mornings. Approximately 4-5 hours later, the mice received an injection of 2 mg/kg MA and were confined to the opposite compartment. Then mice were tested for the expression of place-conditioning in a drug-free state. Then mice were trained to nose-poke for delivery of a 20 mg/L MA solution under FR1 to FR5 schedules of reinforcement, followed by dose-response testing (5-160 mg/L MA). As observed in males, the majority of females tested to date (57%) exhibited a conditioned place-preference (> 100 sec in the MA- versus saline-paired compartment), while 33% of the mice were MA-ambivalent and a minority (16%) exhibited a conditioned place-aversion (greater than 100 sec in the saline- vs. MA-paired compartment). However, unlike males, the place-conditioning phenotype did not relate to MA-reinforced nose-poking behavior or MA intake at any point during training or dose-response testing in female subjects. While only one MA-conditioning dose has been assayed to date, these data indicate that sex does not majorly shift the proportion of C57BL/6J mice that perceive MA's interoceptive effects as positive, neutral or aversive. However, a sex difference exists in the predictive relation between the motivational valence of MA and subsequent drug-taking behavior, with females exhibiting MA-taking behavior and reinforcement, despite their initial perception of this stimulant's interoceptive effects as neutral or aversive. Future studies seek to understand the role for ovarian hormones in regulating the motivational valence of MA in females as it relates to subsequent drug-taking behavior and relapse-related behaviors.

Disclosures: C.N. Brown: None. **A. Page:** None. **E.K. Fultz:** None. **J. Shahin:** None. **A.F. Healy:** None. **T.E. Kippin:** None. **K.K. Szumlinski:** None.

Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 506.18/AAA21

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA024044
NIH Grant DA039168
UCSB Academic Senate
College of Research and Creative Activities

Title: Binge-drinking history augments the positive subjective effects of methamphetamine in both male and female C57BL/6J mice

Authors: *C. L. JIMENEZ CHAVEZ, E. K. FULTZ, K. R. SERN, K. K. SZUMLINSKI
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Abstract: A high degree of co-morbidity exists between methamphetamine (MA) addiction and alcohol use disorders and sequential alcohol-MA mixing increases risk for coabuse. As little preclinical work has focused on the biobehavioral interactions between MA and alcohol within the context of animal models of drug reward, we tested the effects of a prior history of binge-drinking (14 days of 2h-access to 5, 10, 20 and 40% alcohol) upon the perception of MA's subjective effects as either appetitive or aversive using place-conditioning procedures in C57BL/6J mice. As female mice tend to binge-drink more alcohol than males and female rodents tend to be more sensitive than males to the psychomotor-activating properties of MA, we compared the dose-response functions for MA-induced place-conditioning (4 pairings of 0.25, 0.5, 1, 2, or 4 mg/kg IP) between male and female mice. As expected, female mice binge-drank more alcohol than males over the course of the 14-day drinking period and exhibited higher levels of MA-induced locomotion during the conditioning sessions. Interestingly, despite these sex differences, no sex difference was apparent in the shift upwards in the dose-response function for MA-induced place-conditioning produced by a prior history of binge-drinking. Further, no sex difference was apparent in the potentiation of locomotor sensitization elicited by the mid-range MA doses observed in binge-drinking animals. These data extend prior observations from males that a binge-drinking history heightens the positive subjective effects of MA to females and argue that sex does not contribute majorly to this alcohol-MA interaction. If relevant to humans, these data argue that both males and females with a prior binge-drinking history are similarly vulnerable to MA abuse and it remains to be determined whether or not the neural substrates underpinning this increased vulnerability reflect common or sex-specific adaptations in reward-related brain regions.
Funding: National Institutes of Health [grant numbers AA024044 and DA039168] to KKS, UCSB Academic Senate (KKS) and College of Research and Creative Activities (EKF).

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Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 506.19/AAA22

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA024044

Title: ERK activation within the medial prefrontal cortex regulates the positive motivational valence of methamphetamine in mice

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Abstract: While illicit methamphetamine (MA) abuse remains a significant public health concern, the neurobiological mechanisms driving MA addiction remain largely unexplored. Prior unpublished data from our laboratory suggested a positive correlation between conditioned place-preference (CPP) scores in C57BL/6J mice and increased pERK:ERK expression within the medial (mPFC), where high methamphetamine place-preferring mice predicted increased ERK activity. A follow-up experiment sought to elucidate the role of mPFC ERK in the positive motivational valence of MA. For this, adult, male C57BL/6J mice were surgically implanted with bilateral guide cannulae aimed over the mPFC. Following recovery, mice underwent place-conditioning procedures (4 pairings of 2 mg/kg) and the presence of a CPP was verified in a drug-free state. Then, mice were examined for changes in CPP magnitude in a series of additional tests, immediately prior to which animals were infused with different doses of the MEK inhibitor U0126 (0, 1, 10 and 100nM) into the mPFC. Mice were infused with one U0126 dose per day, with the order of dosing counterbalanced across days. To control for the effects of repeated microinjections upon the magnitude of a CPP, a group of control mice received only saline microinjections. Microinjections of saline vehicle into the mPFC did change place-preference scores, even with repeated testing. In contrast, U0126 dose-dependently reduced the magnitude of the CPP, with the highest U0126 doses blocking the conditioned response. This effect was observed despite no U0126-induced change in locomotor activity during testing. These results provide novel evidence that ERK activity within the mPFC is key in regulating the positive subjective effects of MA, and implicate ERK hyperactivity within mPFC as a pathological state driving enhanced sensitivity to MA reward.

Disclosures: E.K. Fultz: None. **K.K. Szumlinski:** None.

Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 506.20/AAA23

Topic: G.08. Drugs of Abuse and Addiction

Support: FAPESP
Capes

Title: Role of basolateral amygdala in context-induced the reinstatement of alcohol seeking after punishment-imposed abstinence

Authors: *T. S. YOKOYAMA[1], J. MOREIRA[2], R. A. MAEDA[2], P. PALOMBO[2], C. R. ZANIBONI[2], P. C. BIANCHI[3], R. M. LEÃO[4], F. C. CRUZ[2]
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Abstract: Introduction: Alcohol addiction is a chronic relapsing brain disease. About 80% of patients relapse to alcohol use during the treatment. The main risk factor to relapse in human addiction is exposure to environmental cues that were previously associated with alcohol use. The basolateral amygdala (BLA) has been involved in cue-induced relapse to drug seeking. However, the role of this subregion in context-induced alcohol seeking is not completely understood. **Objective:** We investigated whether context-induced reinstatement of alcohol seeking after punishment-imposed abstinence, would be mediated by activation the basolateral amygdala. **Material and methods:** We trained male Long-Evans rats to self-administration ethanol in context A and extinguished the lever pressing under a punishment protocol in a distinct context B. In the extinction phase, for one group, alcohol-reinforced response was punished by adding quinine in the alcohol solution; two other groups either received a solution of quinine without alcohol or water. On the test day, context-induced reinstatement of alcohol seeking was tested by placing rats back in the drug-paired context (A). We also determined the effect of context-induced alcohol seeking on Fos expression in BLA. **Results:** In context B, animals that received alcohol+quinine were more resistant to suppression of alcohol-taking behavior than the quinine or water group (average of active lever presses in the 7 first extinction session: alcohol+quinine 125±20; quinine 94±26; water 90±9).
However, the reinstatement of alcohol self-administration induced by contextual cues was not different among the groups (lever pressing in context A or B respectively: alcohol+quinine 35±11 and 22±7; quinine 34±3 and 11±2; water 33±6 and 28±7).
Moreover, context-induced reinstatement of alcohol seeking after punishment-imposed abstinence was associated with increased Fos expression in BLA (Fos expression on context A or B respectively: alcohol+quinine 97±6 and 20±2; quinine 82±1 and 57±4; water 63±9 and 30±2).
Conclusion: Our results suggest that our procedure can be used as model to study context-induced relapse to alcohol seeking after alcohol-taking to have been suppressed by adverse consequences. We also found that activation of the BLA is correlated with context-induced alcohol seeking after punishment-imposed abstinence.

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Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

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Topic: G.08. Drugs of Abuse and Addiction

Support: FAPESP - 2013/24986-2
FAPESP - 2017/26225-0

Title: biperiden reduces drug reward effects

Authors: *P. PALOMBO[1], R. A. MAEDA[1], S. A. ENGI[1], P. C. BIANCHI[2], C. ZANIBONI[1], T. YOKOYAMA[1], P. C. J. D. SANTOS[1], J. C. F. GALDUROZ[3], F. C. CRUZ[1]
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Abstract: Recent studies suggest that nicotinic and muscarinic cholinergic receptor mediate dopamine release in the mesolimbic system and can alter the drug's reinforcing value. It was demonstrated that systemic treatment with the biperiden, a muscarinic cholinergic (*M1)* antagonist receptor blocked the expression of cocaine conditioned place preference (CPP) in mice. Here, we examine the effect of systemic biperidene injection (1, 5 and 10mg / kg ip) on alcohol conditioned place preference. The CPP procedure consisted of the following phases: habituation, conditioning and testing. It was used a three-chamber 'unbiased' apparatus. During the habituation, each male Swiss mouse was placed in the neutral compartment with the guillotine doors removed to allow access to the entire apparatus for 15 min for 3 days. On day 3, mice were placed in the apparatus the time spent in each compartment was recorded. For conditioning, mice were randomly paired to alcohol or saline administration. Conditioning was performed using a protocol consisting of 8 injections of 2.0 mg/kg i.p. of alcohol or saline over 8 alternate and consecutive days. The test was conducted 24 h after the last conditioning session. Thirty minutes before the test mice were grouped in 4 groups and were injected with biperiden at the doses of 1 or 5 or 10 mg/kg and were placed in the neutral compartment with the guillotine doors removed to allow access to the entire apparatus. The time spent in each compartment was recorded for 15 min. Biperiden 10 mg/kg blocked the alcohol CPP expression (Saline: pretest - 35.20% ± 0.02; test - 59.61 ± 0.04; Bip 1mg/Kg: pretest - 34.55% ± 0.03; test - 48.71% ± 0.14; Bip 5 mg/Kg: pretest - 35.17% ± 0.02; test - 50.51% ± 0.03; Bip 10 mg/Kg: pretest - 33.18% ± 0.03; test: 45.28% ± 0.02; $p<0.05$). Our results add to growing evidence that biperiden might be a promising drug for drug addiction treatment.

Disclosures: P. Palombo: None. **R.A. Maeda:** None. **S.A. Engi:** None. **P.C. Bianchi:** None. **C. Zaniboni:** None. **T. Yokoyama:** None. **P.C.J.D. Santos:** None. **J.C.F. Galduroz:** None. **F.C. Cruz:** None.

Poster

506. Drugs of Abuse and Addiction: Memory and Relapse

Location: SDCC Halls B-H

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Program #/Poster #: 506.22/AAA25

Topic: G.08. Drugs of Abuse and Addiction

Support: FAPESP (Proc. nº 2016/25894-2)
FAPESP (Proc. nº 2013/24986-2)

Title: The influence of ventral striatum direct pathway on alcohol context-induced reinstatemet: Functional and molecular findings

Authors: *C. R. ZANIBONI, III, J. MOREIRA, P. PALOMBO, T. YOKOYAMA, R. MAEDA, F. C. CRUZ
Pharmacol., Univ. Federal De São Paulo - UNIFESP, Sao Paulo, Brazil

Abstract: Alcohol addiction is a world health problem and is associated with a higher rate of relapse during the treatment. Learned associations play a significant role in addiction. The nucleus accumbens direct and indirect pathway have been implicated in learning associations between contextual cue and drug reward effects. However, the precise mechanisms that underlie these functions remain unclear. Here, we studied the role of projections to substantia nigra reticulate (SNr) from nucleus accumbens (NAc) in context-induced relapse to alcohol-seeking. For this propose, male Long-Evans rats were trained to self-administrate ethanol in context A and extinguished lever pressing in a distinct context B. On the test day, the context-induced reinstatement of ethanol seeking was tested in the ethanol context (A). First, we measured the neuronal activity marker Fos in the SNr. Next, we used an anatomical asymmetrical disconnection procedure to demonstrate the role of the projections from NAc to SNr (direct pathway) in context-induced relapse to alcohol seeking. In this procedure, rats were ipsilateral cannulated into NAc and SNr and, 10 minutes before the test, received microinjections of saline or $CoCl_2$ on SNr and SCH23390 (D1 antagonist) on NAc to block this pathway (Experiment 2). Context-induced reinstatement of alcohol seeking was associated with decreased Fos expression in SNr neurons (Fos expression on context Homecage, B and A respectively Mean±SEM: 8.14±3.32; 7.33±2,0; 15.36±3.67). Further, Injections of D(1)-family receptor antagonist SCH 23390 into NAc and $CoCl_2$ into SNr decreased context-induced reinstatement (Mean±SEM - Active bar press SCH23390/CoCl 2: 0.6667 ± 0.3333 x Active bar press Saline: 44.00 ± 9.866; $p \leq 0,05$). Our results suggest the involvement of nucleus accumbens direct pathway in context-induced reinstatement of alcohol seeking behavior

Disclosures: C.R. Zaniboni: None. **J. Moreira:** None. **P. Palombo:** None. **T. Yokoyama:** None. **R. Maeda:** None. **F.C. Cruz:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.01/AAA26

Topic: H.01. Animal Cognition and Behavior

Title: Neurons in the nidopallium caudolaterale (NCL) and entopallium (ENTO) of pigeons (Columba livia) convey category information in a discrimination task between Picasso and Monet paintings

Authors: *C. ANDERSON, R. S. PARRA, M. COLOMBO
Univ. of Otago, Dunedin, New Zealand

Abstract: In 1995, Watanabe and colleagues demonstrated that pigeons could successfully discriminate between Picasso and Monet paintings, and even generalise this discrimination to other cubist and impressionist paintings. To add to the behavioural findings of Watanabe et al. (1995), we recorded neural activity via single-unit electrophysiology while pigeons performed a similar task to that of Watanabe et al. (1995). The avian nidopallium caudolaterale (NCL) is generally considered to be an analogue of primate pre-frontal cortex (PFC). Both PFC and NCL have been implicated in categorisation behaviour (i.e. Kirsch et al., 2009; Freedman et al., 2001). The avian entopallium (ENTO) is a higher-order visual area that is thought to be similar to striate cortex in primates, and is also involved in categorical processing in birds based on lesion studies (see Watanabe 1991; 1996). We recorded from the NCL and ENTO of four birds during a Picasso/Monet painting discrimination task similar to that of Watanabe et al. (1995). Half the birds were trained with Monet paintings as the S+, and the other half were trained with Picasso paintings as the S+. Pigeons were required to peck the S+ stimulus in order to receive a food reward, but refrain from pecking the S- stimulus, which was never rewarded. We found that for both NCL and ENTO, cells in the left hemisphere appeared to carry category-relevant information, as there was a significant difference in activity from baseline inter-trial interval activity for both S+ and S- stimuli. There was also a significant difference between activity to the S+ and the S- minus stimuli, with more activity occurring when the S+ stimulus was presented than when the S- stimulus appeared. Furthermore, we found that reward-related activity was present in the NCL, but not in ENTO. In NCL, activity during the reward period also deviated from baseline levels, and was also significantly different between S+ and S- trials.

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Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.02/BBB1

Topic: H.01. Animal Cognition and Behavior

Support: Spanish Ministry of Economy and Competitivity, grant nº BFU2017-82375-R

Title: A 4-Hz oscillation in the prefrontal cortex and in the accumbens nucleus characterizes prosocial but not food rewards in rats

Authors: *F. ROCHA-ALMEIDA, A. CONDE-MORO, J. DELGADO-GARCÍA, A. GRUART
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Abstract: As a basic physiological need, food is a natural reward used in many experimental procedures with rodents to study learning processes or decision-making abilities. On the other hand, social interactions also play an important role in the good development of these species and it could be used as a positive reinforcement. The main goal in this study was to determine rat's preferences and to study the local field potentials (LFPs) in selected cortical and subcortical brain structures when presented with these two types of reinforcements: food or social interactions. For this aim, we used two modified and adjacent Skinner boxes divided into two equal-size compartments separated by a guillotine door. One of these Skinner boxes had two available levers: one lever that, when pressed, provided access to food pellets, with a 1:1 fixed ratio schedule; and another lever that, when pressed, allowed 10 s of visual and partial physical contact with another rat located in the adjacent box. To increase the needs for social interactions, selected rats were fed *ad libitum* and were placed in social isolation for one month. Rats were implanted with recording electrodes in the medial prefrontal cortex (mPFc), the accumbens septi (NAc) nucleus, the mediodorsal thalamic (MD) nucleus and the hippocampal CA1 area (CA1). It is well known that all these brain areas are related to motivational circuit loops, including reward-related phenomena, appetitive, and decision-making processes in rodents. Our results showed a preference for the food reward in all rats, but the social isolation helped to increase the number of lever presses to obtain a social interaction. The analysis of recorded LFPs showed the presence of different peaks in the spectral power in the delta range (1.5 - 4 Hz) of frequencies, for the two rewards. The dominant spectral power during eating (~3 Hz) seems to be lower than the one present (~ 4 Hz) during social interactions. These slow oscillations are particularly present in the mPFc and in the NAc. In addition, the spectral power in the theta band was significantly higher when interacting with the other rat than when eating. The hippocampal CA1 area presented a dominant 8-Hz rhythm when the animal was moving during the social interaction, but decreased during eating, because of its immobility. The MD nucleus presented two dominant peaks at 3-4 Hz and ~ 8 Hz reflecting mPFc and hippocampal activities. In conclusion, both the mPFc and NAc seem to be directly involved in decision making responses and their LFPs present specific dominant frequencies for social versus food rewards.

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Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.03/BBB2

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA031695

Title: Establishing a role for ACC in the modulation of directionally selective neurons in DMS in rats performing a stop-change task

Authors: *A. T. BROCKETT[1,2], S. S. TENNYSON[1,2], F. GAYE[1], M. R. ROESCH[1,2]
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Abstract: Cognitive control, or the ability to flexibly adjust behavior in accordance with internally maintained goals, while simultaneously suppressing more automatic responses that distract from this goal, is an essential component of cognition and is often diminished in patients with schizophrenia and depression (Kollings et al., 2016; Shenhav et al., 2016). The neuroimaging literature has suggested that deficits in cognitive control correspond to diminished or abnormal activity in the anterior cingulate cortex (ACC) (Dalley and Robbins, 2017). Utilizing a stop-change task in rats, recent data suggests that ACC is important for detecting conflict between two competing inputs, showing higher firing rates on STOP trials, that are positively correlated with behavioral accuracy and movement speed (Bryden et al., 2018). These early findings are some of the first to suggest that ACC detects response competition in rodents. However, it remains unclear what the downstream consequences of successful conflict detection are. Previous research suggests that the dorsal medial striatum contains neurons that are directionally selective during performance of the stop-change task (Bryden et al., 2012). To examine whether putative 'conflict' signals in ACC are important for regulating overall behavior we infused ibotenic acid unilaterally to lesion neurons and passing fibers in ACC, while simultaneously recordings from downstream neurons in the DMS as rats performed a stop-change task. We predicted that unilateral lesions will disrupt performance on STOP trials only when the STOP signal is presented on the side of the rat that is contralateral to the lesion. These data are important for establishing the physiological and behavioral relevance of the apparent 'conflict' signals generated in ACC.

Disclosures: A.T. Brockett: None. **S.S. Tennyson:** None. **F. Gaye:** None. **M.R. Roesch:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.04/BBB3

Topic: H.01. Animal Cognition and Behavior

Support: Life Sciences Research Foundation
Klingenstein-Simons
MQ
NARSAD
Whitehall
R01DA042038

Title: Punishment history modulates medial prefrontal cortex responses to ambiguous stimuli

Authors: *F. LUCANTONIO, A. J. CHANG, J. Y. COHEN
Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: Making optimal decisions in the face of ambiguous information is fundamental to adaptive behavior. These decisions are influenced by context: prior exposure to punishments in an environment biases decisions about ambiguous outcomes toward avoidance and away from approach. The medial prefrontal cortex (mPFC) is involved in context-based decision making, but how its neurons regulate behavioral responses to ambiguous stimuli is unclear. To address this question, we trained head-restrained mice on a Pavlovian discrimination task in which one odor predicted sucrose (an appetitive sweet solution), while a different odor predicted denatonium (an aversive bitter solution). Mice showed anticipatory licking responses after sampling the positive, sucrose-predicting cue and withheld licking after sampling the negative, denatonium-predicting cue. Mice were assigned to two groups, one in which they were also exposed to an odor that predicted an unavoidable air puff delivered to their face, the other in which they were exposed to an odor that predicted no outcome. After learning, we measured behavioral responses to ambiguous stimuli by exposing mice to mixtures of varying proportions of sweet- and bitter-predicting odors, without reinforcement. Licking rates for odor mixtures scaled with the proportion of the mixture that was the sweet-predicting odor, indicating that mice responded to parametrically varying ambiguous stimuli with smoothly varying behavioral responses. Mice exposed to air puffs responded to ambiguous odor mixtures with fewer licks during the anticipatory period, consistent with a negative bias to the ambiguous stimuli. During the task, we recorded action potentials extracellularly from mPFC. Firing rates in mPFC neurons in mice exposed to air puffs were enhanced selectively during ambiguous mixture trials, compared to neurons in mice not exposed to air puffs. Given the enhanced firing rate in neurons of mice exposed to air puffs, we next asked whether manipulation of mPFC activity would

modify behavioral responses to ambiguous stimuli. We expressed channelrhodopsin-2 in pyramidal neurons in mPFC and excited them during ambiguous mixture trials. Mice showed decreased licking responses during these trials, mimicking the effects observed in mice exposed to air puffs. These results demonstrate that exposure to negative events can bias decisions under ambiguity by altering the activity of mPFC neurons.

Disclosures: F. Lucantonio: None. **A.J. Chang:** None. **J.Y. Cohen:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.05/BBB4

Topic: H.01. Animal Cognition and Behavior

Title: Ventromedial thalamic projection neurons to prelimbic cortex in cost-benefit decision-making

Authors: *B. SIEVERITZ, M. GARCIA-MUNOZ, G. W. ARBUTHNOTT
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Abstract: Ventromedial thalamic projection neurons target and drive prelimbic corticostriatal neurons (Arbuthnott et al., Neurosci 38:1, 1990; Collins et al., Neuron, 2018) that are involved in cost-benefit decision-making. Cost-benefit decision-making provides animals with a choice between a high cost/high reward and low cost/low reward option. Optogenetic inhibition of prelimbic corticostriatal neurons increases the choice of rats for the high cost/high reward option, while optogenetic stimulation increases the choice for the low cost/low reward option (Friedman et al., Cell 161:6, 2015). Ventromedial thalamic nucleus has also been implied in predicting choice behaviour (Tanaka, J Neurosci 27:44, 2007) and as such ventromedial thalamic input to prelimbic cortex may play a crucial role in cost-benefit decision-making. The aim of the presented study was to determine, if ventromedial thalamic projection neurons to prelimbic cortex are involved in cost-benefit decision-making.
We trained five week old male Sprague-Dawley rats on a benefit-benefit, cost-cost, and cost-benefit decision-making task. These tasks offer animals a choice between i- a high and low reward option, ii- a high and low cost option, and iii- a high reward/high cost and low reward/low cost option. The concentration of the low reward, diluted sweetened condensed milk, was adjusted for each animal so that animals chose the low reward/low cost option in roughly 50% of the trials on the cost-benefit decision-making task. As soon as animals acquired the task, either a virus expressing archaerhodopsin (AAV5-CAG-ArchT-GFP) or a control virus not expressing archaerhodopsin (AAV5-CAG-GFP) was injected into ventromedial thalamic nucleus (interaural zero AP +7.0, ML -1.2, bregma DV -6.6). An LED fiber probe was implanted into prelimbic cortex (bregma AP +3.72, ML -0.1, DV -3.6). After two weeks the virus was

expressed in ventromedial thalamic axon terminals in prelimbic cortex and the performance of animals on all three tasks was tested under two conditions; with and without administering optogenetic inhibition to ventromedial thalamic axon terminals in prelimbic cortex. The choice behaviour of animals was compared between conditions. Early results suggest that on the cost-benefit decision-making task optogenetic inhibition increases the preference of animals for the high cost/high reward as compared to the low cost/low reward option by about 15%; from choosing the high cost/high reward option in about 60% of the trials to choosing it in about 75% of the trials. The preference of animals remained unchanged on the other two tasks.

Disclosures: B. Sieveritz: None. **M. Garcia-Munoz:** None. **G.W. Arbuthnott:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.06/BBB5

Topic: H.01. Animal Cognition and Behavior

Support: Marie Curie SOCIORATS

Title: Characterizing empathy-driven prosocial behavior in rats

Authors: *J. HERNANDEZ-LALLEMENT[1], V. GAZZOLA[2], C. KEYSERS[2]
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Abstract: Showing what is commonly referred to as prosocial behaviors is appreciated and rewarded in human society, whereas anti-social actions often lead to isolation and reclusion. While neuroimaging can explore vicarious activations using correlational approaches, it cannot influence neuronal activity (hence limiting insights into causality), and have a limited spatial resolution. Here, we present a rodent model of empathy-driven prosocial behavior, suited for cutting-edge neuroscientific manipulations, which scrutinizes the response to other's distress in the form of prosocial (help) or anti-social behaviors (aggression). In this task, rats first developed a preference for a higher value option in a binary choice situation. In a second phase, choosing that option led to a punishment to an adjacent conspecific. Accordingly, if other’s distress carries a negative value for some individuals (prosocial) but not for others (instrumental aggressors), the first group should switch preference while the second should stick with the higher value option while accepting the collateral damage to others. Importantly, animals had experienced the shock delivered to the partner in a prior self-experience session. We found that a subset of animals switched their previously acquired preference upon association with a shock to a conspecific, hence behaving pro-socially. Interestingly, the time delay between self-experience and prosocial task was crucial: animals that underwent self-experience shortly before the prosocial task behave

more prosocially than rats that experienced the shock at an earlier period. Moreover, while all animals perceived the conspecific's reaction to the shock, only a subset of animals behave prosocially, raising potential distinctions between prosocial and indifferent/antisocial individuals (i.e., hurting others to obtain food). Hence, this behavioral paradigm provides means to scrutinize both pro- and anti-social behaviors. Indeed, while the *first group* allows examining how the perception of other's distress promotes pro-social behavior, the *second group* enables exploring what predisposes some individuals to disregard the distress of others.

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Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

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Title: Plasticity in the ventromedial prefrontal cortex underlies the therapeutic effects of fear extinction

Authors: *D. PAREDES[1], E. A. FUCICH[1], D. A. MORILAK[2]
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Abstract: Current treatments for stress-related psychiatric disorders such as depression and posttraumatic stress disorder (PTSD) are inadequate. Behavioral therapies can be effective in the treatment of these disorders. However, little is understood about the neurobiological mechanisms underlying behavioral interventions. We have previously shown that fear extinction (i.e. learning that an innocuous cue previously associated with a fearful stimulus no longer predicts that stimulus) can be used to model the effects of exposure therapy on cognitive flexibility that have been compromised in chronically stressed rats. In addition, using Gi-DREADDs, and Gq-DREADDs, we have observed that activity of glutamatergic neurons in the ventral medial

prefrontal cortex (vmPFC) during extinction is necessary and sufficient for the therapeutic effects of extinction learning on cognitive flexibility and coping behavior. Thus, in these experiments we set out to test the hypothesis that fear extinction restores stress-induced hypo-responsivity in the mPFC. We found that CUS reduced mPFC responsivity, assessed by measuring afferent-evoked field potentials in the mPFC, and this reduction was reversed by extinction treatment. Additionally, we investigated whether the expression of glutamate receptors in the mPFC is altered by chronic stress and extinction. Preliminary results suggest that GluA1 expression is decreased in stressed animals, and fear extinction following chronic stress normalizes the expression of GluA1 back to control levels. Thus, plasticity in the vmPFC underlies the long-lasting beneficial effects of fear extinction on cognitive flexibility.

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Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

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Wellcome Trust UK Grant 105238/Z/14/Z

Title: Global and local effects of focused ultrasound neuromodulation on resting-state connectivity

Authors: *L. VERHAGEN[1], C. GALLEA[4], D. FOLLONI[1], C. CONSTANS[5], D. JENSEN[1], M. SANTIN[4], S. LEHERICY[4], K. KRUG[2], R. B. MARS[3,6], M. F. RUSHWORTH[1], P. POUGET[7], J.-F. AUBRY[5], J. SALLET[1]
[1]WIN, Dept. of Exptl. Psychology, [2]Dept. of Physiology, Anatomy, and Genet., [3]WIN, Nuffield Dept. of Clin. Neurosciences, Univ. of Oxford, Oxford, United Kingdom; [4]Inst. du Cerveau et de la Moelle épinière - ICM, Ctr. for NeuroImaging Res. - CENIR, Inserm U 1127, CNRS UMR 7225, Sorbonne Université, F-75013, Paris, France; [5]Inst. Langevin, ESPCI ParisTech, CNRS 7587, UMRS 979 INSERM, Paris, France; [6]Donders Inst. for Brain, Cognition and Behaviour, Radboud Univ. Nijmegen, Nijmegen, Netherlands; [7]Inst. du Cerveau et de la Moelle épinière - ICM, UMRS 975 INSERM, CNRS 7225, UMPC, Paris, France

Abstract: Introduction
We aim to investigate the effect, efficacy, and reproducibility of focused ultrasound

neuromodulation (FUN) using resting-state fMRI (rs-fMRI) in *Macaca mulatta*. We compare stimulation targeted at two frontal regions, supplementary motor areas (SMA) and frontal polar cortex (FPC).

Methods

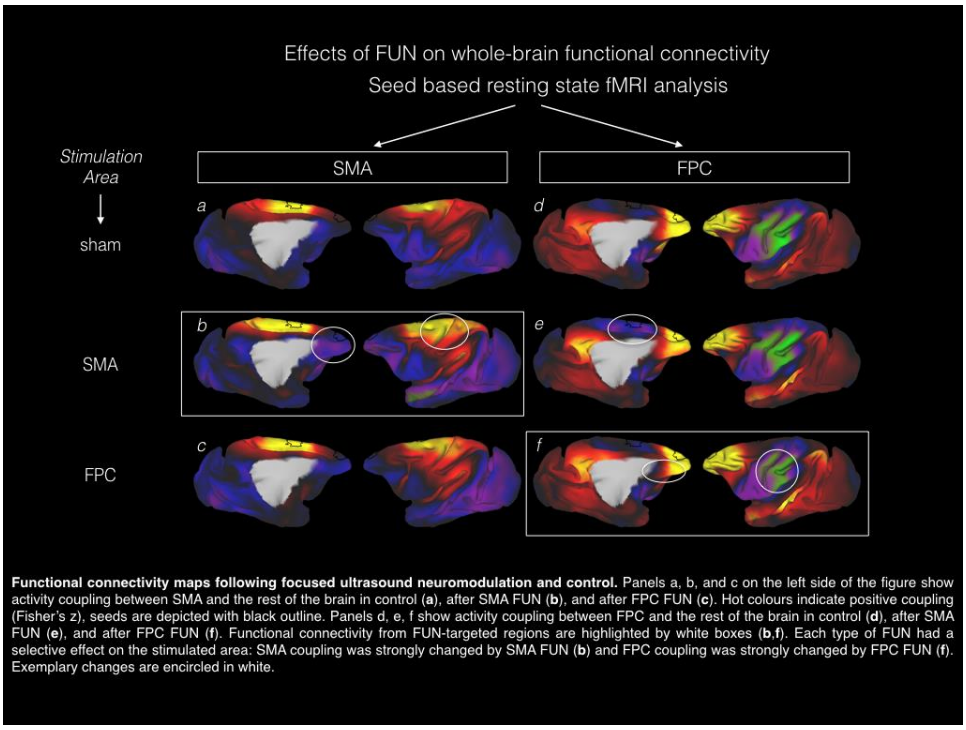
A single-element ultrasound (US) transducer, focused at ~5cm, was used to stimulate either SMA or FPC or used in a sham procedure in 3 macaque monkeys. We delivered US waves at 250 kHz in 100ms bursts for 40 seconds, targeted based on each animal's individual anatomy by neuronavigation. We subsequently acquired rs-fMRI data for up to 90 minutes at 3T under isoflurane anaesthesia.

Results

We investigated the off-line effects of FUN targeted at SMA and FPC by quantifying changes in functional connectivity between these areas and the rest of the brain. First, we found that FUN induced signal changes in the cerebral spinal fluid leading to widespread synchronisation in this compartment, suggesting that it sometimes exerted an extensive vascular effect. Importantly, however, in the grey matter FUN induced region-specific changes in coupling with the stimulated area. Namely, FUN applied to SMA transiently and reversibly changed its coupling with the sensorimotor system and prefrontal cortex. Consistently, FUN targeted at FPC changed coupling with prefrontal and cingulate regions. FUN increased coupling between the stimulated area and areas normally closely connected with it while, at the same time, decreasing coupling between the stimulated area and areas normally less closely connected with it. These effects were replicated in a set of control animals (n=3), and across repeated sessions (n=4) in a single individual.

Conclusion

FUN leads to a sharpening of the stimulated region's connectivity profile in a non-invasive and reversible manner with high efficacy, spatial resolution, and reproducibility.



Functional connectivity maps following focused ultrasound neuromodulation and control. Panels a, b, and c on the left side of the figure show activity coupling between SMA and the rest of the brain in control (**a**), after SMA FUN (**b**), and after FPC FUN (**c**). Hot colours indicate positive coupling (Fisher's z), seeds are depicted with black outline. Panels d, e, f show activity coupling between FPC and the rest of the brain in control (**d**), after SMA FUN (**e**), and after FPC FUN (**f**). Functional connectivity from FUN-targeted regions are highlighted by white boxes (**b**,**f**). Each type of FUN had a selective effect on the stimulated area: SMA coupling was strongly changed by SMA FUN (**b**) and FPC coupling was strongly changed by FPC FUN (**f**). Exemplary changes are encircled in white.

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Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

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Program #/Poster #: 507.09/BBB8

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 4R00AA021780-02
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Whitehall Foundation

Title: The role of the secondary motor cortex in feedback integration to guide decision-making

Authors: *D. C. SCHREINER[1], C. M. GREMEL[1,2]
[1]Psychology, [2]Neurosciences Grad. Program, Univ. of California San Diego, La Jolla, CA

Abstract: While much research has focused on motivational control of decision-making (e.g. do I want the outcome), less understood is how decision-making integrates and responds to ongoing feedback (e.g. was my action successful). Feedback can also include ongoing, internal representations of progress such as confidence or action plans. The neural mechanisms responsible for integrating feedback in goal-directed decision-making are unclear. We adapted a self-initiated, self-paced, and un-cued lever press task in mice to assess feedback during decision-making. Mice are trained to hold down a lever for at least a given duration to earn a food reward across days (i.e. >400ms to >800ms to >1600ms). Mice modify their lever press duration based on whether or not they successfully met the target on the previous press. If mice fail to reach the target they increase the duration of their next press, whereas if they meet the target they decrease the duration of their next press (on average). When we manipulated reward probability we found internal feedback (confidence) resulted in a subsequent change in next lever press duration similar to external food delivery cues. Secondary motor cortex (M2) has been implicated in associative integration for behavioral selection. Preliminary evidence suggests that acute chemogenetic inhibition of M2 impairs task performance and decreases the feedback-induced change in subsequent lever press duration. Optogenetic inhibition of M2 projection neurons across the duration of lever presses similarly decreased feedback-induced changes in press duration. Interestingly, inhibition during only the first 400ms of a lever press increased the subsequent change in lever press duration and increased task performance. We used fiber photometry to record calcium activity in M2 projection neurons. Preliminary evidence shows preparatory calcium activity in M2 prior to action initiation followed by suppression of calcium activity during early action performance, with the magnitude of calcium activity suppression increasing with longer press durations. Our results provide evidence for M2 as a key locus in utilizing internally and externally generated evidence (e.g. feedback) to modulate ongoing goal-directed action contingencies during decision-making.

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Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

Support: NIH grant 5-R01-MH108358

Title: Neural dynamics underlying decision making in a dynamic environment

Authors: A. PIET[1], *A. EL HADY[2], C. BRODY[2]
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Abstract: How are choices made within constantly-changing noisy environments? The gradual accumulation of noisy evidence is considered to be a fundamental component of decision making, but has usually been studied in stationary environments. We trained rats on an auditory decision-making task in a changing environment (Piet 2018). Crucially, in a dynamic environment, subjects must discount old evidence that may no longer be informative about the current state of the environment. Using high-throughput behavioral training and quantitative modeling, we find that rats can optimally discount evidence in a dynamic environment. The optimal timescale for evidence discounting is a function of both the environmental variability, and the reliability of the noisy evidence. The reliability of the noisy evidence in turn depends on both the noisy stimulus, and the subject's sensory noise. When accounting for sensory noise, the find that rats accumulate and discount evidence on the optimal timescale. Additionally, we demonstrate that individual rats rapidly adjust their discounting timescales in response to changes in the environmental variability. Due to the dynamic nature of each trial, subjects change their mind often during each trial allowing experimental measurement of changes of mind within one trial. Further, these changes of mind are driven by internal estimates of accumulated evidence. Our behavioral task thus facilitates the investigation of neural mechanisms underlying evidence integration and discounting, as well as changes of mind. Previous studies of rat decision making have identified a cortical structure, the Frontal Orienting Fields (FOF) as a potential substrate for upcoming choice memory (Erlich 2011, Erlich 2015, Hanks 2015, Piet 2017). We recorded spike trains from FOF neurons, and analyzed their dynamics and their relationship to the dynamic evidence.

Disclosures: A. Piet: None. **A. El Hady:** None. **C. Brody:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

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Program #/Poster #: 507.11/BBB10

Topic: H.01. Animal Cognition and Behavior

Support: NIH/IRP

Title: Neural representation of a Bayesian belief in the macaque prefrontal cortex during reinforcement learning

Authors: *R. BARTOLO, R. C. SAUNDERS, A. R. MITZ, B. B. AVERBECK
NIMH/NIH, Bethesda, MD

Abstract: In a noisy environment, learning requires organisms to keep track of choices and their associated outcomes across successive decisions to form beliefs about value in the world. This allows them to predict future outcomes and to update their belief after each outcome. The

primate prefrontal cortex (PFC) integrates information carried by reward circuits, in addition to its role in working memory. The present study explores the PFC computations related to updating current beliefs in multifaceted reward environments. We conducted high-channel count single-unit recordings in two male macaques (N=3225 neurons), while they executed a two-armed bandit reversal learning task, responding with a saccade towards the chosen target. Through trial and error, animals associated either screen locations or images with a reward. In each block of 80 trials, one of two images (WHAT blocks) or one of two locations, at which the images randomly appeared (WHERE blocks), had a higher reward probability with respect to the other. The block type was randomized and not cued, so the animals had to form a belief about whether WHAT or WHERE determined the reward during each block. The reward contingencies were reversed near the middle of each block at a randomly defined trial within a fixed interval (trials 30-50), requiring the animals to reverse their choice preference. Critically, the monkeys were highly familiar with the fact that there were two possible block types and that a reversal would occur within each block. Behavioral analyses showed that they used this prior knowledge to guide reversals in their choice preference. Detailed knowledge of the task structure also allowed us to fit a Bayesian model to the monkeys' choice data, from which we estimated posterior distributions over block type and the reversal trial for each block of trials. Next, we looked for associations between the Bayesian posterior estimates and activity of prefrontal cortex neurons. We found persistent encoding of posterior estimates of the block type, as well as encoding of posterior probability that a reversal occurred. We also found strong encoding of saccade direction, regardless of the block type. This contrasted with relatively weak encoding of the stimulus identity of the chosen option. Overall these results suggest that prefrontal neurons encode oculomotor decisions associated with Bayesian subjective values and highlight the role of the PFC in representing a belief about the current state of the world.

Disclosures: R. Bartolo: None. **R.C. Saunders:** None. **A.R. Mitz:** None. **B.B. Averbeck:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.12/BBB11

Topic: H.01. Animal Cognition and Behavior

Title: Spatial attention and value encoding in the dorsolateral prefrontal cortex

Authors: *Y. XIE, W. ZHANG, T. YANG
Inst. of Neurosci., Shanghai City, China

Abstract: Both spatial attention and reward value have been shown to modulate neuronal activities in the dorsolateral prefrontal cortex (DLPFC) during decision making. However, their

interaction is unknown. Here we developed a behavioral paradigm that allowed us to tease apart the two factors. Two monkeys were first trained to learn the associations between five shapes and their respective rewards, which were 0, 1, 2, 4, 8 drops of juice. After the monkeys learned the stimulus-reward association, we then trained them to perform a visual detection task. The monkeys were required to fixate at a center point when two shapes were presented on both the left and the right sides of the fixation point. After a random period, the luminance of one of the shapes changed (go cue), and the monkeys had to report this change by saccading to a target 6 degrees above the fixation point within 400 ms after the go-cue onset. A square frame was presented for 400 ms at 200ms before the shapes as the attention cue. For 85% of the trials (valid), the go cue appeared on the opposite side of the frame. For the other 15% of trials (invalid), the go cue appeared on the same side of the frame. If the monkeys correctly detected the visual change, a reward was delivered at the end of the trial. The reward was randomly chosen between the associated rewards of the two shapes presented in the trial. The accuracy and the reaction time measurements indicated that the monkeys performed the task and assigned their attention appropriately.
We then recorded single unit activity in the DLPFC. Divided by their spatial preferences, 27.2% of the DLPFC neurons' activities were higher when monkeys attended to the contralateral location and 21.1% of the neurons' activities were higher when monkeys attended to ipsilateral location. Divided by their value preferences, 39.8% of the neurons preferred higher value while 16.5% preferred lower value. The neurons that were spatially selective and preferred higher value signaled only the value of their preferred location. The neurons that preferred lower value signaled the average value of the two stimuli. The neurons that showed no significant spatial preference but value preference also encoded the average value. Our results suggest that spatial attention and reward value are encoded differently by different groups of DLPFC neurons.

Disclosures: Y. Xie: None. **W. Zhang:** None. **T. Yang:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.13/BBB12

Topic: H.01. Animal Cognition and Behavior

Title: Developing a task for examining the contribution of reward and cost to decision-making

Authors: S. TANIMOTO[1], *M. KONDO[1,3], K. MORITA[2], M. MATSUZAKI[1]
[1]Grad. Sch. of Med., [2]Grad. Sch. of Educ., The Univ. of Tokyo, Tokyo, Japan; [3]JSPS Reserch Fellow, Tokyo, Japan

Abstract: Animals choose something and act appropriately in their daily life. Since all sorts of actions need energy and cost, animals have to compute the reward expected from individual

actions and the cost to act before they decide which action should be chosen. One of the inevitable and simple costs is the physical cost accompanying muscle contractions. To address how the relationship between the reward expectancy and the physical cost affects the decision-making, we developed a simple behavioral task in which mice chose whether to pull the lever or not in response to two different tones. Two different tone cues were respectively assigned to two different probabilities of water delivery (reward probabilities) after a successful lever pull. No reward was delivered when the lever was not successfully pulled. If the mouse learns that the cost value to pull the lever with its right forelimb is higher than the expected value of the reward associated with a tone cue, the mouse will not pull the lever in response to this cue. As expected, after two-week training sessions, the probability to pull the lever stayed approximately 100% when the tone cue assigned to a high reward probability was presented, while it decreased to 0-30% when the other tone cue with a low reward probability was presented. However, the probability to pull the lever did not necessarily depend on the absolute value of the reward probability because the mice pulled the lever frequently in response to a tone cue with a relatively low reward probability if the other cue was assigned to a much lower reward probability. These results suggest that the mice used the relative value of the tone cue rather than the absolute value for decision-making in the lever-pull action. In order to clarify how the value of each cue and the cost value are computed in the mouse brain, we are trying to fit the changes in the mouse behaviors during learning of the task to reinforcement learning scheme. This task will help us understand the neural mechanisms underlying the computation of the reward expectancy and the physical cost.

Disclosures: S. Tanimoto: None. **M. Kondo:** None. **K. Morita:** None. **M. Matsuzaki:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

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Program #/Poster #: 507.14/BBB13

Topic: H.01. Animal Cognition and Behavior

Title: Risk-dependent choice following the lesion of medial prefrontal cortex in the rat

Authors: *Y.-H. YANG[1], C.-Y. CHUANG[2], S.-F. CHEN[3], R.-M. LIAO[4]
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Abstract: Despite a growing body of research showing the cortico-striatal systems involved in the decision making under risk, how the subareas of prefrontal cortex modulate in the risk-based decision making remains unclear. This study used a T-maze task of risk dependent choice which the rat was required to assess a certain level of risk through choosing either a small and certain

reward arm or a large but uncertain reward one. The choice of latter option was given with a probability (*p*) of 0.5, 0.25, or 0.125 correspondingly given by 2, 4, or 8 sweet pellets in three different reward ratios, whereas the choice of former one was always ended by 1 pellet given for certain (in $p = 1$). This risk choice task was then run with the expected value in equal for binary choice options. The rats first received ibotenate lesion in the medial prefrontal cortex (mPFC) and followed by post-lesion behavioral examination. The rats were randomly assigned to six groups; each received either lesion or sham lesion and tested under a specific reward ratio. A risk-dependent choice pattern appeared in the rats with sham lesion control over a 7-day test. They chose more large/risky than small/certain reward when $p = 0.5$ to obtain 2 pellets, and it shifted to a risk-averse style when larger reward given in lower *p*. The mPFC lesion did not significantly disrupt the acquisition of aforementioned risk-dependent choice. Neither the gross motor action nor the discrimination capability was impaired by the present mPFC lesion. These results, together with our lesion data of orbitofrontal cortex (OFC), suggest that the mPFC and OFC might be dissociated in the acquisition of risk-dependent choice.

Disclosures: Y. Yang: None. **C. Chuang:** None. **S. Chen:** None. **R. Liao:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.15/BBB14

Topic: H.01. Animal Cognition and Behavior

Title: A two alternative forced choice paradigm using homecage training to reduce training time in an Air-Track floating platform

Authors: *A. NASR[1], M. NASHAAT[2], S. DOMINIAK[2], R. SACHDEV[2], M. LARKUM[2]
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Abstract: Training of head fixed mice to perform complex behaviors is a time-sink, almost a full time job in itself. Not only do highly expert neuroscientists spend a lot of time training mice to perform tasks, but often it is not clear that the head fixed behavior is natural. Optimally, animals should perform a task that is not too deviant from normal behavior and it should be possible to use available techniques for recording from the brain, many of which could involve head-fixation (2-photon imaging, whole-cell patch recordings, etc.). Here, we try to make it easier to use the floatingplatform method, the Air-Track system (Nashaat et al., 2016, J. Neurophys), in a two-alternative forced-choice paradigm by training mice in their home cages, without head fixation, and we examine whether the behavior is natural. We trained mice (n=10) in a Y-maze in which the animals choose between the two alternative lanes on the basis of sound and light cues. Rodents typically take several weeks to learn two-alternative type tasks while head-fixed (Burgess et al., 2017, Cell Reports). However, the advantage of the Air-Track system is that it

can be easily adapted to a freely-moving homecage version in which animals can learn in an automated (unsupervised) environment. This reduces the time investment of the researcher significantly. Here, we present data showing that when pre-trained in the homecage version using the AirTrack apparatus in the Y-maze configuration, animals retain the knowledge of the task in the head-fixed condition. After habituation to head-fixation on the floating platform, and in the Air-track, animals rapidly reach the >80-90% performance, that they had in the homecage within 1-2 days. Furthermore, while the sequence of behaviors emitted by the animal when performing the task freely in the home cage and when head fixed in the Air-Track were similar, the speed of movement was slower when animals were head-fixed. Both the homecage and Air-Track environments can be easily manufactured for <$1000 and all the CAD diagrams and control software are publicly available. We conclude that by combining AirTrack with homecage pre-training, it is not only possible to reduce the researcher supervised time spent per experiment but also to train mice in more complex tasks which would normally not be possible due to time constraints.

Disclosures: A. Nasr: None. **M. Nashaat:** None. **S. Dominiak:** None. **R. Sachdev:** None. **M. Larkum:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.16/CCC1

Topic: H.01. Animal Cognition and Behavior

Support: 100 talents program,Chinese Academy of Sciences

Title: The role of frontal eye fields in mixed-strategy decision-making

Authors: *S. XIE, M. C. DORRIS
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Abstract: The primate prefrontal lobes are implicated in the abstract computation required for complex cognitive behaviors such as decision-making. The transformation from such abstract computation into premotor commands necessary for enacting choice remains unclear. The Frontal Eye Fields (FEF) may be important in this process because it receives diverse prefrontal inputs and sends premotor commands to the brainstem Superior Colliculus (SC). Here, we examined the role of the FEF during strategic saccadic decision-making. We trained monkeys to perform a saccadic version of the mixed-strategy game Matching Pennies. On each trial, monkeys directed a saccade to one of two targets, one of which was placed in an FEF neuron response field. A computer opponent dynamically exploited monkeys' choice pattern, hence monkeys approached the Nash Equilibrium strategy of choosing stochastically. FEF activity

became increasingly predictive of upcoming choices as the deadline for saccade approached. To test causality, we applied sub-threshold microstimulation to the FEF in an effort to enhance FEF activity for a particular vector but at a level unable to directly trigger saccades. Indeed, microstimulation biased choice, but unexpectedly, away from the stimulation vector rather than towards it. To examine possible reasons for this counterintuitive result we performed a number of control microstimulation experiments. Extending microstimulation throughout the decision and motor epochs further exacerbated the biasing effect.
To determine whether this biasing-away effect was confined only to strategic decisions, we designed a perceptual guided decision task. As much as possible we kept the parameters the same but, instead of volitional choices, monkeys were trained to saccade towards the brighter of two targets. Notably, sub-threshold FEF microstimulation also shifted monkeys' psychometric curves away from the stimulation site during perceptual decision-making.
Our neuronal recording and microstimulation results demonstrate that FEF plays an active role in mixed-strategy saccade decision-making. However, the mechanism underlying the biasing-away effect of microstimulation still needs more empirical evidence. Some possibilities include: a) FEF plays a monitory role and provides negative feedback signals for the decision process, b) microstimulation activates inhibitory circuits with greater efficacy, c) microstimulation recruits additional cortical areas and/or the indirect FEF◊Basal Ganglia◊SC inhibitory pathway. Ultimately, optogenetic tools may be required to isolate the role of the direct FEF◊SC excitatory pathway.

Disclosures: S. Xie: None. **M.C. Dorris:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.17/CCC2

Topic: H.01. Animal Cognition and Behavior

Title: Identification of differential gene expression profile in rats showing risk-averse and risk-seeking preferences in rat gambling task

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Abstract: Measuring expected risk is important for making rational decisions, and maladaptive decision making may underlie various psychiatric disorders. However, genetic and neural correlates involved in this process are still largely unknown. Rodent version of the gambling task (rGT) has been developed to measure decision-making in rodent by adopting the same principle of Iowa Gambling Task in humans. In the present study, we examined using next-generation

sequencing (NGS) whether there are differences in gene expression profiles in the brain when rats make different choices toward risk in rGT. Rats were trained in a touch screen chamber to learn the relationships between 4 different light signals on the window of the screen and accompanied reward outcomes or punishments set up with different magnitudes and probabilities. Once they show a stabilized pattern of preference upon free choice, rats were classified into risk-averse or risk-seeking group. Besides, an additional group of rats were raised in home cage without any exposure to rGT training. After classification in rGT, rats were decapitated, the prefrontal cortex (PFC) and the nucleus accumbens (NAc) were dissected out from their brains, and NGS was performed with total RNA extracted. We found that there were significant differences in 7,875 genes (fold change>1.5, $p<0.05$) up or down-regulated in rGT compared to control rats, regardless of their brain regions or risk preferences. When comparing risk-averse group to risk-seeking group regardless of their brain regions, 21 genes were found to be significantly different. Interestingly, however, when looking at each brain region separately, 68 genes were identified as significantly different in the PFC, while no genes identified in the NAcc, between risk-averse and risk-seeking groups. These results suggest that differential gene expression profile appearing in the PFC may importantly contribute to the preference toward risk choice in rGT.

Disclosures: M. Gwak: None. **S. Jung:** None. **W. Kim:** None. **M. Ku:** None. **Y. Chung:** None. **J. Kim:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.18/CCC3

Topic: H.01. Animal Cognition and Behavior

Support: HELMHOLTZ, ERC Grant Agreement #610110

Title: functional ultrasound reveals single trial cerebral activation in non-human primates during behavior

Authors: *A. DIZEUX[1,2], M. GESNIK[2], H. AHMINE[3], K. BLAIZE[4], F. ARCIZET[3], S. PICAUD[4], T. DEFFIEUX[2], P. POUGET[3], M. TANTER[2]
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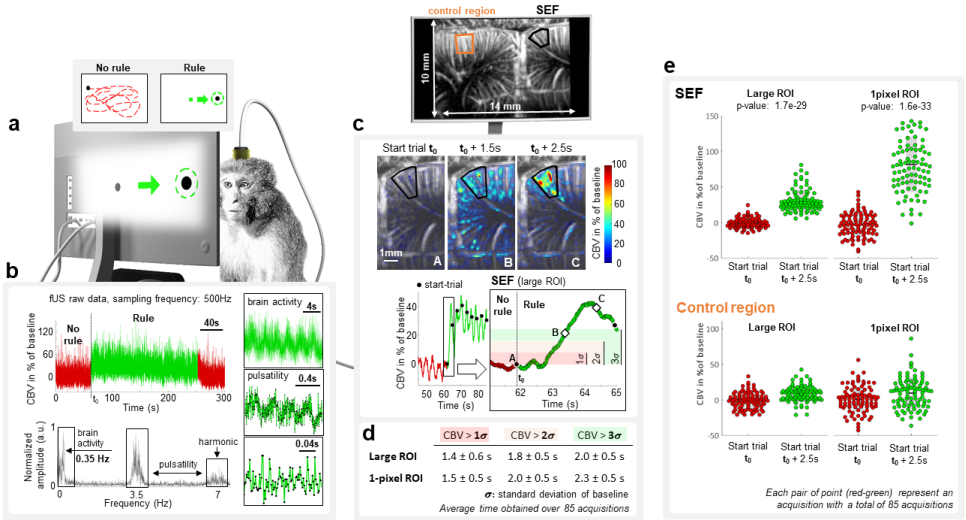
Abstract: In the current study, we captured the cerebral blood volume (CBV) variations from the supplementary eye field (SEF), a dorso-medial frontal cortex area active during eye movements tasks in non-human primate using functional ultrasound (fUS) [1]. We recorded SEF region in the context of cognitive tasks when a primate is awake and freely behaving without the need for any statistical averaging.

Functional data were acquired with 2 trained captive-born macaques (Maccaca Mulatta) performing baseline (rest phase), fixation, pro-saccade and anti-saccade trials in a blocked design of 60 seconds each (~ 20 trials/task) for a total of 85 different acquisitions (Fig 1.a). Eye position of primate was monitored at 1 kHz with an eyetracker camera which enabled live control of behavioral paradigm and delivery of liquid reward based on success or failure of visual task. Variation of CBV was measured using a linear ultrasound probe (15 MHz, 110x100 µm² of spatial resolution, FOV 14×10 mm^2) inserted in an electrophysiology recording chamber and driven by an ultrafast ultrasound research scanner. Filtered ultrasound images (11 steered ultrasound plane-waves fired at 5500 Hz) revealed both brain activity (~0.35Hz) and pulsatility (~3.5Hz) (Fig 1.b). A spatio-temporal movie of CBV in SEF (Fig 1.c) was then reconstructed (temporal sliding window of 250ms, increment 20ms). For all the sessions, peak amplitude of the CBV signal increased in the SEF on average by 31.3 ± 15.2 % over baseline in large ROI and up to 84.8 ± 38.7 % in 1-pixel ROI. Only a single pixel was thus sufficient to detect a significant modulation of CBV signal (Fig 1.e). Moreover, even in a single pixel ROI, only the first single trial of each block was needed to increase and detect CBV above 2 standard deviation from baseline after just 2.0 ± 0.5 s (Fig 1.d).

Our study demonstrates the capacity and the interests of using fUS to map cortical brain areas in awake non-human primates at a single trial level.

Figure 1: The high sensitivity to CBV changes of fUS (functional Ultrasound) Imaging give access to single trial detection of Supplementary Eye Field (SEF) activation during visual tasks



Disclosures: A. Dizeux: None. **M. Gesnik:** None. **H. Ahmine:** None. **K. Blaize:** None. **F. Arcizet:** None. **S. Picaud:** None. **T. Deffieux:** None. **P. Pouget:** None. **M. Tanter:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.19/CCC4

Topic: H.01. Animal Cognition and Behavior

Support: Lundbeck Foundation

Title: Time to decide: How decision time affects choices

Authors: *J. MARTIN, D. KVITSIANI
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Abstract: One of the functions of the brain is to integrate environmental information with internal states to produce behavior. In probabilistic environments optimal decision-making is guided by past experiences such as rewards, a process that is marvelously captured by reinforcement learning (RL) models. In this project, we investigate how elapsed time prior to the choice affects the decision process. To this end, we established a dynamic matching task in mice similar to the task performed in monkeys by Lau et al. (2005). Briefly, after correct trial initiation, the animal can choose freely between two ports, where water rewards are delivered independently and probabilistically on a concurrent variable rate schedule. In addition to reward probabilities, however, we systematically manipulate the wait durations during trial initiation. According to Herrnstein's matching law animals assign their choices relative to the experienced reward ratio. We find that this sensitivity is different for distinct wait delays with a seemingly higher sensitivity on longer trials. Moreover, animals tend to switch more often between options upon short wait delays independent of the preceding reward experience. Regression analysis reveals that this is due to an increased influence of past choices while the impact of past rewards remains similar. This suggests that animals use different choice strategies depending on the elapsed waiting time by integrating previous experiences to different degrees. We are currently in the process of testing various models ranging from Win-Stay-Lose-Shift to RL models and a mixture of these to understand the mechanisms that may contribute to the observed behavior. Furthermore, in order to reveal the neural representation of task relevant variables we are simultaneously recording in the medial prefrontal cortex (mPFC). Because previous work by Kvitsiani et al. (2013) showed that Parvalbumin (PV) interneurons in the mPFC encode elapsed time, we focus our analysis on optogenetically identified PV cells enabling us to dissect their potential function in the underlying circuit.

Disclosures: D. Kvitsiani: None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.20/CCC5

Topic: H.01. Animal Cognition and Behavior

Support: Lundbeck Foundation: Grant: R191-2015-1506

Title: Neural population analysis of reward expectation and choice trace in mouse medial prefrontal cortex

Authors: *D. KVITSIANI[1], J. LOPEZ[2], J. MARTIN[1]
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Abstract: Reinforcement learning (RL) models have been successfully used to explain animal choices and activity of selected neurons in decision making tasks. In the RL framework, the reward expectation and the choice trace are key variables that dictate the probability of the upcoming choice. However it is not entirely clear how a neural population as opposed to single neurons encodes those variables. To address this question we set up a free-choice task in mice while recording neurons from the medial Prefrontal Cortex (mPFC). In this task, the animals were asked to choose between two side ports that delivered water rewards probabilistically. These probabilities changed in a blockwise manner without providing any cues for the transitions. Thus, the animals had to rely on their internal estimate of reward income to adjust their choices, which they quickly accomplished. The performance of the animals was best captured by an improved-version of RL model that allowed us to map the extracted learning rates of the reward expectation and choice traces to the neural representations using the mean of multivariate LASSO regressions. Despite diverse representations across individual neurons, we found that the information about choices and reward expectation was best captured by population activity. To further validate the experimentally observed neural representations, we built a recurrent neural network (RNN) that recapitulated some of the key aspects of biologically observed neural dynamics. Our results suggest that task relevant- information is distributed in neural population.

Disclosures: D. Kvitsiani: None. **J. Lopez:** None. **J. Martin:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.21/CCC6

Topic: H.01. Animal Cognition and Behavior

Support: ERC-CoG-617142

Title: ACC inactivation impairs performance monitoring in mice

Authors: *R. F. OLIVEIRA[1], I. O. R. VAZ[1], T. AKAM[2], R. M. COSTA[3]
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Abstract: When a musician performs a difficult piece, actions have to be performed with striking accuracy. Previous work has shown that after a self-paced action sequence has been rehearsed, the trial-to-trial variability in performance decreases (precision increases). Furthermore, if the action is complex the modulation of behavior and neural variability is contingent to the relevance of each dimension (e.g. speed, duration) to the task. However, it is unclear whether animals can monitor and report their performance on a particular trial before the outcome is presented or not. To assess this we trained mice to execute a sequence of 4 or 5 lever presses to obtain a cached reinforcement. After training, animals had to wait for 8 seconds before the outcome was received, and could choose whether to wait to know the outcome or abort the trial and start again. Mice aborted more trials after incorrect than correct sequences. This leads to a U curve distribution of aborted trials with its lowest point centered around the target lengths (4 and 5). Logistic regression analysis showed that the probability of aborting the current trial depends on the recent history of aborted trials and current trial performance. We think the former reflects slowly changing task engagement, and the latter a fast performance monitoring process. Optogenetic inactivation of Anterior Cingulate Cortex impairs performance monitoring leaving effort/cost as the main fast variable determining the decision to abort or not the current trial. This translates in a shift of the U curve and a lower fraction of long sequence trials aborted when the ACC is inactivated. These results show that mice learn to perform sequences of movements within narrow constraints and that they are capable of monitoring their own accuracy in executing actions. Moreover, the data shows that variables with different time dynamics are involved in assessing action performance.

Disclosures: R.F. Oliveira: None. **I.O.R. Vaz:** None. **T. Akam:** None. **R.M. Costa:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.22/CCC7

Topic: H.01. Animal Cognition and Behavior

Support: Pew Charitable Trusts
Swiss National Science Foundation
The Simons Collaboration on the Global Brain

Title: Movement-related activity dominates cortex during sensory-guided decision making

Authors: *S. MUSALL[1], M. T. KAUFMAN[1,2], S. GLUF[1], A. K. CHURCHLAND[1]
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Abstract: The brain continually exhibits a wide array of self-generated activity related to internal state transitions and body movements. During behavior, this “internal backdrop” affects the processing of task-relevant stimuli and may have substantial consequences for decision-making. To understand the joint effects of internal backdrop and task-imposed variables on neural activity, we trained GCaMP6f-transgenic mice on a delayed two-alternative forced choice paradigm and measured neural activity across the entire dorsal cortex using a tandem lens macroscope. Concurrently, we monitored changes in internal backdrop through various self-generated parameters including pupil diameter, breathing, whisking and body motion. To attribute neural activity in specific cortical areas to internal or task-imposed variables, we used a multivariate linear regression model. The model accurately predicted changes in neural activity throughout the cortex, confirming expected areas as involved with different sensory or motor events. Surprisingly, the model revealed that internal backdrop dominated neural activity across the entire dorsal cortex and dwarfed task-related variables like sensory stimuli. Model-based reconstruction of imaging data also showed that many features that are found in a trial average are best explained by the internal backdrop. To assess whether this was true for individual neurons, we used two-photon microscopy and recorded activity over many neurons in frontal cortex. The same linear model revealed that internal backdrop had an even stronger impact on individual neuron recordings. In particular, we found that model variables that were based on animal movements were highly predictive for both meso-scale population activity as well as for single-cell data. By accounting for multiple dimensions of internal backdrop we were also able to uncover obscured signatures of truly task-related computations and identify cortical areas and individual neurons that were most likely to reflect sensory processing or decision making. Detailed quantification of movements and internal state therefore captures a fundamental

dimension of neural activity and enables previously inaccessible insights into task-related computations.

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Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.23/CCC8

Topic: H.01. Animal Cognition and Behavior

Support: NIH grant R01MH108358

Title: A modified evidence accumulation task to probe the decision time/evidence strength relationship in rats

Authors: *D. GUPTA[1], C. KOPEC[1], C. BRODY[1,2]
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Abstract: Gradual accumulation of evidence is a core cognitive process which has been shown to be involved in a wide range of decisions. In recent years, the study of evidence accumulation for perceptual decision making has been extended to rodents which has enabled a greater access to experimental methods for measurement and perturbation of underlying neural activity. However, currently most rodent tasks assay subject's decisions after a fixed duration of stimulus presentation, prohibiting the subject from responding as soon as it has made its decision. This obscures the time that was required to reach the decision, a behavioral measurement that is highly informative for mapping neural activity to the gradual decision process. To this end, we modify our existing evidence accumulation task in rats, the Poisson clicks task (Brunton et al., 2013), in order to measure decision times.
The classic Poisson clicks task involves presenting the rat subject with two simultaneous streams of randomly-timed discrete pulses of evidence (clicks), one from a speaker to their left and the other to their right, for a fixed duration. The subject must maintain fixation throughout the entire stimulus, and subsequently orient towards the side which played the greater number of clicks. The discrimination difficulty is controlled on each trial by varying the ratio of the generative Poisson rates of the two click streams.
Here we modified the Poisson clicks task by requiring the subject to sample the stimulus only until a minimum amount of evidence is reached (|total clicks left - total clicks right| > threshold), with no limit to how much longer they can choose to sample the stimulus, before they select a side response.
We find that in this new task, subjects' stimulus sampling times scale with trial difficulty, even

when considering trials in which they did not complete the experimenter-required sample time. This finding can be accounted for by a bounded evidence accumulation mechanism, similar to previous work in humans and non-human primates using reaction-time versions of accumulation of evidence tasks. We will quantitatively compare this model with alternative behavioral strategies using trial-by-trial model fitting.

Disclosures: D. Gupta: None. **C. Kopec:** None. **C. Brody:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.24/CCC9

Topic: H.01. Animal Cognition and Behavior

Support: ONR Grant no. N00014-17-1-2041

Title: Neural mechanisms of recurrent neural networks with interneurons and dendrites performing context-dependent decision making

Authors: J.-A. LI[1], *G.-Y. R. YANG[2], X.-J. WANG[3]
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Abstract: Recurrent neural network (RNN) training has been a useful tool for studying neural computation mechanisms crucial for cognition and behavior. However, most existing RNN models do not take into account the many different cell types in the brain, and ignore the subcellular information processing within neurons. RNN models that did take into account distinct cell types only focused on distinguishing excitatory and inhibitory neurons (Dale's principle). Here, we trained RNNs with excitatory neurons and three types of inhibitory neurons to mimic multi-compartmental pyramidal cells and parvalbumin (PV)-expressing, somatostatin (SST)-expressing and vasoactive intestinal peptide (VIP)-expressing interneurons in the real cortical circuits (Fig. 1a). The broad connectivity pattern across all populations was specified based on experimental findings, while the detailed connection weights are trained with stochastic gradient descent. We studied the neural mechanisms of such networks performing a generalized version of a context-dependent decision-making task (the Mante task) (Fig. 1b). Our results showed that after training, dendrites of excitatory neurons became selective for sensory inputs. Meanwhile, inhibitory neurons developed selectivity for contextual control signals (Fig. 1c), allowing them to inhibit and disinhibit dendrites of excitatory neurons to perform the task. We also found that when there are more dendrites for pyramidal neurons, the networks prefer to gate sensory inputs on dendrites rather than on somas of excitatory neurons (Fig. 1d). These results indicate that the interaction between inhibitory neurons and multi-compartmental excitatory

neurons can support flexible context-dependent cognitive functions by inhibition, disinhibition and gating. This study can provide a basis for studying computational mechanisms of multi-cell-type RNNs and shed light on how function is related to broad connectivity in those networks.

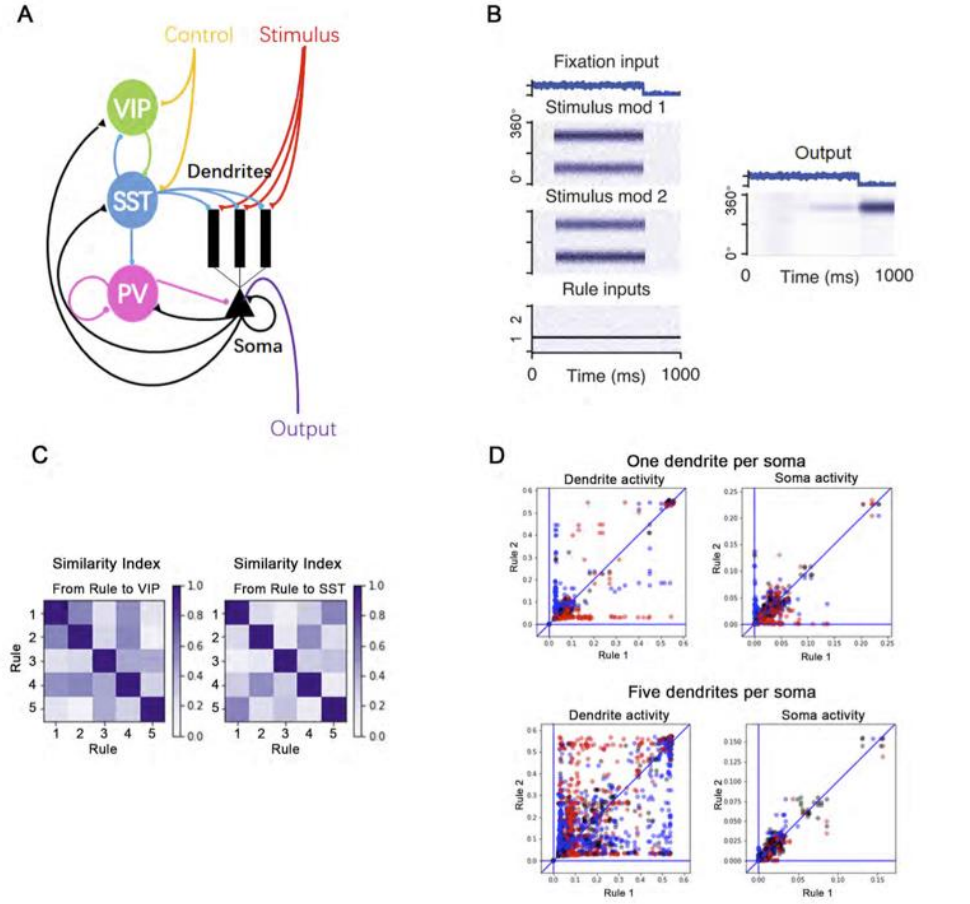

Fig. 1. (A) The circuit model. The recurrent neural network models contain multi-compartmental pyramidal neurons (dendrites and somas) and three types of interneurons, VIP, SST and PV. The control signal (the rule) targets on VIP and SST and the stimulus signal goes to dendrites. The connectivity and proportion were set mimicking microcircuits in the real cortical circuits. (B) The Mante task. In the task, there are inputs encoding a fixation signal, stimuli from two modalities (rings of units), and a rule signal indicating which modality should be focused on. The networks were required to ignore signals from the irrelevant modality and to respond to the stronger stimulus in the correct modality. The original Mante task was generalized to five modalities for our networks. (C) The similarity matrix of connections from five rules to VIP (left) and SST (right). Off-diagonal elements were close to zero, indicating interneuron population developed segregation according to rules. (D) The variance of activity of dendrites and somas under different contexts when there is one dendrite per soma or five dendrites per soma. Comparisons for all dendrites or somas under all pairs of contexts are shown. Each dot is the variance of the activity of one unit (dendrite or soma) given one pair of rules. The dot is colored red if it received stronger connections from one rule, blue if received stronger from the other and black if received equal from both. When there are more dendrites, somas are less selective for contexts, indicating the networks prefer to gate sensory inputs on dendrites rather than on somas.

Disclosures: J. Li: None. **G.R. Yang:** None. **X. Wang:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.25/CCC10

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant NS078127
The Sloan Foundation
The Klingenstein Foundation
The Simons Foundation
The McGovern Institute

Title: Dorsomedial frontal and anterior cingulate cortex support cognitive reasoning about errors in a hierarchical decision making task

Authors: *M. SARAFYAZD, JR[1], M. JAZAYERI[2]
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Abstract: Monitoring performance and reasoning about errors is central to mental computation that supports intelligent behavior. Previous work has established that action outcome monitoring relies on signals in the dorsomedial frontal (DMFC) and anterior cingulate cortex (ACC). However, real-world actions may result from a hierarchy of decisions (What are the task rules? What is the best course of action? What should I do next?) making the source of errors ambiguous. To characterize the neural circuits and mechanisms that resolve this ambiguity, we trained monkeys to perform a hierarchical decision task. Within each trial, animals had to perform a time interval bisection task and report their choice by making a pro- or anti-saccade eye movements. Across blocks of trials, task rules that specify correct response contingencies (i.e., prosaccade for “Short” and antisaccade for “Long”) switched covertly motivating animals to accumulate information about errors within single trials to infer rule switches across trials. Animal’s behavior and fitted computational models indicate that following an error trial, animals relied on their degree of uncertainty about the time interval to infer whether or not the error was caused by an incorrect choice of rule.
To investigate the underlying neural mechanisms, we recorded from DMFC and ACC and focused on activity in the intertrial intervals when the animal had to evaluate errors. Both areas had a representation of timing error after individual trials that varied with expected accuracy. ACC activity was additionally modulated by cumulative errors across trials providing a substrate for reasoning about errors due to rule switches. Electrical microstimulation of ACC provided evidence that ACC was causally involved in animal’s decision about rules. Finally, given the different timescales of error representation in DMFC (single trials) and ACC (across trials), we

hypothesized that ACC might rely directly or indirectly on DMFC to compute switch evidence. We tested this possibility by applying electrical microstimulation in DMFC while recording in ACC. Results indicated that DMFC stimulation increased spiking activity in ACC in the hierarchical decision task but not in control task where errors were not ambiguous (i.e., externally cued rule). Overall, our results demonstrate how DMFC and ACC support cognitive reasoning about errors in nonhuman primates.

Disclosures: M. Sarafyazd: None. **M. Jazayeri:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.26/CCC11

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant K01ES025442
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Title: Dorsal prefrontal cortex tracks projected outcomes in a dynamic competitive game

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Abstract: The ecological niches occupied by most organisms, including humans, are both dynamic and uncertain, requiring that actions be taken in real time. However, most studies of dynamic decision-making to date have explored either repeated trials of the same task under slow changes or interactions between agents from a restricted action space. These limitations may severely constrain our understanding of the neural mechanisms that mediate strategic interactions. To address this gap, we examine data from repeated trials of a real-time strategic interaction with continuous freedom of movement. We trained monkeys to play a game in which the goal of one (the "shooter") was to move a colored dot (the "puck") from the left to right side of a computer monitor using joystick input. The goal of the second monkey (the "goalie") was to block the dot by moving a vertical line along the right-hand side of the screen to intercept it. Thus, each player controlled an avatar with at least one continuous degree of freedom, in principle allowing for dynamic coupling between the two. We analyzed these data by modeling the trajectory of each player as the output of a linear control model applied to a latent goal state. This goal represented an onscreen position toward which each player directed his avatar at each moment. These goal positions followed a Markov dynamics governed by a "kinetic energy" that favored smooth trajectories and a "potential energy" that depended on the current state of each

player. This characterization allowed us to directly look for correspondences between goals and neural activity. We recorded 353 single units from the lateral and medial dorsal prefrontal cortex of three rhesus macaques (137 DMPFC; 216 DLPFC) during 130 sessions in which the recorded monkey played as the shooter. We found that in 58% of DMPFC cells (79/137) and 43% of DLPFC cells (92/216) spiking activity was modulated following shooter wins. In fact, this signal often began to emerge even before trial end, at the moment the outcome of the trial became apparent. In addition, we used LFADS (Pandarinath et al.) to infer latent factors that drove firing rates across units and sessions. These latent factors were correlated with variables that tracked progress through the trial and variables related to variability across trials. In particular, multiple latent factors were correlated with the momentary entropy of the shooter's strategy, suggesting an instantaneous measure of decision complexity. Taken together, these findings suggest that single neurons in dorsal PFC not only encode evaluative signals necessary to update behavioral policies, they do so online as the prospects of winning dynamically evolve.

Disclosures: J.M. Pearson: None. **S. Iqbal:** None. **C. Drucker:** None. **J. Gariepy:** None. **M.L. Platt:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.27/CCC12

Topic: H.01. Animal Cognition and Behavior

Title: The neural basis of flexible decision-making in rodents

Authors: *M. PROSKURIN[1], M. MANAKOV[1], E. KULESHOVA[1,2], M. RYSAKOVA[2], A. LUSTIG[1], R. BEHNAM[1], D. TERVO[1], A. Y. KARPOVA[1]
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Abstract: The ability to adjust one’s behavioral strategy in complex and variable environments in the absence of instruction is at the core of higher cognition. One proposal is that such behavioral flexibility is enabled by a targeted exploration of a set of working hypotheses, or beliefs, about an environment’s governing rules. However, little is known about how an animal’s beliefs about its environment are represented in neural circuits. Our initial efforts to probe the neural basis of the representation of beliefs about the environment’s rules — an internal model of the environment — focused on settings that induce dramatic changes in these beliefs. The detection of corresponding changes in population dynamics allowed us to pinpoint the anterior cingulate cortex in the rodent as a likely region involved in the encoding of these beliefs. Over the past few years, we have developed techniques to monitor and manipulate neural activity using wireless headstages in freely behaving animals in a way that does not impair behavioral

flexibility. We will discuss our results from experiments that take advantage of behavioral tasks where animals flexibly explore different hypotheses about their environment. These experiments have permitted us to focus on the neural mechanisms of encoding internal models, how they are updated through experience, and used to direct behavior.

Disclosures: M. Proskurin: None. **M. Manakov:** None. **E. Kuleshova:** None. **M. Rysakova:** None. **A. Lustig:** None. **R. Behnam:** None. **D. Tervo:** None. **A.Y. Karpova:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.28/CCC13

Topic: H.01. Animal Cognition and Behavior

Support: Howard Hughes Medical Institute

Title: Anterior cingulate cortex and the exploration of alternative strategies

Authors: *D. G. TERVO[1], E. KULESHOVA[2], M. KARLSSON[3], M. PROSKURIN[2], A. LUSTIG[2], M. MANAKOV[2], R. BEHNAM[2], A. Y. KARPOVA[4]
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Abstract: The ability to adjust one's behavioral strategy in complex and variable environments in the absence of instruction is at the core of higher cognition. Recent work has posed that the brain makes the potentially unwieldy problem of mapping the multitude of uncertain situations onto behavioral choices tractable by first re-evaluating the set of learned strategies before deciding to construct new ones (Donoso et al., 2014). Functional imaging studies in humans supported this theoretical framework and suggested that anterior cingulate cortex (ACC), driven by internal estimates of the need to question the reliability of the ongoing one, plays a role in switching to alternative learned strategies (O'Reilly et al., 2013). These findings dovetailed with the body of findings in humans (e.g. Behrens et al., 2007), primates (e.g. Blanchard et al., 2014) and rodents (Karlsson et al., 2012) implicating ACC in keeping track of alternative learned strategies, and in learning higher order statistics about the environment that can inform internal estimates of reliability. However, whether ACC plays an active role in strategy switching, or merely monitors behavioral performance remains unclear. Over the past few years, we have developed molecular tools that permit robust circuit dissection in rodents (Tervo et al., 2016; Brown et al., 2018). We will discuss our findings from perturbation experiments these tools enabled geared to elucidate the precise role ACC plays in strategy arbitration.

Disclosures: D.G. Tervo: None. **E. Kuleshova:** None. **M. Karlsson:** None. **M. Proskurin:** None. **A. Lustig:** None. **M. Manakov:** None. **R. Behnam:** None. **A.Y. Karpova:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 507.29/CCC14

Topic: H.01. Animal Cognition and Behavior

Support: MQ
Klingenstein-Simons
Whitehall
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R01NS104834

Title: Reward-predictive persistent membrane potential dynamics in prefrontal cortex

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Abstract: The prefrontal cortex (PFC) has a crucial role in integrating and transforming internal and external information into complex cognitive behavior. Persistent activity, in which task-relevant information is held "online" after its disappearance from the environment, is thought to be a key mechanism underlying these processes. Although previous studies using extracellular recordings showed diverse patterns of persistent activities, the underlying mechanisms that generate and maintain these persistent activities remain largely unknown.
Therefore, to understand the neural mechanism underlying persistent activity in PFC, we measured the subthreshold membrane potential (Vm) in layer 5 pyramidal neurons using in vivo whole-cell recordings combined with optogenetically-induced perturbations in head-restrained, behaving mice. In addition, by using a GFP-expressing plasmid, we reconstructed a subset of neurons to identify their morphologies and the depth of the recordings.
Thirsty mice were trained to perform a behavioral task in which different odor cues predicted the delivery of water reward following different delays. Vm and action potentials (AP) that were measured during the task revealed three distinct reward-predicting persistent activities in layer 5 pyramidal neurons: 1) sustained Vm depolarization and increased AP firing during the delay between stimulus and predicted reward; 2) sustained Vm hyperpolarization and cessation of AP firing during the delay; and 3) Vm depolarization and increased AP firing after reward delivery. Recording depth estimates showed that the first types of responses were located predominantly in upper layer 5 where cortico-striatal and cortico-cortical neurons are found, whereas the second

type was located predominantly in lower layer 5 where pyramidal track neurons are found, indicating that different types of persistent activity may reach different postsynaptic targets. To understand the mechanisms responsible for these differences, we recorded from pyramidal neurons in these two sublayers in anesthetized mice and found different intrinsic membrane properties. Next, to test whether intrinsic mechanisms lead to persistent changes, we perturbed Vm during the delay period and found that Vm immediately returned to unperturbed levels. This indicates that persistent membrane potential dynamics are stable states that are robust to perturbation. Thus reward-predictive persistent firing rates changes are due to stable changes in Vm, carried by different subtypes of neurons, that may send different information to distinct downstream targets.

Disclosures: E. Kim: None. **B.A. Bari:** None. **J.Y. Cohen:** None.

Poster

507. Animal Cognition and Behavior: Decision Making: Prefrontal Cortex

Location: SDCC Halls B-H

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Program #/Poster #: 507.30/DDD1

Topic: H.01. Animal Cognition and Behavior

Support: R01MH107491

Title: Strategy selection based on trial feedback in a rule-based categorization task

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Abstract: In uncertain and changing environments, trial-and-error feedback is important to make decisions to optimize reward. To test how feedback affects categorical decision making we trained two monkeys to perform a rule-selection categorization task. Two circular stimuli were presented in sequence that differed in position and size. In blocks of trials, monkeys were rewarded for determining the relationship of the second stimulus to the first, either with respect to size (‘larger than’, or ‘smaller than’) or to position (‘left’, or ‘right). Under the size categorization rule, monkeys made a saccade to the second stimulus if it was larger than the first (‘Go’ trial), or withheld the saccade if it was smaller (‘NoGo’ trial). Under the spatial categorization rule, the 'Go' versus 'NoGo' decision was based on the relative positions of the two targets. The categorization rule was not explicitly instructed. Rather, monkeys inferred the correct rule in each block using trial-and-error feedback. Contrary to our expectation that monkeys would form two discrete rules and apply them to categorize the relevant stimulus dimensions independently, we found that monkeys generated compound categories based on combinations of size and spatial relationships (‘smaller left’, ‘larger left’, ‘smaller right’, and

‘larger right’). Two such compound categories were 'congruent' in the sense that they required the same response regardless of the rule in force (‘larger left’ and ‘smaller right’). The other two compound categories were 'incongruent' in the sense that monkeys had to switch from a 'Go' to 'NoGo' response strategy to those categories when the rule changed. We found that performance on congruent compound categories was high (≥80%) and remained high when the rule switched, reflecting the constant response strategy required for the two rules in these cases. Conversely, performance on incongruent compound categories dropped after a rule switch to ~40% and showed strong learning effects - monkeys reached asymptotic performance (~80%) in 30-40 incongruent trials. Trial feedback on incongruent trials was informative about the rule switch, whereas trial feedback on congruent trials was not. We hypothesized therefore that trial feedback was differentially processed on congruent and incongruent trials. We computed success probability as a function of trial feedback on the preceding trial, and found this differed according to whether the preceding trial was congruent or incongruent (chi-square 40.12, d.f. = 3, $p < 0.001$). The animals were more likely to perform correctly after a rule switch following an error on an incongruent trial in comparison to an error on a congruent trial.

Disclosures: M. Park: None. **D.A. Crowe:** None. **M.V. Chafee:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 508.01/DDD2

Topic: H.01. Animal Cognition and Behavior

Title: Spatial representations in the marmoset hippocampus during free navigation

Authors: *H. COURELLIS[1,2], M. J. METKE[2], S. U. NUMMELA[3], G. W. DIEHL[5], R. BUSSELL[4], G. CAUWENBERGHS[1], C. T. MILLER[2]
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Abstract: Neurons encoding spatial information have been detected in the hippocampal CA fields and dentate gyrus of a number of animals including rodents, bats, as well as both human and non-human primates. However, a clear representation of self-position encoded in the firing rates of pyramidal neurons in primate hippocampus, that is, so called canonical place cells, remain elusive during active navigation. A combination of hardware and experimental design challenges in the case of the non-human primate, and surgical contraindication in the case of human epilepsy patients, has made investigation of place encoding in the primate hippocampus difficult thus far. In recent years, the common marmoset (*Callithrix jacchus*) has emerged as a

powerful model for primate neurophysiology. The marmoset hippocampus exhibits a great degree of similarity to other old-world primates both in gene expression and structural organization, but whose in-vivo electrophysiological dynamics have never been characterized. We sought to characterize those dynamics in the context of free navigation in several spatial environments consistent with previous studies of rodents, and specifically characterize spatial tuning of hippocampal neurons during unrestrained, high velocity locomotion. To this end, we implanted chronic microwire arrays into marmoset hippocampus using a structural-MRI guided surgical procedure. Neurons recorded in marmoset hippocampus during high velocity track exploration displayed significant encoding of information about the marmoset's current position within the track. Furthermore, these neurons exhibit statistically significant coherence with the phase of the underlying local field potential in a frequency band similar to the theta band in rodents. However, we did not observe a very high amplitude and temporally consistent theta oscillation during locomotion of the implanted marmosets.

Disclosures: H. Courellis: None. **M.J. Metke:** None. **S.U. Nummela:** None. **G.W. Diehl:** None. **R. Bussell:** None. **G. Cauwenberghs:** None. **C.T. Miller:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 508.02/DDD3

Topic: H.01. Animal Cognition and Behavior

Support: R01 DC012087

Title: Spatial representations of self and others in marmoset hippocampus

Authors: *M. J. METKE[1], H. COURELLIS[2], J. F. MITCHELL[4], W. FREIWALD[5], D. A. LEOPOLD[6], C. T. MILLER[3]
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Abstract: A large corpus of literature has shown that the hippocampus plays an important role in representing the surrounding environment during free navigation. Studies in rodents and bats have demonstrated the existence of spatially-tuned place cells that fire preferentially when the individual occupies a particular region of space - "place field." - Whether primate hippocampus achieves a similar spatial representation during active navigation, however, remains an open question. Primates rely heavily on their vision in particular to explore their surroundings, and the visual sensory information they acquire is known to contribute to spatial representations in the medial temporal lobe. The reliance on visual exploration suggests that there may be spatial

encoding mechanisms that are not exclusively related to physical occupation of space, a pattern consistent with data observed during both human and non-human primate neurophysiology studies. A more thorough characterization of the electrophysiological dynamics of the primate hippocampus at the single neuron level is required, particularly in the context of concurrent visual and physical exploration of a naturalistic environment. Here we demonstrate a novel paradigm developed to investigate how primates represent space while navigating a 3-dimensional environment either alone or with conspecifics. We record the activity of single units in the hippocampus of freely-moving marmosets while simultaneously tracking spatial location and head direction of all monkeys in the environment. We will present behavioral and neural data in this paradigm related to fundamental questions of how primates represent and explore physical and social space in hippocampus.

Disclosures: M.J. Metke: None. **H. Courellis:** None. **J.F. Mitchell:** None. **W. Freiwald:** None. **D.A. Leopold:** None. **C.T. Miller:** None.

Poster

508. Head Direction Cells and Spatial Navigation

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Program #/Poster #: 508.03/DDD4

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01 DC012087

Title: Cross-modal representation of individual identity in marmoset hippocampus neurons

Authors: *C. T. MILLER[1], G. CAUWENBERGHS[2], H. COURELLIS[3]
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Abstract: The convergence of multi-modal sensory information in the hippocampus facilitates the internal representation of a complex external world. A human, for example, integrates information acquired from an individual across multiple sensory modalities, such as the sight of their face or the sound of their voice, to establish a cohesive representation of that individual's identity, a process supported by mechanisms in hippocampus. Here we sought to interrogate whether neurons in the hippocampus of an awake marmoset monkeys (Callithrix jacchus) exhibited mechanisms for individual identity representation. Like humans, this primate species routinely uses both visual and acoustic social signals to mediate their conspecific social interactions. We presented subjects with concurrent visual and auditory signals - faces and vocalizations - collected from their family members and unrelated animals in the colony. We hypothesized that single units in the marmoset hippocampus would be differentially responsive to these sensory signals when presented separately and presented concurrently. We further

hypothesized that a sub-population of neurons would be sensitive to the congruence of these signals for representing the individual identity of the monkey. We implanted chronic multi-electrode arrays into marmoset hippocampus using a structural-MRI guided surgical procedure. Marmosets were head-fixed before a digital display and a speaker to present both auditory and visual stimuli. Task structure involved a brief fixation after which either a vocalization, face, or combined audiovisual stimulus were presented. Audiovisual stimuli were further sub-divided into matched and mismatched stimulus identity. We found hippocampal single units to be significantly differentially responsive to audiovisual combinations of sensory stimulation. Furthermore, we identified a population of neurons sensitive to the congruence of identity between auditory and visual stimuli. These initial analyses suggest that neurons in marmoset hippocampus contribute to a cross-modal representation of individual identity.

Disclosures: C.T. Miller: None. **G. Cauwenberghs:** None. **H. Courellis:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

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Program #/Poster #: 508.04/DDD5

Topic: H.01. Animal Cognition and Behavior

Title: Encoding of spatial variables in retrosplenial cortex during landmark dependent navigation

Authors: *L. FISCHER[1], R. MOJICA[2], E. H. S. TOLOZA[1], D. BARNAGIAN[1], M. T. HARNETT[1]
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Abstract: Retrosplenial cortex is an associative cortex that has been found to be critical for spatial navigation and route planning. Monosynaptically restricted anatomical tracing using rabies virus show that it receives direct inputs from primary visual, secondary motor and anterior cingulate cortices, as well as multiple thalamic nuclei. Direct connectivity of RSC with hippocampal regions, however, is limited. This suggests a role in integrating visual and motor feedback during navigation. To test the hypothesis that RSC is critical for using visual landmark information to guide navigation, we developed a spatial task for head-fixed mice in virtual reality that requires the integration of visual inputs and motor feedback during a path integration period to locate a reward zone along a linear corridor. Animals are required to learn different distances to hidden reward locations associated with different visual landmarks. We find that inactivation of RSC reduces task performance only when both components, landmark utilization and motor feedback, are required for task completion. A purely visually guided version of the task was not affected by inactivation. 2-photon population imaging in layers 2/3 and layer 5 of GCaMP6f-labeled neurons shows highly specific encoding of landmarks and path integration periods. However, the majority of these neurons are inactive, or are attenuated, in amplitude and

robustness, when a movie of the same environment is passively replayed to the animal. Population analysis shows similar subpopulations of neurons are being active during path integration, regardless of the distance required to travel to the reward, while landmarks are encoded by less overlapping subsets of neurons. To gain a better understanding of the computations carried out by RSC, we imaged axonal boutons originating in V1. Unexpectedly, we found that V1 boutons also show complex receptive fields responding to during landmarks and path integration periods. Together these results show that RSC is important for landmark-dependent navigation and that its populations encode both integration of visual features that provide spatial information and execution of navigation to a goal location. However, V1 provides more sophisticated inputs than previously thought and the specific contributions of RSC and V1 during landmark-dependent navigation remain to be established.

Disclosures: L. Fischer: None. **R. Mojica:** None. **E.H.S. Toloza:** None. **D. Barnagian:** None. **M.T. Harnett:** None.

Poster

508. Head Direction Cells and Spatial Navigation

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MIT Research Support Committee - NEC Corporation Fund for Research in Computers and Communications

Title: Somato-dendritic encoding of head-direction in mouse retrosplenial cortex

Authors: *J. VOIGTS[1], M. T. HARNETT[2]
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Abstract: Efficient navigation requires the context-dependent integration of a multitude of signals. A familiar landmark on an animal's right side, for instance, has a different meaning depending on whether the animal is facing north or south. Retrosplenial cortex (RSC) has been proposed to serve a central role in solving such computations by translating between egocentric and allocentric representations of the environment. Neurons in RSC integrate multiple navigational variables, including egocentric visual information and position relative to landmarks, allocentric location within an environment, and heading. These mixed representations in RSC neurons, in which individual inputs can change the impact of other inputs, form a convenient model system for studying associative neuronal computations. Dendrites, which endow individual cells with complex nonlinear processing capability, may play an important part in these computations. Here, we examine the subcellular computations underlying the encoding

of heading direction in RSC using calcium imaging in mice exploring a physical 2-dimensional environment. We developed an experimental approach that permits mice to freely rotate their heads in the azimuthal plane with negligible inertia and friction during conventional 2-photon imaging. We used this system to perform GCaMP imaging at somas and dendrites of pyramidal neurons in retrosplenial cortex. We found that distal apical dendritic tuft segments in RSC neurons encode heading, but only partially predict a cell's head direction or spatial tuning. Our findings indicate that individual RSC neurons receive a variety of tuned inputs in their apical dendrites, that are nonlinearly modulated by other inputs before influencing somatic output. Our results provide insight into the role of dendritic computations in head-direction encoding in RSC and will provide a starting point for studying more general associative dendritic computations.

Disclosures: J. Voigts: None. **M.T. Harnett:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

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NIH #5-T32-NS-058280-08

Title: Simultaneous encoding of head angle, episodic distance, and position by hippocampal activity in a virtual water maze

Authors: *J. J. MOORE[1,2,3,4], M. R. MEHTA[1,2,3,4,5]
[1]W. M. Keck Ctr. for Neurophysics, Los Angeles, CA; [2]Integrative Ctr. for Learning and Memory, [3]Brain Res. Inst., [4]Dept. of Physics and Astronomy, [5]Departments of Neurology, Neurobio., UCLA, Los Angeles, CA

Abstract: The Morris Water Maze is a widely used behavioral test of hippocampus dependent spatial learning, memory and navigation. Yet the neural basis of this behavior is not well characterized, owing to the difficulty of performing single unit recordings in this task and the limited number of trials in a session. To overcome these limitations we have developed a virtual water maze task[1] with only visual cues defining position, in which rats can run more than 100 trials per session[2]. This allows us to perform robust statistical analyses of the contribution of different parameters to neural firing and how these firing properties relate to behavioral performance. Here we focus on three parameters: head angle, episodic distance, and allocentric position.Well trained rats follow fairly stereotyped paths in this task, and so tuning in one domain may generate false selectivity in another due to partial collinearity between parameters.

Hence, we developed a generalized linear model with added regularization to estimate the simultaneous contributions of head angle, episodic distance, and allocentric position to the firing of >1000 hippocampal pyramidal cells. The regularization term also allows robust estimates using small amounts of data, so tuning changes can be tracked within a single session.From this experimental and statistical-model based approach we report five findings:
1. Despite good task performance, we observed very little allocentric spatial selectivity.
2. A substantial proportion of cells were modulated by episodic distance, and the distribution of peak locations was biased towards the beginning of trials.
3. Many cells were modulated by head angle, and the population of these cells was biased towards the quadrant containing the hidden reward zone.
4. Across sessions, the percentage of neurons that were tuned to any of these parameters was positively correlated with behavioral performance.
5. Both behavioral performance and the activation of neurons increased with experience within a single session.
Thus, even though there is little hippocampal allocentric spatial selectivity during this task, other navigationally relevant parameters are encoded by the hippocampus, and the degree of this tuning is correlated with behavior. These experience based changes may be driven by similar mechanisms of synaptic plasticity demonstrated in studies on linear tracks[3-5], thus linking behavioral learning with hippocampal activity and cellular mechanisms of plasticity.
1. Cushman et al, PLoS One (2013); 2. Moore et al, SfN Abstract 263.03 (2016); 3. Mehta, McNaughton, NIPS 741-745 (1997); 4. Mehta et al, PNAS 94, 8918-8921 (1997); 5. Mehta et al, Neuron 25, 707-715 (2000).

Disclosures: J.J. Moore: None. **M.R. Mehta:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

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Program #/Poster #: 508.07/DDD8

Topic: H.01. Animal Cognition and Behavior

Title: Multisensory mechanisms of hippocampal slow oscillations

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Abstract: The hippocampal theta oscillations differ across species and experimental conditions. Specifically, the hippocampal 8 Hz theta rhythm (Buzsaki & Vanderwolf, 1983) is readily seen in rodents during spatial exploration. Several mechanisms of the theta rhythm have been

suggested including the medial septal (Winson, 1978) as well as multiple generators within (Kocsis et al., 1999) and outside (Moore et al., 2013) of the hippocampal system. However, the 8 Hz theta rhythm is not seen in the healthy bats' or primates' hippocampus. Instead, infrequent bouts of low frequency oscillations are observed. In addition, the nature of the theta rhythm in humans is debated. These differences could arise due to various reasons such as differences in task demands, behavioral state or sensory cues. Thus, the sensory and behavioral mechanisms governing hippocampal slow oscillations remain to be fully understood.
We hypothesized that one of the reasons for these differences is the nature of multisensory cues available under different conditions (Ravassard et al. 2013). To test this hypothesis, we compared the nature of the hippocampal theta oscillations on the same electrodes when rats run on a linear track either in the real world (RW) or in virtual reality (VR). The main differences between the two environments are in the nature of linear acceleration and multisensory cues except visual cues. We found that the power of theta oscillations is comparable between RW and VR, and the speed-dependent increase in theta power is also similar. This suggests that the differences in multisensory or vestibular cues are not critical for the speed-dependence of theta amplitude. However, the speed-dependence of theta frequency in VR is shown to be abolished in some studies (Ravassard et al. 2013; Bourboulou et al., 2018), but preserved in others (Fuhrmann et al., 2014). We found that these differences arise due to differences in analytical methods used to detect the theta rhythm. We developed a robust method which showed that speed dependent increase in theta frequency is indeed abolished in VR, but the same method shows reliable increase in theta frequency in the RW.
Finally, we found that electrodes that were well localized within the hippocampus showed an additional oscillation at about 4Hz in VR. The amplitude of this oscillation also increased with the running speed but its frequency remained unchanged. This 4Hz oscillation was not seen in the RW. As a result, the activity of hippocampal single units was strongly influenced by both the 4 Hz and the 8 Hz rhythms in VR. These results show that the nature of multisensory cues have a profound influence on the amplitude and frequency of hippocampal slow oscillations.

Disclosures: K. Safaryan: None. **M.R. Mehta:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 508.08/DDD9

Topic: H.01. Animal Cognition and Behavior

Title: Medial precentral cortex transforms spatial and directional information into planned action

Authors: *D. A. NITZ[1], J. M. OLSON[2], J. LI[3]
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Abstract: Fluid navigation requires constant updating of motor plans as obstacles and goals change across space. In order for the brain to achieve this, the neural substrate must receive spatial and sensory information and have motor targets as outputs. Based on its anatomical connectivity, medial precentral cortex (MPC), a frontal association cortex of the rat, is a prime candidate for this role (Reep et al., Neurosci. Lett., 1984). There exists extensive reciprocal connectivity between MPC, posterior parietal cortex (PPC), and retrosplenial cortex (RSP), and large populations of PPC and RSP neurons have spiking activity that maps animals' positions within the space of complex routes as well as those that correlate with turning behaviors (Nitz, Neuron, 2006; Alexander and Nitz, Nat. Neurosci, 2015). Smaller populations provide signals as to head orientation relative to the environment. Completing the hypothesized sensory to motor pathway, MPC projects to primary motor cortex as well as along the corticospinal tract to the spinal cord (Donoghue and Wise, J. Comp. Neurol., 1982). Anatomically, the MPC subregion of prefrontal cortex is ideally suited for transformation of knowledge of current position into a plan for specific motor actions. We conducted electrophysiological recordings of individual neurons in medial precentral cortex of rats while they navigated a complex multi-route maze. As hypothesized and supported by previous recordings in the area, we report activity that encodes current actions (left/right turns) in MPC as well as activity encoding upcoming actions. These representations of actions are robust across environmental factors, including the direction of travel, spatial location, and position within the route being traversed. They are even robust to whether the action is at a choice point or if only one possibility exists. To then test the hypothesis that transformation into action occurs in the MPC circuitry, we investigated evidence of spatial and other contextual information being represented in the region. Individual neurons and the population as a whole reliably discriminate environmental position, direction, route position, and either choice vs forced turns. These results support a model in which spatial and contextual information is transformed to egocentric frames of reference for the purpose of fluid, efficient navigation.

Disclosures: D.A. Nitz: None. **J.M. Olson:** None. **J. Li:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

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Program #/Poster #: 508.09/DDD10

Topic: H.01. Animal Cognition and Behavior

Support: NIH 5R01MH092925-02

W.M. Keck Foundation
NSF EAGER
NIH T32 NS058280-04S1
NIH 1 F31 MH102969

Title: Visual cues alone are insufficient to generate robust grid cells and head-direction cells in the medial entorhinal cortex

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Abstract: The medial entorhinal cortex (mEC) is thought to play a crucial role in allocentric navigation—a task that is heavily influenced by visual cues, e.g. in the water maze task. Navigation requires information about spatial position and direction. The activity of mEC neurons exhibit spatial and directional selectivity, in the form of grid and head-direction cells' firing patterns respectively. The mEC projects to the downstream area CA1 (*1*), and dorsal CA1 neurons show spatial and direction selectivity, hypothesized to be generated from the mEC spatially selective grid cells (*2*, *3*) and mEC head-direction cells. To test these hypotheses, we measured rats' mEC responses in a purely visual virtual reality (VR), and compared it with their responses in a visually identical real-world (RW). The task design was such that the VR session was performed in between two RW sessions, thus allowing us to examine the activity of the same cell across these conditions.

Consistent with our prior findings, the activity of grid cells was severely disrupted in VR. These neurons showed intact spatial modulation in RW, but despite similar levels of firing rates across all sessions, their spatial modulation was abolished in VR. Thus, visual cues alone are insufficient to generate mEC grid pattern. This finding could also explain the loss of spatial selectivity in CA1 place cells in VR, as predicted by previous models (*2*, *3*).

Direction selectivity of neurons in VR manifested two surprising findings. First, there was a small but significant fraction of cells with directional selectivity with respect to the VR visual cues (but not to the animals' head-direction in the RW reference frame). Second, in contrast to our findings in CA1—where direction selectivity was intact in VR and even comparable to that in the RW—here, direction selectivity was diminished for the majority of head-direction cells. This shows that visual cues alone are sufficient to generate direction selectivity in a small fraction of mEC neurons while other mEC cells require multisensory cues to generate spatial and directional tuning. Further, this suggests that while CA1 spatial selectivity may be inherited from mEC, it is possible for CA1 directional selectivity to arise by some other mechanisms—independent of mEC inputs—such as the inputs from LEC (*4*).

1. T. T. G. Hahn, J. M. McFarland, S. Berberich, B. Sakmann, M. R. Mehta, *Nat. Neurosci.* **15**, 1531-1538 (2012).
2. T. Solstad, E. I. Moser, G. T. Einevoll, *Hippocampus*. **1031**, 1026-1031 (2006).

3. M. R. Mehta, *Cell*. **147**, 968-70 (2011).
4. S. S. Deshmukh, J. J. Knierim, *Front. Behav. Neurosci.* **5**, 69 (2011).

Disclosures: Z. M. Aghajan: None. **A.L. Kees:** None. **P. Varanasi:** None. **S. Sandhu:** None. **M.R. Mehta:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 508.10/DDD11

Topic: H.01. Animal Cognition and Behavior

Support: Kavli - KIBM #2015-055

Title: Place versus places: Spatially-specific activity in subiculum encodes structural similarities among interconnected paths

Authors: *A. B. JOHNSON[1], J. M. OLSON[1,3], E. L. TAO[4], X. WANG[4], L. CHANG[4], A. C. PHUTISATAYAKUL[4], D. A. NITZ[2]
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Abstract: To reveal potentially novel functions of subiculum (SUB) in spatial cognition, we studied and compared activity of CA1 neurons, SUB neurons, and posterior parietal cortex (PPC) neurons while animals navigated a maze having 6 distinct, but interconnected paths. Four of the paths partially overlap and lead the animal to a reward location. The remaining two are non-overlapping and bring the animal back to the rewarded paths' shared starting location. The rewarded paths have the same lengths but dissociate through differing sequences of three 90 degree left/right turns. The return paths have the same lengths, flank either side of the environment, and are made of two 90 degree turns. This path network structure results in reward paths and return paths that vary in spatial separation, direction of travel, and required action sequences. However, among the four reward paths and return paths, there exist multiple non-overlapping locations that are spatially 'analogous' in sharing combinations of the animal's direction of travel, proportion of distance through a path, current action, and/or axis of travel. We observe here that PPC neurons' activity patterns are most closely related to progression through a route and/or current action. CA1 neurons typically exhibited one place-specific firing field. The spatial distribution of the multiple-field exhibiting CA1 neurons was seemingly random. This data is consistent with prior conceptions of PPC and CA1 generating complementary representations of the rat's location in route and environmental spaces, respectively. In stark contrast, SUB neurons often exhibited multiple fields and the spatial distribution of these fields was mostly non-random. For the majority of individual SUB neurons,

spatially-specific firing fields were distributed across analogous locations of 2 or more paths. This tendency and its contrast to CA1 and PPC neuron populations was quantified through correlation of individual neuron positional rate vectors and through correlation matrices examining ensemble correlations between all pairs of path network locations. A decision-tree analysis applied to all 6 positional rate vectors of each neuron was implemented to determine which spatial and directional variables were key to generating similar firing across analogous path locations.
These data indicate that a unique role for SUB in spatial cognition lies in extracting and encoding structural features of a path network. Furthermore, the findings highlight the importance of SUB as a potential region able to extract, compare, and respond to similarities between otherwise distinct experiences.

Disclosures: J.M. Olson: None. **E.L. Tao:** None. **X. Wang:** None. **L. Chang:** None. **A.C. Phutisatayakul:** None. **D.A. Nitz:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 508.11/DDD12

Topic: H.01. Animal Cognition and Behavior

Support: NSF Career #0969034
NIH/CRCNS #1-R01-MH-092925-01
W. M. Keck foundation.

Title: Simultaneous representations for virtual and real spaces in the rat hippocampus

Authors: *C. PURANDARE[1,2,3,4], K. CHOUDHARY[5,2,3,4], M. R. MEHTA[6,2,3,4]
[1]Bioengineering, Univ. of California Los Angeles, Los Angeles, CA; [2]W. M. Keck Ctr. for Neurophysics, [3]Integrative Ctr. for Learning and Memory, [4]Brain Res. Inst., [5]Physics and Astronomy, UCLA, Los Angeles, CA; [6]Departments of: Physics & Astronomy, Neurology, Neurobio., Univ. of California at Los Angeles (UCLA), Los Angeles, CA

Abstract: During unconstrained real world (RW) exploration, rodent hippocampal activity shows robust spatial selectivity, which is hypothesized to be governed by distal visual and locomotion cues, along with contributions from other sensory-motor cues. To dissect the contributions of these different variables on hippocampal spatial selectivity, we have recently developed a virtual reality apparatus. Here, the rat runs on a spherical treadmill that floated freely on an acoustically quiet air cushion, to receive liquid rewards through a tube in front of the rat. Our VR system employs a hinged harness that gently body-fixes the rats but allows for head movements around body. The harness, reward tube and VR chassis constitute a novel,

constrained real world (c-RW) where the rat's legs and head can move freely but his body does not. Movement of his legs cause a rotation of the spherical treadmill that induces a change in the virtual scene, i.e. virtual movement, without any significant change in the rat's position in the c-RW position. In previous studies we found that during random foraging in our VR, spatial selectivity is markedly reduced while directional modulation was comparable to RW [1, 2]. Here, we investigated the selectivity in c-RW while the rat performed two dimensional navigational tasks in the VR space. We find that a substantial number of neurons showed selectivity to the rat's head angle in the c-RW environment, in the absence of task demands in the c-RW frame and in the absence of active navigation driven changes in c-RW position (owing to body restriction). Our results suggest that hippocampal neurons can simultaneously maintain representations of real and virtual environments and have important implications for the growing use of virtual reality for scientific, and commercial uses.

1. Aghajan et al, (2015), Nature Neuroscience volume 18 2. Acharya et al, (2016), Cell 164, 197-207

Disclosures: C. Purandare: None. **K. Choudhary:** None. **M.R. Mehta:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 508.12/DDD13

Topic: H.01. Animal Cognition and Behavior

Support: NIH-CRCNS
W. M. Keck Foundation
NSF EAGER
Kaplan Grant UCLA Biophysics

Title: Bistable attractor dynamics in the medial entorhinal cortex membrane potential *in vivo*

Authors: *K. CHOUDHARY[1,3,4,5], S. BERBERICH[6], J. M. MCFARLAND[7], T. T. HAHN[8], M. R. MEHTA[1,2,3,4,5]
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Abstract: Persistent neural activity is thought to be a neural substrate for mediating working memory during behavior, as it can establish a representation of a stimulus that persists after the

stimulus is extinguished. Recent *in vivo* work in rodents during slow-wave sleep [1] has shown a close link between persistent activity in layer III neurons of the medial entorhinal cortex (MECIII) and the up-down state (UDS) oscillations in the afferent neocortex, where neurons show a ubiquitous pattern of synchronized transitions between active periods of tonic firing (UP states) and periods of quiescence (DOWN states). Interestingly, while the membrane potential of neurons in MECIII show both persistent activity [1] and inactivity [2] in response to cortical dynamics, this persistence is absent in neighboring lateral entorhinal cortex (LECII) neurons. While several models have been proposed to explain neocortical UDS [3, 4] and *in vitro* MEC persistent activity [5] separately, the link between the two has been left unexplored. Here, we present a model, based on a bi-stable attractor, to understand the mechanisms underlying cortico-entorhinal coupled dynamics during UDS. The MECIII is modeled as a bi-stable network of excitatory and inhibitory neurons, and this network is coupled to an oscillatory two-state neocortical network. The MECIII network takes the periodic input from the neocortex and responds such that a state change is induced only when the input exceeds a prescribed threshold. These results reveal a possible biophysical mechanism behind the experimentally observed persistent activity in membrane potential *in vivo* and suggest a potential contribution of this coupled behavior to cortico-entorhinal-hippocampal interaction, which is thought to be involved in working memory, the learning of long behavioral sequences during behavior, and memory consolidation during sleep. [1] Hahn et. al., Nature Neuroscience (2012) ; [2] Berberich et. al., SfN Abstract (2015); [3] Ghorbani et. al., Physical Review E (2012); [4] Jercog et. al., eLife (2017); [5] Fransen et. al., Neuron (2006).

Disclosures: K. Choudhary: None. **S. Berberich:** None. **J.M. McFarland:** None. **T.T. Hahn:** None. **M.R. Mehta:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 508.13/DDD14

Topic: H.01. Animal Cognition and Behavior

Support: Frontiers of Innovation Scholars Program (FISP) Fellowship, UCSD

Title: Rule-based fragmentation of environmental space yields trajectory-specific encoding in posterior parietal cortex, but not hippocampus

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Abstract: The current study examined environmental subspace representations using a task-defined, behavioral rule to demarcate the division of a room into two subspaces, rather than by a

concrete feature or visible dividing line. Rats traversed a T-shaped track placed in one of four locations. The task was structured into blocks of five trials at each position. Rats were trained to turn left when the track was placed in one half of the room, and to turn right when placed in the other half.
Behavioral results indicate that rats can learn such logical fragmentation, as evidenced by high accuracy during probe trials in which the track was placed in novel locations. Furthermore, while performance at all track positions was well above chance, accuracy was poorer for track locations near the fragment boundary.
Neurons in both the hippocampus (HPC) and posterior parietal cortex (PPC) were recorded during task performance. Spatial firing patterns in both regions followed track, not room, position at each of the four positions, an effect that was expected for posterior PPC neurons, but was unexpected for HPC. Furthermore, PPC ensembles, but not HPC ensembles, were prospective in discriminating L- versus R-going trajectories past the halfway point along the stem.
The first trial of any block demanded that the animal apply the fragmentation rule while performance on trials 2-5 could be derived from the success/failure outcome of the first. Therefore, we also examined whether trial number within each block was a variable that could differentiate PPC and HPC firing patterns. Firing patterns in both areas differentiated trial 1 from subsequent trials maximally at early stages in each run, an effect that was stronger and persisted past the halfway point of the stem for HPC ensembles.
The findings indicate that rats are capable of learning a rule-based spatial division of the environment and that task performance is associated with unexpected spatial firing properties of HPC and PPC neurons. PPC neurons exhibited prospective encoding of choice behavior. HPC did not and, further, exhibited spatial firing activity tied to the track's frame of reference. We interpret the trial number impact on HPC firing patterns as reflecting the heightened spatial awareness needed to perform the task when the track is moved to a new location.

Disclosures: L.E. Shelley: None. **D.A. Nitz:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 508.14/DDD15

Topic: H.01. Animal Cognition and Behavior

Title: Effect of multisensory cues on directional tuning of hippocampal cells

Authors: *S. DHINGRA[1,2,3,4,5], M. SHAHI[1,2,3,4], R. SANDLER[1,2], R. RIOS[1,2,5], C. VUONG[1,2], L. ACHARYA[6], M. R. MEHTA[7,2,3,4]
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[5]Dept. of Physics and Astronomy, [1]UCLA, Los Angeles, CA; [6]Neurosci. Dept., Baylor Col. of Med., Houston, TX; [7]Departments of: Physics & Astronomy, Neurology, Neurobio., Univ. of California at Los Angeles (UCLA), Los Angeles, CA

Abstract: Hippocampal CA1 cells have known to exhibit allocentric spatial selectivity [1], which has been extensively studied over years. Several different theories have been hypothesized to explain the origin of this selectivity. These include cognitive mapping, largely based on visual landmarks, or path integration, which relies on internal variables, such as orientation and steps taken. Our lab recently proposed that hippocampal activity patterns can be explained by combinations of multisensory cues in the environment. This is supported by the observation that hippocampal activity and the nature of spatial selectivity are quite different in Virtual Reality (VR), even when the visual and locomotion cues are comparable to Real World (RW) [2]. Atop the spatial selectivity, we also showed the presence of directional selectivity in CA1 cells during random foraging [3] in RW and VR, which were found to be comparable in these environments. In fact, individual visual cues exerted a causal effect on the directional response of the entire hippocampal ensemble. We found that the directional preference of the cells rotated with the distal cues, and their tuning widths changed with the width of the visual cues. In this work, we investigate the contribution of mulitsensory cues to the directional selectivity in CA1 cells using novel experimental manipulations and analytical methods.

The experimental paradigms used in this work involved rats random foraging on an open platform in 2D environments, with combinations of distal and proximal visual cues, without any reward association to these cues. Manipulations of multisensory cues in these setups included changing position, orientation and size of the distal visual cues, and suspending a similarly sized and shaped proximal visual cue above the platform. For analyzing the data, we make use of generalized linear model (GLM) [3], which provides an estimate of the independent contributions of rat's position, direction, speed etc., on single unit responses.

By employing these techniques, we are able to dissociate the spatial and directional tuning of each cell. We find the directional tuning of the cells to be dependent on experimental conditions used, and follow the visual cue's position, while responding differently to distal and proximal cues. We also find that in the RW setups rich in distal visual cues, the contribution of spatial selectivity to the activity of hippocampal cells is significantly greater than that of directional selectivity.

[1] O'Keefe, J., & Dostrovsky, J., *Brain research*, 1971.
[2] Aghajan, Z. M., et al., *Nature neuroscience*, *18*(1) (2015): 121.
[3] Acharya, L., et al., *Cell* 164.1-2 (2016): 197-207.

Disclosures: S. Dhingra: None. **M. Shahi:** None. **R. Sandler:** None. **R. Rios:** None. **C. Vuong:** None. **L. Acharya:** None. **M.R. Mehta:** None.

Poster

508. Head Direction Cells and Spatial Navigation

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Topic: H.01. Animal Cognition and Behavior

Support: NIH/CRCNS #1-R01-MH-092925-01
W. M. Keck foundation.
NSF EAGER
Whitehall foundation

Title: A statistical model based approach to decipher the mechanisms governing spatial and directional tuning of hippocampal neurons

Authors: *M. SHAHI[1,2,3,4], S. DHINGRA[1,2,3,4], R. SANDLER[1], R. RIOS[1,2,3,4], C. VUONG[1], L. ACHARYA[5], M. R. MEHTA[6,2,3,4]
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Abstract: Hippocampal CA1 cells show allocentric spatial selectivity [1], which has been extensively investigated. In addition, our lab recently showed the presence of robust directional selectivity in CA1 cells during random foraging in real world (RW) and virtual reality (VR) [2]. The direction selectivity was found to be comparable in both the worlds, even though vestibular cues were substantially reduced in the latter. Alongside, we recently reported that rodent hippocampal neurons can show directional tuning to the maze center in virtual reality (Dhingra et al. SfN 2017, Shahi et al. SfN 2017). These results indicate that hippocampal neurons contain information about multiple behaviorally relevant variables, such as spatial position, head direction, speed, etc., and are differentially influenced by multisensory cues in the maze. These variables often co-vary, which makes it difficult to disentangle their contribution to neural responses. To address these challenges, we measured neural responses under a variety of conditions and developed a statistical model based approach. The experimental setups used in this work involved random foraging on an open platform in 2D environments, in RW and VR, with specific combinations of proximal and distal visual cues, without any reward association to these cues. These manipulations included changing the position, orientation and size of the distal visual cues, and suspending a similarly sized and shaped proximal visual cue above the platform, which alters the spatial relationship of the visual cue without altering rat's behavior (Sandler et al. SfN 2016). To decipher the spiking activity of cells we further developed the generalized linear model (GLM) framework we recently employed [2]. To cross validate our findings, we

applied GLM to synthetic data that consisted of spike trains generated using behavioral data and inhomogeneous rate-modulated Poisson processes. By employing these techniques, we can dissociate the mechanisms governing different types of spatial and directional responses in hippocampal CA1 neurons. Our GLM framework provides an estimate of the relative influence of these variables on the spiking activity of individual cells. This method allows us to identify the nature of the directional selectivity of these cells in the presence of other tuning parameters, and under various multisensory conditions. These results provide novel insights about the mechanisms governing place cells, and have important implications for theories of hippocampal function.
[1] O'Keefe, J., & Dostrovsky, J., Brain research (1971)
[2] Acharya, L., et al., Cell 164.1-2 (2016): 197-207

Disclosures: M. Shahi: None. **S. Dhingra:** None. **R. Sandler:** None. **R. Rios:** None. **C. Vuong:** None. **L. Acharya:** None. **M.R. Mehta:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 508.16/DDD17

Topic: H.01. Animal Cognition and Behavior

Support: R01MH112169
R01MH095297

Title: Mixed selectivity in the rodent medial temporal lobe and related regions

Authors: *C. MIKKELSEN[1], M. W. HOWARD[2]
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Abstract: Previous work has established that the macaque prefrontal cortex utilizes a mixed selective coding strategy (Rigotti, et al., 2013). Mixed selectivity is notable in that it requires many cells to respond to conjunctive pairings of different variables. Although previous work has argued that conjunctive coding develops in the rodent hippocampus and related regions (e.g., Komorowski, et al., 2009) and is important for learning associations, to our knowledge there has not thus far been a quantitative and systematic study of mixed selectivity in the rodent MTL. We used existing rodent data from the same contextual association task to ask whether mixed selectivity is observed in the rodent MTL, including studies of the hippocampus (McKenzie, 2014), lateral entorhinal cortex, medial entorhinal cortex and perirhinal cortex (Keene et al., 2016). In addition, we also analyzed datasets from the rodent orbitofrontal cortex (Farovik et al. 2015) and a previously unpublished dataset from the medial prefrontal cortex. The recordings encompass a total of approximately 2,000 single units. Although there are perhaps some subtle

differences across regions in the emphasis placed on variables for spatial/contextual and object information, the most notable result is that all regions showed robust mixed selectivity. This suggests that performance in the contextual association task makes use of a widespread network of interacting brain regions that use the same form of coding.

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Disclosures: C. Mikkelsen: None. **M.W. Howard:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

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Brain Behavior Research Foundation #23723
Canada Research Chairs Program

Title: Grid cell dysfunction in the medial entorhinal cortex correlates with path integration deficits in an amyloid mouse model of Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease popularly characterized by the presence of beta-amyloid (AB) plaques at the cellular level. Human patients typically show spatial memory impairments in the form of disorientation and difficulty navigating familiar environments. One potential circuit-level mechanistic explanation for these symptoms is that the onset of AB plaques causes a disruption of spatial coding in the brain's navigation system that consists of grid cells, head-direction cells, and border cells in the medial entorhinal cortex (MEC). In support of this view, previous in-vivo electrophysiological recordings in the Tg2576 mouse model of AD have confirmed that place cell degradation correlates with increased plaque load in the hippocampus. Here, we employed in-vivo electrophysiological recordings in the MEC of the freely behaving transgenic J20 mouse model of AD, which expresses an onset of beta-amyloid (AB) plaques in the hippocampus at five months of age. We demonstrate that grid cells are disrupted in aged J20 animals (months 5-7), evidenced by substantially fewer neurons that exceed our significance threshold for a metric designed to capture the spatial periodicity of grid cells. Even grid-like cells in J20 mice exhibit irregularity in the location of firing field. Network-level impairments of non-classified cells in the MEC are detectable in young J20 animals (months 2-4), preceding the formation of plaques. To corroborate our physiological findings, we aimed to better characterize the nature of spatial memory impairment seen in AD and to propose a function for the MEC in navigation and memory. J20 mice were tested in a path integration food-foraging task in darkness where they must integrate self-motion cues such as heading direction and movement speed to continuously update their perceived location in space. Without allocentric visual cues, this task provides an opportunity to characterize the classic navigational deficits seen in AD patients as well as the role of specific MEC cell types in navigation. Our data show that aged J20 mice demonstrate impaired path integration behaviour which correlates to the observed physiological dysfunction. Overall, our results suggest that grid cells in the MEC are important targets for future therapies to restore spatial cognitive function in human AD patients.

Disclosures: J. Ying: None. **A. Keinath:** None. **M.P. Brandon:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

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Title: Spatial correlates of the retrosplenial cortex during free exploration

Authors: *L. C. CARSTENSEN, A. S. ALEXANDER, J. R. HINMAN, M. E. HASSELMO
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Abstract: The retrosplenial cortex (RSC) is an association area that is highly interconnected with sensory and motor processing regions as well as structures including the hippocampal formation (HPC), entorhinal cortices (EC), and anterothalamic nuclei (ATN) that are known to represent an animal's position or heading direction with respect to the external environment. Given this anatomy, it is perhaps no surprise that neural ensembles of the RSC encode numerous variables relevant to spatial navigation, including: position within a well-known route, position or heading within a global and/or local environment, and the current or upcoming actions of the animal. Investigations of the HPC, EC, and ATN have often focused on spatial responses observed while the animal freely explores an open arena. In contrast, RSC spatial representations have, with a few exceptions, been primarily examined in linear environments while the animal performs track running tasks. Given that RSC serves as both an input and output hub for the broader neural spatial circuitry, it is important to register RSC spatial responses in the two-dimensional (2D) environment with respect to place cells, grid cells, and head-direction cells of the HPC, EC, and ATN. In the current work, we sought to further characterize RSC spatial representations during free exploration. To do so, we performed in vivo electrophysiological recordings while rats explored familiar and novel arenas that had varying shapes or visual cue configurations. Consistent with previous work, we observed both allocentric and egocentric spatial representations within the region during open field exploration. We report that individual RSC neurons can exhibit complex 2D spatial correlates that are reliable across sessions and can anchor to either local or distal cues. RSC neurons also exhibited linear and non-linear speed related firing as well as other self-motion correlates. Finally, a sub-population of RSC neurons exhibited activity that was tuned to the egocentric relationship of the animal with respect to environmental boundaries. Collectively, these results identify multiple features of RSC spatial mapping in 2D environments that may have interesting implications for the formation or anchoring of spatial correlates in regions reciprocally connected with the RSC.

Disclosures: L.C. Carstensen: None. **A.S. Alexander:** None. **J.R. Hinman:** None. **M.E. Hasselmo:** None.

Poster

508. Head Direction Cells and Spatial Navigation

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Canada Research Chairs Program

Title: Hippocampal representations of rooms with multiple entryways

Authors: *A. T. KEINATH[1], A. NIETO-POSADAS[2], M. P. BRANDON[3]
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Abstract: Outside of the laboratory, environments are often defined by multiple entryways; yet little is known about how multiple entryways might shape hippocampal map. Previous work examining the hippocampal representations of rodents in multiroom environments has demonstrated that rooms with similar spatial geometry and entryway directions elicit similar hippocampal maps (Spiers et al., 2013). Map similarity is minimized when these rooms are disambiguated by unique entryway directions (Grieves et al., 2016), suggesting that entryway direction may be an especially important determinant of the hippocampal representation of an environment. Here, we tested whether and how multiple entryways affect the hippocampal map within a given room. To do so, we simultaneously recorded calcium transient activity of large populations of place cells in CA1 as mice repeatedly explored a multiroom environment. In this environment, each room shared the same square spatial geometry, internal cues, and a common entryway direction, but was disambiguated by an additional unique entryway direction which was offset either 90°, 180°, or 270° from common entryway. We found that entryway direction modulated the hippocampal map both within and across rooms at the population level. Within each room, common-entrance maps and unique-entrance maps were similar; however, map similarity was lowest for the 180°-offset room. Across rooms, unique-entrance maps exhibited less repetition than common-entrance maps. Unique-entrance maps did not rotate relative to common-entrance maps, indicating that entryway direction modulated map identity but not map orientation. Together, these results demonstrate that entryway direction modulates hippocampal map identity within a room on an entrance-by-entrance basis.

Disclosures: A.T. Keinath: None. **A. Nieto-Posadas:** None. **M.P. Brandon:** None.

Poster

508. Head Direction Cells and Spatial Navigation

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Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 MH052090

Title: Schema accommodation in hippocampal memory ensembles

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Abstract: Hippocampal cells are known to remap their firing rates and global responses to immediate changes in task demands (Wood et al., 2000, Smith et al., 2006) and to changes in the environment (Wills et al. 2005, Leutgeb et al., 2005). This results in population codes related by graded similarity for distinct experiences. Gradual changes in the representation, or "drift," have also been observed, which don't affect the day-to-day precision of navigation (Rubin et al., 2015). The study presented here tests how new information that conflicts with a pre-existing spatial memory influences that existing spatial memory in the same population of neurons. The theory of accommodation of schema, also studied as retroactive interference, predicts that an existing representation should be noticeably altered by the integration of new, conflicting information. We studied this process by training mice to perform two different rules on a plus maze, "go East" and "turn right," on separate, consecutive days. We recorded the activity of the same population of cells in dorsal CA1 with calcium imaging, and show how both individual cells and the population code for one rule are altered by learning a second rule. We then compare the stability of population representations in conditions where information is learned in the same environment against learning in different environments. These results advance our understanding of memory maintenance and formation in the presence of interference.

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Poster

508. Head Direction Cells and Spatial Navigation

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Topic: H.01. Animal Cognition and Behavior

Support: CIHR Project Grant #367017
CIHR Project Grant # 377074
NSERC Discovery Grant # 74105
Brain Behavior Research Foundation #23723
Canada Research Chairs Program

Title: Investigation of the head-direction network activity in the Anterodorsal Thalamic Nucleus using miniaturized microscopes in freely behaving mice

Authors: *Z. AJABI[1], M. P. BRANDON[2]
[1]Integrated Program in Neurosci., [2]Psychiatry, McGill Univ., Montreal, QC, Canada

Abstract: Head direction (HD) cells are the most abundant spatially tuned neurons in the brain. HD cells are found in a series of regions starting in the brainstem and extending through the hypothalamus, thalamus, and up into the cortex areas that govern navigation and spatial memory. One area of interest is the Anterodorsal Thalamic nucleus (ADN), which contains a high concentration of HD cells (~60%) and is directly downstream of the circuitry believed to initially generate the HD signal, between the dorsal tegmental nuclei and the lateral mammillary bodies. One major obstacle to obtaining data from this region, especially in mice, is its small size (a spherical nuclei with a 0.3mm diameter). Thus, previously reported data has rarely shown recordings of more than 10 HD cells simultaneously. Here, we show calcium imaging of more than 50 HD cells at once and during behaviour. We use a miniaturized microscope built following the guidelines of the Miniscope project at UCLA (miniscope.org). To reach the ADN, we implanted a 0.5mm-diameter GRIN relay lenses, in mice that were injected, beforehand, with a non-specific adeno-associated virus (AAV) to express GCaMP6f, in the target region, which reduced damage to the brain tissue to its minimum and recordings were stable over the course of at least two months. Calcium transients allowed us to identify HD cells by means of polar plots and a correlation measure between fluorescence changes and the stimulus signal that was recreated by fitting a Gaussian curve centered at the angle to which the mean resultant length of the said polar plot points. Our recordings also show a stable preferred firing direction of HD cells for more than two months. Interestingly, our data shows a possible clustering of the HD cells with regards to their preferred firing directions and a potential topographical representation of the animal's head direction in the ADN. This preliminary finding needs to be further investigated. This technique also allowed us to analyze the HD cells' activity from a network perspective. Using dimensionality reduction methods, we were able to track the evolution of the HD system's state space during free exploration, in an open field. Preliminary results suggest a major impact of self-motion in maintaining a high level of activity in the HD network. Whereas, periods of immobility were generally characterized by a low network activity. Calcium imaging of substantial populations of HD cells may thus provide a way to further understand the dynamics of the HD system and can possibly be used to test the validity of the classic theory that defines the HD system as a ring attractor network.

Disclosures: Z. Ajabi: None. **M.P. Brandon:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

Support: 5R01MH051570-22

Title: Coding of what and when in lateral entorhinal cortex and hippocampus during a delayed matching task

Authors: *J. H. BLADON, M. HOWARD, W. NING, L. WERNECK
Psychology, Boston Univ., Boston, MA

Abstract: Episodic Memory involves the integration of events into the spatial and temporal context within which they occurred. The Lateral Entorhinal Cortex (LEC) is a central node in the episodic memory network and is thought to provide the majority of object or event related information entering the hippocampus. The LEC is hypothesized to buffer object and event information so that it may be properly integrated into a spatiotemporal context within the hippocampus (HPC). Recent finding have suggested that the LEC may be a source of temporal information feeding into the hippocampus (Tsao, 2017; Meister & Buffalo, 2017; Tsao & Moser, 2017). We employed simultaneous LEC and HPC (CA1) tetrode recordings during a memory task known to generate time cells in the hippocampus. Units in both the LEC and HPC exhibited object specific responses during object presentation and during the delay. We will characterize the similarities and differences in temporal and object coding between these two structures.
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Disclosures: J.H. Bladon: None. **M. Howard:** None. **W. Ning:** None. **L. Werneck:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

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Program #/Poster #: 508.23/DDD24

Topic: H.01. Animal Cognition and Behavior

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CIHR Project Grant # 377074
NSERC Discovery Grant # 74105
Brain Behavior Research Foundation #23723
Canada Research Chairs Program

Title: Investigating the role of medial septal cell types in generating the hippocampal code for time

Authors: *H. YONG[1], M. P. BRANDON[2]
[1]Integrated Program in Neurosci., McGill Univ., Montreal, QC, Canada; [2]Psychiatry, McGill University, Douglas Hosp. Res. Ctr., Montreal, QC, Canada

Abstract: Recent work has shown that hippocampal neurons code for the time spent in the delay period of a delayed spatial alternation task. These 'time cells' have been shown to require input from the medial septum, as muscimol inactivation of the medial septum disrupted the activity of time cells and impaired memory performance. However, the exact role of the medial septum in time cell function remains unclear as muscimol-induced inactivation of the medial septum persisted for the entire duration of the behavior task. It remains possible that time cells may require information computed outside of a delay zone by other brain regions that rely on the medial septum. Moreover, inactivation of the medial septum with muscimol silences the activity of every septal neuronal population, thus it is unknown which cell population within the medial septum supports time cell activity. We therefore pursued an optogenetic strategy to selectively silence genetically-defined cell populations within the medial septum only when animals were running on the treadmill in the delayed spatial alternation task. We show that inhibition of GABAergic neurons not only led to reduction in theta amplitude recorded from CA1 region of the hippocampus, but also had heterogeneous effects on time cell activities. Moreover, there was significant reduction in mean and peak firing rates of time cells when GABAergic neurons were inhibited. Moreover, we tested the role of cholinergic neurons in the medial septum by using ChAT::Cre transgenic mice. In this approach, we injected Cre-dependent viral vector to induce expression of Archaerhodopsin in septal cholinergic neurons. These animals were trained to run reliably on the motorized treadmill and to alternate between the left and the right arms of the maze for water reward. They were required to run for 10 seconds on the treadmill between each alternation trial. Activity of time cells was recorded from CA1 region of the hippocampus with tetrodes while septal cholinergic neurons were selectively silenced with a green laser (520nm) when animals ran on the treadmill. We are currently analyzing the extent by which time cells and behavioral performance are disrupted during optogenetic silencing of septal cholinergic neurons. Next, we plan to assess the role of glutamatergic neurons in the medial septum. Together, this data will reveal how each septal population is involved in time cell function in the hippocampus, which will in turn help us shed light on the underlying mechanisms that code for time in the hippocampus.

Disclosures: H. Yong: None. **M.P. Brandon:** None.

Poster

508. Head Direction Cells and Spatial Navigation

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Topic: H.01. Animal Cognition and Behavior

Support: R01 MH60013
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Title: Retrosplenial and entorhinal cortical representation during visually-based triangulation

Authors: *A. S. ALEXANDER, M. E. HASSELMO
Boston Univ., Boston, MA

Abstract: Visual information can define the boundaries or spatial structure of the observable environment, and thus can anchor or orient map-based spatial representations observed in the anterothalamic nuclei, medial entorhinal cortex (MEC), and hippocampus. The retrosplenial cortex (RSC) is an association area that is reciprocally connected to visual processing regions and the aforementioned structures. Critically, visual information is initially processed in egocentric coordinates as the relationship between the positions of visual landmarks and the animal itself. Thus, in order for this information to be incorporated into allocentric spatial representations a translation between egocentric and allocentric coordinate systems must occur. RSC may be important for reference frame transformations required to integrate visual landmark information with externally-referenced head-direction or grid cell representations observed in MEC. To explore the neural mechanisms underlying such a process we recorded the activity of neurons in the MEC and RSC while animals performed a novel visually-guided triangulation paradigm. On each trial, rats were required to determine the relative relationships among multiple visual cues to navigate to a hidden zone in the two-dimensional plane that when entered would trigger reward delivery to a random part of a large open field. Visual cue positions and the corresponding reward zone shifted across trial blocks with the goal of forcing rats to repeatedly compute relationships between their current location, distal visual cues, and discrete allocentric locations. Animals quickly learned the task and were able to rapidly triangulate to hidden zones using a variety of behavioral strategies. We observed complex activity correlates across spatial reference frames in both MEC and RSC, including responses anchored to visual cues or to single or multiple hidden zones. In some cases, hidden zone locations appeared to distort allocentric spatial representations in the two regions. Together these results begin to elucidate features of MEC and RSC activity that could be critical for goal-directed navigation or anchoring spatial representations to visual cues.

Disclosures: A.S. Alexander: None. **M.E. Hasselmo:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

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Program #/Poster #: 508.25/EEE2

Topic: H.01. Animal Cognition and Behavior

Support: R01MH112169
R01MH095297
R01MH051570

Title: Comparison of the compression of time and space in dorsal CA1

Authors: *D. J. SHEEHAN, M. W. HOWARD
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Abstract: The hippocampus contains neurons that robustly code for temporal and spatial relationships between events. It has been shown that hippocampal time cells, which code for temporal relationships, have firing fields that expand in size and decrease in number with the passage of time (e.g., Salz, et al., 2016). The increase in time field size and decrease in number of time fields is consistent with decrease in the accuracy of temporal coding for events that recede into the past. It is thus far not known whether place cells, which code for spatial relationships, exhibit the same form of compression. Whereas time cells code for time since a reference event, because a typical place cell experiment includes many possible landmarks, it is not immediately obvious what spatial relationship a particular place cells represents. Past work has demonstrated that CA1 cells with spatially tuned firing fields can fire in relationship to a movable landmark (Gothard, et al. 1996, 2001). In this study rats with microdrives targeting dorsal CA1 were shaped to run along a linear track paired with a movable start box, coupled with variable lighting conditions. Previous findings indicate that place cells that respond along paths from the movable start box encode distance from the start box, enabling one to establish a zero along the distance axis. The firing characteristics of principal cells of the dorsal CA1 region are investigated with respect to the movable start box. We compare the width of place fields and the number of place fields as a function of distance from the start box. This enables a direct comparison between the form of compression for time and space in the hippocampus.

Disclosures: D.J. Sheehan: None. **M.W. Howard:** None.

Poster

508. Head Direction Cells and Spatial Navigation

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

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Canada Research Chairs Program

Title: Disentangling the role of medial septal cell types in grid cell generation

Authors: *J. ROBINSON[1], M. P. BRANDON[2]
[1]McGill Univ., Verdun, QC, Canada; [2]Psychiatry, McGill Univ., Montreal, QC, Canada

Abstract: The medial entorhinal cortex (MEC) is a high-level cortical region critical for spatial navigation and episodic memory processing. The MEC contains a specialized circuit of spatially tuned neurons including grid cells, which preferentially fire at distinct locations that form a repeating hexagonal pattern. This spatial periodicity is known to be dependent on input from the medial septum (MS), a basal forebrain structure densely connected to the MEC. The MS contains three distinct cell types that project directly to the MEC; GABAergic, glutamatergic and cholinergic neurons. While it is known that a complete inactivation of all cell types in the MS disrupts the spatial firing patterns of grid cells, the role that each cell types plays in the generation of grid cells remains unknown. Here, we aim to resolve the role that MS GABAergic and glutamatergic populations play in the grid cell signal. To achieve this, we used an optogenetic approach to selectively silence each cell type in the MS while simultaneously recording the activity of MEC grid cells in an open field environment. We used VGAT-Cre and VGLUT2-Cre transgenic mouse-lines, which selectively express cre recombinase in the GABAergic and glutamatergic neurons in the septum, respectively. A cre-dependent viral vector (AAV-Flex-ArchT-GFP) was injected into the MS for optogenetic silencing, a fiber optic was placed just above the MS for light delivery, and a four-tetrode microdrive was implanted into the MEC for local field potential and grid cell recordings. Our data shows that optogenetic inactivation of septal GABAergic cells cause a 70-80% reduction in theta power, similar to that observed during pharmacological inactivation of the entire MS. In contrast, silencing glutamatergic neurons did not affect theta power or frequency. We are currently analyzing the effect that these manipulations have on grid cells. Together these experiments will reveal the role of GABAergic and glutamatergic MS populations in generation of the grid cell spatial firing pattern.

Disclosures: J. Robinson: None. **M.P. Brandon:** None.

Poster

508. Head Direction Cells and Spatial Navigation

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Topic: H.01. Animal Cognition and Behavior

Support: NIMH R01 MH60013
NIMH R01 MH61492
ONR MURI N00014-16-1-2832
DFG 322014644

Title: Speed coding by entorhinal cortex speed cells differs across behaviorally relevant time scales and is independent of cholinergic modulation

Authors: *H. DANNENBERG[1], C. KELLEY[1], C. MONAGHAN[2], M. E. HASSELMO[1]
[1]Boston Univ., Boston, MA; [2]McLean Hosp., Belmont, MA

Abstract: Running speed can be coded by the firing rate of a dedicated subpopulation of neurons in the entorhinal cortex which have been called speed cells. This speed code is used in various computational models for path integration. In these models firing rate is considered to be linearly tuned by running speed, and speed tuning curves are assumed to predict spiking at every moment in time. However, many speed cells have saturating exponential tuning curves, and it has currently not been tested if the speed code is linear and accurate at short time scales. We first tested this assumption on data obtained from open field recordings in rats by applying a novel filtering approach differentiating between speed codes at short time scales in the range of a few seconds, presumably relevant for path integration, and long time scales in the range of seconds to minutes, presumably reflecting modulation of brain activity by different behavioral activity states. By analyzing the speed code at different time scales, we demonstrate many cells show a strong linear correlation with running speed across multiple time scales, but slopes of speed tuning curves tend to increase with longer time scales. Modelling demonstrates an increase in speed tuning curve steepness at longer time scales results in an overall saturating exponential speed tuning curve. We further show integration of spiking rates over short time scales has a negative impact on the overall speed score, which cannot be explained by the influence of Poisson noise alone. Moreover, speed coding by spiking rate is most efficient when spiking rate is integrated over many seconds. We validate these results on a mouse data set and further show that optogenetic inhibition of cholinergic neurons in the medial septum/diagonal band of Broca (MSDB) does not affect coding of running speed by firing rate during open field exploration of a familiar environment. These results are relevant for models of path integration and for our

understanding of how behavioral activity states modulate firing rates and information processing in the entorhinal cortex.

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Poster

508. Head Direction Cells and Spatial Navigation

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Canada Research Chairs Program

Title: Remapping in ventral hippocampus during a context fear teleportation task

Authors: *R. R. ROZESKE, L. RUNTZ, M. P. BRANDON
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Abstract: An organism's survival depends upon whether it can discriminate between safe and threatening contexts. The ventral hippocampus (VH) is thought to encode contexts via specialized place cells whose firing is tuned to specific locations within a context, which as a population form a spatial map. Although the VH is necessary for the formation of context fear memories, the defined neuronal circuits and place cell populations that encode threatening and safe contexts have not been thoroughly characterized. To assess the neuronal population activity and potential pathway specificity during context fear discrimination we used a novel fear conditioning paradigm in combination with fiber photometry and miniature microendoscope (UCLA miniscope) calcium imaging. Mice underwent differential context fear conditioning using a large cylindrical LED screen that permitted rapid teleportation between visual contexts. Visual Context A was associated with electric shock delivery, whereas Visual Context B was remained neutral. In the first set of experiments, GCaMP6f was expressed in ventral CA1 and optic fibers were implanted locally to record global fluorescence using fiber photometry during transitions between contexts A and B. Fluorescence was also quantified in vCA1 projection regions during context transitions to determine whether specific vCA1 projection were implicated in context discrimination. A second set of experiments visualized cellular fluorescence following expression of GCaMP6f in vCA1 using miniscope recording, permitting

examination of place cell activity during context transitions. Population level analysis of place cell activity during context discrimination will be presented. Together this study will elucidate how the VH preferentially controls the transmission of context information necessary for context fear discrimination.

Disclosures: R.R. Rozeske: None. **L. Runtz:** None. **M.P. Brandon:** None.

Poster

508. Head Direction Cells and Spatial Navigation

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Topic: H.01. Animal Cognition and Behavior

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ONR MURI N00014-16-1-2832

Title: Neuronal representation of environmental boundaries in egocentric coordinates

Authors: *J. R. HINMAN[1], G. W. CHAPMAN, IV[2], M. E. HASSELMO[2]
[1]Ctr. for Systems Neurosci., [2]Psychological and Brain Sci., Boston Univ., Boston, MA

Abstract: Animals must navigate through the complex spatial environments they inhabit. The sensory information about such environments and the physical movements that comprise navigation are often represented in an egocentric reference frame, one that is centered on the agent. Yet the hippocampus, entorhinal cortex and associated structures store spatial representations in an allocentric or world-centered reference frame involving place, grid, head direction and boundary coding cells. The dorsomedial striatum (DMS) is important for egocentric navigational response strategies. We implanted rats with up to 16 tetrodes targeting the medial portion of the striatum and recorded multiple single units while they foraged in a large open field. A novel spatial cell type was identified that represents the boundaries of the environment in an egocentric reference frame that we have termed egocentric boundary cells (EBCs). Approximately 18% of cells were identified as EBCs, which spike when an environmental boundary occupies a specific orientation and distance relative to the animal. We conducted recordings following a series of different environmental manipulations, including rotating the open field relative to the testing room, changing the size of the environment and changing the visual appearance of the boundaries and found that EBCs maintain the same preferred boundary orientation and distance relative to the animal across each manipulation. Next, we assessed whether EBCs remap across environments, as is observed for the allocentric spatial map in the hippocampal formation. EBCs did not remap across different familiar environments or in a completely novel environment, but rather maintained a stable egocentric

representation of boundaries relative to the animal. In addition to EBCs, head direction cells similar to those in the hippocampal formation were present in DMS, as were cells coding running speed and other self-motion signals similar to those observed in posterior parietal cortex. In a subset of recordings hippocampal theta oscillations were simultaneously recorded in order to assess whether the egocentric spatial representation in DMS maintains a specific theta phase relationship. Some EBCs were found to be significantly phase locked to hippocampal theta oscillations, while others showed no preference for the theta phase at which they fired. Overall, the DMS contains navigation related cells including EBCs, head direction cells and self-motion coding cells that may be part of a network responsible for tranforming and implementing allocentric translation vectors that could be generated by the hippocampal formation.

Disclosures: J.R. Hinman: None. **G.W. Chapman:** None. **M.E. Hasselmo:** None.

Poster

508. Head Direction Cells and Spatial Navigation

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Support: NIH R01 MH052090

Title: Tracking the ontogeny of trajectory-dependent neuronal activity in the hippocampus

Authors: *N. R. KINSKY, W. MAU, D. W. SULLIVAN, H. B. EICHENBAUM, M. E. HASSELMO
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Abstract: Many neurons in the hippocampus encode information beyond the well-established place code. For example, trajectory dependent or “splitter” cells modulate their firing activity in the same location of a T-maze based on the rodent’s past location and/or future trajectory. Despite a number of studies demonstrating the robustness of trajectory dependent activity in over-trained rodents, little is known about the origin of these cells. Does the emergence of splitter cells correlate with learning of a task? Given their importance for task performance, are splitter cells more likely to remain active in subsequent sessions? Do they reliably retain trajectory dependent firing in subsequent sessions, or do they remap at the same rate as place cells? Here, we utilized *in vivo* calcium imaging using a miniscope to reliably track neurons across days and investigate the ontogeny of splitter cells while mice performed a continuous spatial alternation task. We found that the proportion of the active cells exhibiting trajectory dependent behavior correlated with accuracy on the alternation task, suggesting that splitter cells were important for proper task performance. Furthermore, splitter cells were significantly more likely than other cells to be active on subsequent sessions, indicating that behaviorally relevant

cell phenotypes might exhibit greater stability than other cells. Finally, trajectory dependent activity emerged rapidly and decayed slowly, indicating that once trajectory dependent activity emerged a cell was slow to change/remap. Thus, our results fill in gaps in existing literature about the emergence of trajectory-dependent firing and hint that cell phenotype might influence the stability of neurons over subsequent hours to days.

Disclosures: N.R. Kinsky: None. **W. Mau:** None. **D.W. Sullivan:** None. **H.B. Eichenbaum:** None. **M.E. Hasselmo:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 509.01/EEE8

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH113894

Title: Encoding of contextual fear memory in the hippocampal-amygdala pathway

Authors: *J.-H. CHO, W. KIM
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Abstract: In contextual fear conditioning, experimental subjects learn to associate a neutral context with an aversive stimulus and display fear responses to a context that predicts danger. Although the hippocampal-amygdala pathway has been implicated in the retrieval of contextual fear memory, the mechanism by which fear memory is encoded in this circuit has not been investigated. Here, we show that activity in the ventral CA1 (vCA1) hippocampal projections to the basal amygdala (BA), paired with aversive stimuli, is both necessary and sufficient to generate conditioned fear memory. Contextual fear conditioning induced selective strengthening of the vCA1-BA engram cell pathway, which was prevented under anisomycin-induced retrograde amnesia. Moreover, BA engram cells preferentially received monosynaptic inputs from vCA1 engram cells, whose activity was required for contextual fear learning. Our study suggests that strengthening of the vCA1-BA engram cell pathway plays pivotal roles in adaptive fear to a relevant context.

Disclosures: J. Cho: None. **W. Kim:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

Support: National Honor Scientist Program of Korea (NRF-2012R1A3A1050385)
Basic Science Research Program of Korea (NRF-2016R1D1A1B03931525)

Title: Inter-regional synaptic correlates among engram cells underlie memory formation

Authors: J.-H. CHOI, S.-E. SIM, J.-I. KIM, D. CHOI, J. OH, S. YE, J. LEE, T. KIM, H.-G. KO, C.-S. LIM, *B.-K. KAANG
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Abstract: Memory resides in engram cells distributed across the brain. However, the site-specific substrate within these engram cells that underlies memory storage remains theoretical, even though it is generally accepted that synaptic plasticity encodes memories at the synapse. Here, we developed the dual-eGRASP technique to examine synapses between engram cells to identify the specific neuronal site for memory storage. In this study, we found an increased number and size of spines on CA1 engram cells receiving input from CA3 engram cells. In contextual fear conditioning, this enhanced connectivity between engram cells encoded memory strength. We also revealed that CA3 engram to CA1 engram projections showed strong occlusion of long-term potentiation based on increased release probability and enhanced postsynaptic responses. These results suggest that structural and functional enhancements of the connectivity between engram cells across two directly connected brain regions are the synaptic correlate of memory.
(J.-H. Choi, S.-E. Sim, J.-I. Kim, and D. Choi contributed equally to this work)

Disclosures: J. Choi: None. **S. Sim:** None. **J. Kim:** None. **D. Choi:** None. **J. Oh:** None. **S. Ye:** None. **J. Lee:** None. **T. Kim:** None. **H. Ko:** None. **C. Lim:** None. **B. Kaang:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

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Program #/Poster #: 509.03/EEE10

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH091220
NIH Grant NS088421
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NARSAD Independent Investigator Award
MIT Greater China Fund for Innovation

Title: Distinct activated neuronal ensembles differentially modulate contextual fear memory discrimination

Authors: *X. SUN[1], M. BERNSTEIN[1], M. MENG[1], L. YAO[2], A. T. SÖRENSEN[3], X. ZHANG[2], Y. LIN[1]
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Abstract: Memories are hypothesized to be encoded in sparse neuronal ensembles in which enduring molecular and synaptic changes occur. Activity-dependent genes, whose expression is induced in neurons activated during learning, are believed to underlie the plasticity that converts transient experience into long-lasting memory. As a result, the activation of these genes have been used to tag active neuronal ensembles, with the assumption that these ensembles are largely overlapping and functionally similar. Here we report that there exist functionally distinct active neuronal ensembles, defined by different activity-dependent pathways. Based on the Robust Activity Marking (RAM) system that we recently developed, we constructed two activity-dependent reporters, RAM2 and RAM3, which are activated by two different activity-dependent transcriptional pathways. Using these reporters, we identified two functionally distinct active neuronal ensembles in the mouse dentate gyrus (DG) during contextual fear conditioning (CFC). These two ensembles underwent distinct experience-dependent modifications, and differentially modulated the balance of contextual fear memory discrimination and generalization. Using electrophysiological recording and chemogenetic behavioral manipulation, we found that the $RAM2^+$ ensemble neurons recruited stronger local inhibitory inputs and are required for context discrimination. On the other hand, the $RAM3^+$ ensemble neurons received stronger excitatory inputs from the upstream entorhinal cortex (EC) and promote context generalization. Taken together, our findings demonstrated for the first time the functional heterogeneity of active neuronal ensembles, and that encoded memories can be decomposed into discrete neuronal ensembles defined by different activity-dependent transcriptional pathways.

Disclosures: X. Sun: None. **M. Bernstein:** None. **M. Meng:** None. **L. Yao:** None. **A.T. Sörensen:** None. **X. Zhang:** None. **Y. Lin:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

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Program #/Poster #: 509.04/EEE11

Topic: H.01. Animal Cognition and Behavior

Support: NIH 5R01MH106617
NARSAD /BBRF

Title: Prefrontal circuit dynamics associated with context-dependent fear discrimination learning

Authors: *J. MAYER[1], J. PASTORE[1], T. W. BAILEY[2], J. SPEIGEL, III[2], E. KORZUS[1]
[1]Psychology, Univ. of California Riverside, Riverside, CA; [2]Neurosci., Univ. of California Riverside, Riverside, CA

Abstract: Recent studies have revealed molecular and synaptic mechanisms of information storage and it has been postulated that neural representation activated during memory encoding is preferentially recruited during memory retrieval. How specific neuronal representations are recruited to form and maintain memories is unknown. Present studies aim at identifying the neural representation of contextual fear memories and assess circuit dynamics underlying disambiguating safety and danger. Fear behavior is regulated by the medial prefrontal cortex (mPFC) via fear excitation and inhibition, respectively, which may be due to differential connectivity with amygdala. Current research investigates how the PFC is able to act through multiple pathways to exert both excitatory and inhibitory influences on fear responses under the central hypothesis that accuracy of fear memory is attained via extinction of fear responses to non-reinforced stimuli. Alterations of prefrontal network activity during fear modulation associated with context-dependent fear discrimination learning is evaluated via real time network activity assessment using miniaturized head-mounted microscopes followed by computational analysis of large-scale neuronal activity patterns. Head-mounted miniaturized microscopes are capable of measuring calcium transients reflecting neuronal activity from more than thousands neurons in a freely behaving mouse. To evaluate large-scale circuit dynamics associated with fear discrimination learning, the calcium sensitive fluorescent protein GCaMP6f is expressed in the prelimbic subdivision (PL) of the mPFC followed by assessment of real-time prefrontal network changes in response to dangerous and safe context stimuli across the behavioral testing. The functional relationship between fear and context is evaluated using computational analysis of large-scale neuronal activity patterns using chronically head-mounted microscopes. These head-mounted microscopes allow visualization of calcium transients associated with neuronal activity providing insights into emergent circuit dynamics in response to dangerous or safe contextual stimuli within relevant brain regions during different phases of fear discrimination learning to uncover the neural mechanisms underlying the ability to distinguish between danger

and safety. Understanding how fear memories are encoded and kept resistant to confusion is clinically relevant as fear memory overgeneralization is a hallmark of phobias, PTSD and generalized anxiety disorder.

Disclosures: J. Mayer: None. **J. Pastore:** None. **T.W. Bailey:** None. **J. Speigel:** None. **E. Korzus:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 509.05/EEE12

Topic: H.01. Animal Cognition and Behavior

Support: Ministry of Education, Culture, Sports, Science and Technology, Japan 15K18341
Japan Science and Technology Agency, PRESTO

Title: Information coding of fear memory in medial prefrontal cortex

Authors: *M. AGETSUMA[1,2,3], Y. ARAI[3], A. KASAI[4], H. HASHIMOTO[4], T. NAGAI[3]
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Abstract: For efficient and correct information processing in cerebral cortex, neural circuit dynamics must be spatially and temporally regulated with great precision. Medial prefrontal cortex (mPFC) of rodents has been shown important for various types of learning and memory, including fear memory, and related to various psychiatric diseases. However, it has been challenging to understand the computational mechanism in the mPFC, of which major problems are the complexity and heterogeneity of the prefrontal networks. While recent studies based on electrical or optical recording in the mPFC demonstrated that neuronal responses are heterogeneous and dynamically modulated throughout the learning process, it still remains unclear how population of neurons in this region enables the information processing, depending on learning states. Little is known especially about the mechanism underlying fear memory. Here we investigate this by chronic two-photon Ca^{2+} imaging from populations of neurons in mouse mPFC *in vivo*, which allows us to 1) record activities simultaneously from large number of neurons at the single cell resolution with high temporal resolution, and 2) investigate changes of neuronal responses depending on the learning states. We focus on the change in population responses of mPFC neurons for the fear memory by developing a new device to perform and test Pavlovian fear conditioning under the microscope. While many of the previous imaging studies for the mPFC relied on the invasive method, our system can minimize such damage by

introducing a microprism-based observation method.
Currently, we investigate population coding underlying memory recall as well as extinction.

Disclosures: M. Agetsuma: None. **Y. Arai:** None. **A. Kasai:** None. **H. Hashimoto:** None. **T. Nagai:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

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Topic: H.01. Animal Cognition and Behavior

Support: NIH 5R01MH106617
NARSAD /BBRF

Title: Balance of prefrontal division-mediated excitation and inhibition drives context-dependent fear discrimination learning

Authors: *T. W. BAILEY[1], J. SPEIGEL, III[2], J. MAYER[4], J. PASTORE[3], E. KORZUS[2]
[1]Neurosci., [2]Psychology, [3]Univ. of California Riverside, Riverside, CA; [4]Psychology, Univ. of California Riverside, Riverside, CA

Abstract: Failure to discriminate between aversive and harmless stimuli due to the similarity of external cues that were present during trauma in humans can lead to the intrusive recollection of aversive memories. Overgeneralized fear evoked by trauma reminders is typical of anxiety disorders, including posttraumatic stress disorder (PTSD), and is believed to be triggered by cues resembling the traumatic experience despite a currently secure environment. Our long-term goal is to characterize the mechanisms of fear memory accuracy versus generality and how these mechanisms translate into the control of neural circuits, behavior, and mental disorders. The central hypothesis of this project, based on our preliminary data and a large body of previous work, is that fear memory accuracy is attained via a medial prefrontal cortex (mPFC)-dependent mechanism involving the reduction of fear responses to harmless non-reinforced stimuli. Fear behavior is differentially regulated by the prelimbic (PL) and infralimbic (IL) regions of the mPFC via fear excitation and inhibition, respectively, which may be due to differential connectivity with the amygdala. Current research investigates how the mPFC is able to act through multiple pathways to exert both excitatory and inhibitory influences on fear responses under the central hypothesis that the accuracy of fear memory is attained via the extinction of fear responses to non-reinforced stimuli. A coactivator of transcription and histone acetyltransferase, cAMP response element binding protein (CREB)-binding protein (CBP) is required for long-term memory consolidation. The expression of the selective inhibitor of long-term memory consolidation CBPΔHAT in PL neurons results in severe deficits in fear

discrimination learning but not in fear conditioning. In addition, independent manipulations targeted specifically to the IL suggests that IL neurons may be also directly involved in coding new memories associated with in fear discrimination learning. In addition, real-time evaluation of neural ensembles of contextual memories with opposite valence in mPFC using head-mounted miniaturized microscopes shows alterations of context-dependent memory representations within the mPFC during fear discrimination learning, These findings provide strong support for our hypothesis that fear discrimination learning is a result of balancing the PL-mediated excitation and IL-mediated inhibition of fear responses. The impaired fear discrimination learning caused by maladaptations in the prefrontal cortex/amygdala circuits are likely to be relevant to neuropsychiatric disorders such as PTSD.

Disclosures: T.W. Bailey: None. **J. Speigel:** None. **J. Mayer:** None. **J. Pastore:** None. **E. Korzus:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

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Program #/Poster #: 509.07/EEE14

Topic: H.01. Animal Cognition and Behavior

Support: NSFC Grant 91632103

Title: The specific role of GABAergic interneurons in fear extinction

Authors: *X. ZHANG, Y. ZHOU, W. LI
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Abstract: Neural circuits and synaptic mechanisms involved in fear memory acquisition have been studied for several decades. However, fear extinction seems to play crucial part in the treatment of some stress disorders. Previous studies have found that the interneurons in BLA region (basolateral amygdala) play key roles in fear extinction. Nevertheless, mechanism of fear extinction has not been involved in the relationship between the function of interneurons and behavior performance. Our team successfully construct ArcCreERT2, cFosCreERT2, GAD67CreERT2 transgenic mice, which can be crossbreed with R26RSTOP-floxed-tdTomato mice to mark various types of neural circuits stimulated by fear acquisition and extinction. Furthermore, we construct interneuron-specific adenovirus associated virus (AAV) combined with DREADDs to specifically regulate interneurons fired during memory extinction. With the help of these transgenic mice, DREADDs and in-vivo calcium imaging, our data provide direct evidence of the interneurons in fear extinction.

Disclosures: X. Zhang: None. **Y. Zhou:** None. **W. Li:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

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Program #/Poster #: 509.08/EEE15

Topic: H.01. Animal Cognition and Behavior

Support: NIMH R01MH108623
NIMHR01 MH111754
One Mind

Title: Anatomical, molecular, and experience dependent organization of a ventral hippocampal circuit

Authors: K. CLAUSING, *V. S. TURNER, M. KHEIRBEK
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Abstract: The ventral hippocampus (vHPC) has been implicated in encoding a diverse array of information and modulating a number of behaviors including anxiety-related behavior, reward seeking and fear learning. These multiple functions have been attributed to the routing of information from the vHPC to a number of distinct downstream targets, including the prefrontal cortex (PFC), nucleus accumbens (NAc), lateral hypothalamus (LH), and basal amygdala (BA). For example, projections to the medial PFC and LH have been implicated in anxiety-related behavior, projections to the NAc in reward seeking, and projections to the BA in context fear learning. However, there remain gaps in our knowledge related to 1) the long-range circuit organization of the vHPC with respect to its inputs and outputs 2) the molecular profile of cells defined by their targets and 3) the differential recruitment of vCA1 cell-types by behavioral experiences. In this study, we used viral and transcriptional approaches to define the wiring and molecular organization of the vHPC circuit. Using a rabies-based viral approach to trace the relationship between input and output of the vHPC, we determined whether vHPC neurons projecting to the mPFC, NAc, LH, or BA have similar or distinct presynaptic inputs. Next, we profiled vHPC projection neurons using viral translating ribosome affinity purification to determine whether vCA1 projection neurons are molecularly distinct. Finally, we performed activity-dependent capture of vCA1 transcripts to determine the profile of neurons recruited by distinct experiences. By transcriptionally profiling cells captured by Fos activation (as a proxy for neural activity) we determined whether exposure to innately rewarding or aversive stimuli, or the encoding or retrieval of a fear memory recruit molecularly distinct populations of vCA1 neurons. These studies will provide an anatomical and molecular blueprint for the extended vHPC circuit and insight into the pathways and cell-types recruited by distinct experiences.

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Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

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Program #/Poster #: 509.09/EEE16

Topic: H.01. Animal Cognition and Behavior

Support: NIMH R01 MH108623
NIMH R01 MH111754
IMHRO/One Mind Rising Star Award

Title: Dynamic and stable coding of emotional stimuli in the ventral hippocampus

Authors: *J. BIANE[1], F. STEFANINI[3], T. KRAUSZ[4], M. A. S. LADOW[4], N. I. WOODS[2], S. P. BODDU[5], A. FAN[5], D. L. APODACA[5], M. KHEIRBEK[6]
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Abstract: Mood and anxiety circuits are widely distributed, comprised of interconnected networks at the local and brain-wide level. Within some areas, stimuli with orthogonal emotional valence are encoded by distinct subsets of neurons. In the ventral hippocampus (vHPC), a crucial node for anxiety-related behavior, cells with distinct projection streams have been reported to differentially encode anxiety-provoking environments, reward locations, and control aspects of fear learning. However, how the vHPC represents and learns about salient stimuli in the environment remains unclear. Here, we use functional calcium imaging to ask whether vCA1 neurons 1) have mixed selectivity for stimuli with differing valence, 2) have stable representations to emotionally relevant stimuli over time, and 3) encode associations between conditioned and unconditioned stimuli. Mice were injected with a virus encoding the calcium indicator GCaMP6f into vHPC and a GRIN lens was implanted above vCA1 for optical access. In our first series of experiments, we used freely moving microendoscopy to test whether single vCA1 neurons harbor 1) distinct representations to distinct stimuli, 2) representations to a particular valence class of stimuli, or 3) mixed selectivity to multiple stimuli regardless of valence. Activity in vCA1 was recorded during serial exposure to positive (sucrose, female interaction, appetitive odor) or negative (shock, open arms of elevated plus maze (EPM), aversive odor) stimuli. The following day, stimuli were presented again to assess the stability of neural representations. Within vCA1, a fraction of cells could be classified as either sucrose or shock responsive, with a small proportion selective for both. Interestingly, percentages of sucrose and shock responsive neurons did not differ between closed arm and open arm preferring neurons in the EPM. To assess whether these neural representations of task features in vCA1 change during associative learning, a separate cohort of mice underwent tone-sucrose trace

conditioning while performing 2-photon imaging of vCA1. In a fraction of vCA1 neurons, the representation of sucrose reward was maintained across learning. Conversely, the representation of the predictive tone cue was dynamically transformed, with tone-responsive neurons emerging over the course of training. Current efforts are aimed at understanding how these encoding dynamics differ along the dorsoventral axis of CA1 and among different projection streams from vCA1 to cortical and subcortical targets. Collectively, these experiments elucidate mechanisms by which innately salient stimuli are represented and learned within the vHPC.

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Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

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Program #/Poster #: 509.10/EEE17

Topic: H.01. Animal Cognition and Behavior

Support: NIMH R01 MH108623
NIMH R01 MH111754
IMHRO/One Mind Rising Star Award

Title: Population level coding of olfactory information in the dentate gyrus

Authors: N. I. WOODS[1], F. STEFANINI[2], *M. KHEIRBEK[1]
[1]Univ. of California, San Francisco, San Francisco, CA; [2]Columbia Univ., New York, NY

Abstract: A central goal of neuroscience is to understand how stimuli are encoded within ensembles of neurons, and how these representations are modified by learning. The hippocampus (HPC) has a well-documented function in encoding spatial information, however, it also encodes non-spatial information crucial for memory formation. Granule cells (GCs) in the dentate gyrus (DG) receive input from the lateral entorhinal cortex (LEC), which is known to process olfactory information. Here, we used *in vivo* 2-photon calcium imaging and behavior to determine the mechanisms by which DG GCs represent odor information and how learning alters these representations. We developed a fear conditioning task where mice discriminate between three odorants, two similar (methyl butyrate (CS+) and ethyl butyrate(CS-)) and one distinct (isoamyl acetate (CS-)). Silencing LEC input to the DG with tetanus toxin impairs encoding of the CS+ and behavioral discrimination between the similar odors. Population activity in DG GCs was imaged in a baseline pre-conditioning session and a day after conditioning. In both sessions, a subset of DG GCs show odor-selectivity, responding to individual or pairs of odors, or to odor offset. Analysis of the population code in DG GCs showed high similarity in the ensembles of neurons representing repeated presentations of the same odor, while distinct ensembles of

neurons encode each odor. Using machine learning, we were able to predict odor identity from DG GC activity with very high accuracy (>80%) for the three odor identities. Moreover, decoding accuracy was just as high among similar odors as distinct odor pairs, consistent with the theory that the DG takes overlapping, similar inputs and converts them into highly dissociable patterns of activity. To determine how neural representations change with learning, we trained our decoder with neural data from the preconditioning session and tested on the data after conditioning. This revealed accurate decoding of the CS- odors, suggesting stability in the ensembles, but not the CS+ odor, indicating that the representation in the DG changed with associative learning. This was supported by examining the similarity of recruited ensembles, which were more similar across sessions for CS- than the CS+ odor. Finally, examining fear discrimination scores revealed a correlation between decoding accuracy and fear discrimination, with the best odor discriminators at a behavioral level exhibiting the highest odor decoding accuracy. These results demonstrate that odor identity is strongly encoded in an LEC to GC circuit and the changes imposed by associative learning are reflected in selective changes in the population code.

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Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 509.11/EEE18

Topic: H.01. Animal Cognition and Behavior

Support: NIH IRTA postdoc fellowship

Title: Critical dynamics and short-term memory in neuronal networks

Authors: *T. L. RIBEIRO[1], M. J. BERRY, II[2], D. PLENZ[3]
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Abstract: The property of short-term memory in neuronal circuits of the brain has been a subject of study for a long time, with different approaches being proposed as possible explanations for this important feature. For instance, previous models have shown temporal coding when slow neuronal properties are incorporated, such as paired-pulse facilitation (PPF) and slow inhibitory postsynaptic potentials (IPSPs) (Buonomano et al., 1995) or distant-dependent synaptic delays (Wyss et al., 2002). In the context of recovering information about stimulus intensity, another study demonstrated that getting closer to criticality improves short-term memory (White et al., 2004). Furthermore, echo state networks (Jaeger & Haas, 2004), which could potentially be implemented by neuronal circuits, not only are well known for their extended memory capacity

but are also optimized at the edge of chaos (Legenstein & Maass, 2007; Busing et al., 2010). In the present work, we expand on the ideas linking criticality and short-term memory by simulating a simple network composed of cellular automaton units randomly connected (Larremore et al., 2014). The weights of these connections (20% of which are negative, representing inhibitory synapses) are controlled in order to tune the network to the critical point. We then proceed to present, in random order, two possible stimuli to this network. Both stimuli have the same intensity, and each is directed to a small, non-overlapping, subpopulation of the network. Finally, by applying a machine learning algorithm -- Support Vector Machine (SVM; Bishop, 2006) --, we aim to detect which stimulus was presented as function of time after the stimulus is turned off. The decoding takes part on the so-called reservoir, which are the units in the network that were not directly stimulated. We show that the decoder accuracy is maximized at the critical point during and, most importantly, after the stimulus presentation, indicating information about the stimulus is preserved in the network for a longer period of time at criticality.

Disclosures: T.L. Ribeiro: None. **M.J. Berry:** None. **D. Plenz:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

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Topic: H.01. Animal Cognition and Behavior

Support: CIHR Grant #125984
CIHR Grant #153111
AA022821 (CCL)
AA023786 (CCL)

Title: Neural activity in rat medial prefrontal cortex is predictive of memory performance in an odor span task

Authors: *E. DE FALCO[1], L. AN[2], A. ROEBUCK[3], C. C. LAPISH[1], J. G. HOWLAND[3]
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Abstract: Medial prefrontal cortex (mPFC) is known to play a fundamental role in working memory, attention regulation, and behavioral inhibition. However, the neural computations that underlie these are poorly understood. Here we recorded the activity of neurons in the mPFC in awake, behaving rats performing an odor span task (OST). This task is designed to assess working memory capacity in rodents (Dudchenko et al., 2000) and is impaired following mPFC inactivation (Davies et al., 2013). Neural activity was assessed via principle component analysis

to identify how firing changed throughout a trial of the task. Neural populations were observed that encoded distinct task epochs. We found that the transitions between task epochs is accompanied by abrupt remapping of neural activity patterns in mPFC and that the temporal characteristics of remapping are predictive of span. Furthermore, increases in interneuron activity were only observed at the termination of the delay thus indicating that local processing in inhibitory networks was a unique (and possibly key) feature to initiate foraging. During foraging, neural activity patterns associated with the approach to a familiar odor were weak. However, robust changes in neural activity were observed upon approach to a novel odor. Collectively these data indicate that mPFC plays a critical role initiating new action plans (e.g. foraging, digging) and changes in neural activity patterns reflect this process.

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Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

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Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI JP 16K18380
KAKENHI JP 16H01283
KAKENHI JP 16H02061

Title: A dynamic neural mechanism for encoding spatial targets and behavioral contexts in rat perirhinal cortex

Authors: *T. OHNUKI, Y. SAKURAI, J. HIROKAWA
Grad. Sch. of Brain Sci., Doshisha Univ., Kyotanabe Kyoto, Japan

Abstract: Perirhinal cortex (PRC) has long been implicated in cue-target association for object memory. This region receives sensory inputs from various cortical areas of almost all modalities, contextual information from prefrontal cortex and reward-related signals from ventral tegmental area and amygdala. Integration of such diverse information would enable PRC to create abstract representations of objects. A fundamental and unsolved question in information processing of PRC is whether and how the same objects in behaviorally different conditions are encoded while distinguishing the contextual information. Here we show that PRC neurons systematically switch their responses to spatial targets between different contexts. We trained rats in a two-alternative spatial choice task with unimodal visual and olfactory stimuli as cues and recorded multiunit activities from the PRC during the task performance. In each trial of the task, either a visual or an olfactory cue was presented, and the rats chose the left or right port based on a cue-target

association rule. Choices to the correct port were immediately rewarded by a drop of water. We analyzed neural activities during the two contexts: cue-presentation and reward. Individual neurons responded to the spatial target in combination with or without the context. A subset of those neurons dramatically reversed their preferential firings for the target between the contexts. This unexpected property of the neurons indicates that individual PRC neurons not only integrate information about objects, space and behavioral contexts but also distinguish behavioral contexts. A population analysis reliably decoded the spatial targets and the contexts with the presence of those neurons. Our results suggest a mechanism that enables PRC to keep track of target information across behaviorally different contexts.

Disclosures: T. Ohnuki: None. **Y. Sakurai:** None. **J. Hirokawa:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 509.14/EEE21

Topic: H.01. Animal Cognition and Behavior

Support: Jacobs Foundation

Title: Gone or misplaced?: Investigation of memory engrams across development

Authors: *S. POWER, C. ORTEGA, L. MARKS, J. O'LEARY, T. RYAN
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Abstract: Infantile amnesia, the developmental loss of memories formed in early childhood (prior to 2-4 years), affects 100 % of humans. Although behavioural neuroscience has already demonstrated that rodents display infantile amnesia, little is known about the basic neurobiology of the phenomenon. This project aims to probe the question of how memories are stored in the brain throughout development, by integrating recently developed engram labelling technology with various rodent models of infantile amnesia.
Infant mice (P17) were trained using contextual fear conditioning (CFC), where recall was tested 1 day, 1 week and 3 weeks after training. As demonstrated in previous studies, P17 mice exhibit forgetting as early as one week after training, while P56 mice show continuous memory retention. Crucially, we tested whether optogenetic stimulation of ChR2-EYFP expressing engram neurons in the DG, labelled during encoding of a fear memory in infancy, is sufficient for recall of that fear memory in adulthood. FosTRAP (Fostm1.1(cre/ERT2)Luo) mice were crossed with Ai32(RCL-ChR2(H134R)/EYFP) to produce an Ai32-FosTRAP line that allows for permanent labelling of engram cells, and compound transgenic mice were trained using CFC at P17. After behavioural demonstration of forgetting, the delivery of blue light to the DG activated ChR2-EYFP expressing neurons (neurons labelled during encoding of the fear memory) and

resulted in freezing behaviour. These data demonstrate that memory engrams retain information following infantile amnesia, and that when these cells are reactivated by blue light in a context different from the original one used for the conditioning, these animals display freezing behaviour, giving evidence of fear memory recall.
To determine whether the engram cells activated at the time of encoding are also active during recall, we quantified the number of *c-fos* positive cells overlapping with ChR2-EYFP positive cells as a measure of engram reactivation We characterized engram cell activity during recall trials at developmental stages prior to, and after, forgetting in infant mice. We also assayed the effect of optogenetically activated infant DG engrams on downstream engram reactivation in the hippocampus and amygdala of adult mice, giving insights into the nature and extent of the apparent retrieval failure.
This experimental framework will allow for the potential retrieval of seemingly lost-memories from early childhood, as well as a deeper understanding of how long-term memories are stored as an enduring and stable biological change.

Disclosures: **S. Power:** Other; School of Biochemistry and Immunology Trinity College Dublin, Trinity College Institute of Neuroscience. **C. Ortega:** None. **L. Marks:** None. **J. O'Leary:** None. **T. Ryan:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 509.15/EEE22

Topic: H.01. Animal Cognition and Behavior

Title: Epigenetic regulation of neuronal ensemble activity to enhance spatial learning and memory

Authors: *X. LIN, L. CHEN, Y. ZHANG, Y. WU, M. A. WOOD, X. XU
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Abstract: Histone modifications may allow for modulating transcription required for long-term memory processes. Previous studies have shown that histone deacetylases (HDACs) including HDAC3 are highly expressed in the brain, and HDAC3 is a powerful negative regulator of memory formation. However, it is largely unknown how epigenetic mechanisms regulate neuronal ensemble activity required for memory processing. Thus in conjunction with pharmacological inhibition of HDAC3, we use in vivo calcium imaging of neuronal ensemble activity to study neural mechanisms underlying epigenetic modulation of object location memory (OLM) based spatial learning and memory. We specifically test the hypothesis that pharmacological inhibition of HDAC3 via a selective HDAC3 inhibitor (RGFP966) enables stronger neuronal ensemble activity in hippocampal CA1 to enhance spatial learning and

memory in behaving mice. We use head-mounted, miniaturize microscopes, and the animals move around with them very well. This imaging approach enables us to simultaneously examine a large number of the same neurons across different environments and behavioral contexts. Stereotaxic injection of AAV-Camk2a-GCaMP6 was used to selectively express GCaMP6 in CA1 excitatory neurons in wildtype C57 mice (3-5 months old) for simultaneous in vivo calcium imaging of hippocampal CA1 neuronal populations in behaving mice. A subthreshold OLM training design was used to test if RGFP966 enhances OLM encoding compared with the control treatment. The ensemble neural activation strength associated with object exploration was measured by *in vivo* miniscope-based calcium imaging across baseline exploration, OLM training and testing sessions. Both control and RGFP966 treated mice showed an increase in neural activation strength in hippocampal neural ensemble activity during OLM training and testing sessions compared with baseline open-field exploration. Overall the RGFP966 mice exhibited higher neural activation strength associated with the moved object than the unmoved object during the testing session; this association of object/place and neural activation strength did not occur for the vehicle treated mice. Consistent with differential neural ensemble activation, the RGFP966 treated mice showed enhanced memory performance as reflected by the object discrimination index measurements in the testing session. Control mice did not show significant memory with the subthreshold OLM training (3 min). Together, OLM-based spatial learning and memory is enhanced by inhibition of HDAC3, and differential object/place neuronal ensemble activity in CA1 appears to underlie this behavioral memory outcome.

Disclosures: X. Lin: None. **L. Chen:** None. **Y. Zhang:** None. **Y. Wu:** None. **M.A. Wood:** None. **X. Xu:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 509.16/EEE23

Topic: H.01. Animal Cognition and Behavior

Support: NIH DC009836

Title: Multiplexed encoding of sensory and reinforcement cues in the cholinergic basal forebrain supports associative learning and cortical plasticity

Authors: *B. ROBERT[1,2], W. GUO[2], D. B. POLLEY[1]
[1]Harvard Med. Sch., Boston, MA; [2]Eaton Peabody Lab., Massachusetts Eye and Ear Infirmary, Boston, MA

Abstract: The rodent basal forebrain is studded with dense clusters of cholinergic neurons. Artificial stimulation of these areas can produce striking plasticity in sensory cortex, but an

organizing schema for understanding the natural activators of cholinergic basal forebrain units has proven elusive due to the technical difficulty of recording from genetically defined cell types across this distributed deep brain network in behaving animals. Here, we describe an optogenetic antidromic phototagging approach to isolate single cholinergic units in Nucleus Basalis (NB) that project to the auditory cortex (ACx) and characterize their response properties and learning-related plasticity in awake, head-fixed mice.
We found that phototagged cholinergic NB --> ACx units (ChACx) and neighboring non-cholinergic NB units (NChACx) had robust, short-latency responses to meaningless, unconditioned auditory stimuli such as tones or noise bursts. ChACx and NChACx units also showed robust responses to unpleasant stimuli, such as air puffs directed at the face. Because NB unit spike trains multiplex neutral sensory stimuli and unconditioned behavioral reinforcers, we reasoned that they could play a critical role in linking conditioned stimuli with temporally delayed (i.e., distal) reinforcement cues. We tested this by pairing pure tone stimuli (CS+) followed by air puffs (US) 5s later and confirmed behavioral evidence of associative trace learning. We observed a rapid tone-specific plasticity in the frequency receptive fields of ACx units and ChACx units, but not NChACx units. Paired recordings from ACx and NB over the course of conditioning revealed a strong increase in gamma band coherence that parallels a selective potentiation of spike-evoked L2/3 local network activity from ChACx units during the initial CS and US pairings.
These findings identify a new role for cholinergic units in the caudolateral extreme of the basal forebrain (Nucleus Basalis) in driving cortical plasticity that supports learned associations between sensory conditioned stimuli and distal, temporally delayed reinforcement cues. Our ongoing studies utilize deep-brain imaging methods to identify regional differences among cholinergic basal forebrain neurons to sensory stimuli, behavioral reinforcement valence, and the encoding of sensory and reinforcement error signals. By discerning underlying rules for activating these distributed deep brain neuromodulatory neurons, we hope to develop new approaches to efficiently transform neocortical sensory representations.

Disclosures: B. Robert: None. **W. Guo:** None. **D.B. Polley:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 509.17/EEE24

Topic: H.01. Animal Cognition and Behavior

Support: CIHR Banting Postdoctoral Fellowship

Title: Locus coeruleus activity in a classical conditioning task

Authors: *M. OMRANI, G. S. ASTON-JONES
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Abstract: Locus coeruleus (LC) is a small brainstem nucleus (~3,000 neurons in rats & ~30,000 in humans) and is the nearly exclusive source of norepinephrine (NE) to neocortex. Many previous studies have proposed a role for LC in learning. To further explore this idea, we implanted micro-array wires in LC and recorded unit activity in waking rats during a classical conditioning paradigm. During the paradigm, in each block (400 trials) the rats received a tone (5100Hz, 75 db, 300ms) alone (neutral stimuli (NS) in an unconditioned block) or a similar tone followed by air puff to the face (300ms puff, 300ms tone-puff interval; conditioned stimuli (CS) in a conditioned block), while the rat was hanging in a sling. LC neurons exhibit two modes of firing activity: phasic and tonic (Aston-Jones & Cohen, Ann rev Neurosci. 2005). In a sensory driven decision task, sensory stimuli that are relevant to the task (targets) evoke phasic responses in LC as opposed to similar stimuli with no task relevance (distractors). Both NS and CS tones evoked phasic LC activity in our paradigm. We were interested to know whether phasic LC responses differ for similar tones in different contexts. The NS does not have a predictive value, but through conditioning the animal learns that the CS predicts the occurrence of the aversive air puff. Therefore, we initially expected an enhanced phasic response to the CS tone as opposed to the NS tone. To our surprise, phasic responses were smaller in the conditioned block (i.e., for CSs) as compared to the unconditioned block (i.e., for NSs). On the other hand, tonic LC activity (the activity in between tones) was significantly larger in the conditioned blocks, consistent with a role for increased NE release in learning the CS-US association. Next we tested whether changing the task contingency multiple times within a set of blocks changed LC tonic activity accordingly. In this task, during every 80 trials a tone was presented either alone or with a puff. We investigated how LC tonic activity changed through the block and across blocks in relation to tone contingencies. We found that for every switch in task contingency (whether from conditioned to unconditioned or vice versa), tonic LC activity first increased and then gradually decreased to a baseline level during the 80 trials of the block. The increase in tonic LC activity induced by switches were significantly larger in transitions from unconditioned to conditioned blocks. These results are consistent with the idea that the increased tonic activity at the contingency switches may facilitate learning the new tone contingency and the predictive value of the tone.

Disclosures: M. Omrani: None. **G.S. Aston-Jones:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 509.18/EEE25

Topic: H.01. Animal Cognition and Behavior

Support: The Swartz Foundation for Computational Neuroscience fellowship

Title: Deep reinforcement R-learning actor-critic model can explain mouse foraging behavior

Authors: *S. SHUVAEV, S. STAROSTA, A. KEPECS, A. KOULAKOV
Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Behavioral choices can be performed either simultaneously or sequentially. For sequential choices, the decision is often about whether to exploit a current option or to search for a better one. Examples of such behaviors arise in many situations including foraging, employment (whether to accept a job/candidate or seek a better one), mate selection, and economic decisions. In the case of foraging behaviors, an animal's decision is whether to continue to exploit a dwindling food resource or to leave the current source in search of a better one. The average-case optimal choice strategy in this setting is described by the Marginal Value Theorem (MVT), which suggests that the animal should abandon a dwindling resource if the rate of reward falls below the average expected rate for the environment. We designed a foraging task for mice that enables us to infer the trial-to-trial choice strategy. Mice were allowed to run back and forth between two reward ports that provided water upon entry. Re-entry into the same port decreased the amount of water; switching to the other port reset water to the full amount. This behavior allows exploring the dynamics of switch-stay choices as resources are dwindling in an experimentally controlled setting. To interpret the choice patterns, we designed a reinforcement learning algorithm called deep R-learning in actor-critic model. R-learning is the reinforcement learning method that allows optimizing the average rate of reward by similarly weighting both near- and far-term rewards. As a consequence, R-learning can replicate the average behavior described by MVT. We use a deep neural network to infer R-values (the discounted sum of expected rewards), estimated average reward in the environment, likelihood to stay, and likelihood to switch based on the sequence of rewards and choices. The algorithm develops a switch/stay policy, which maximizes a difference between current and average reward. To train the neural network, we use the simulated reward data matching the experimental setup. We show that the behavioral patterns obtained with our model using the simulated data match the statistics of observed mouse behavior. We suggest that, in foraging tasks, mice compare current and average rewards to make a switch/stay decision in a way that can be explained by R-learning reinforcement learning algorithms.

Disclosures: S. Shuvaev: None. **S. Starosta:** None. **A. Kepecs:** None. **A. Koulakov:** None.

Poster

509. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 509.19/EEE26

Topic: H.01. Animal Cognition and Behavior

Title: Dopaminergic and cholinergic modulation of NMDA-mediated behavior

Authors: *I. M. WHITE[1], E. A. COLLINS[2], W. WHITE[1]
[1]Psychology, [2]Neurosci. Program, Psychology Dept., Morehead State Univ., Morehead, KY

Abstract: NMDA antagonists impair wide range of behaviors, simple to complex. Reversal of NMDA-induced impairment varies depending on drugs tested and behavioral measures. Nevertheless, the precise mechanism of drug action on behavior is not well understood. In the present study, we systematically examined behavioral effects following administration of different classes of drugs, including NMDA antagonists (MK801 and PCP), cholinergic antagonists (scopolamine and mechamylamine) or agonist (nicotine), and dopamine agonists (amphetamine and cocaine) and antagonists (SCH23390 and eticlopride). We also examined drug effects on reversal or additive effects of drug combination on behavior. Wistar rats received one or combination of drugs and their performance in learning tasks and open-field activity were measured. Consistent with previous findings, NMDA antagonists, scopolamine, and dopamine agonists produced behavioral excitation, which was blocked reliably by dopamine antagonists. However, drug effects on learning tasks differed: low doses of MK801, scopolamine, SCH23390, or eticlopride impaired learning, whereas low doses of amphetamine or mechamylamine had no effects. Combination of MK801+SCH23390 reversed MK801-induced deficits, but not by other drug combinations, suggesting that D1 antagonist reversed behavioral impairment induced by NMDA antagonist. On the other hand, scopolamine+SCH23390 combination produced severe learning deficits, while other combinations produced minimal changes. Reversal or additive effects of drug combination on learning suggest that behavioral changes mediated by NMDA receptors reflect altering different neural mechanisms. Further study is warranted.

Disclosures: I.M. White: None. **E.A. Collins:** None. **W. White:** None.

Poster

510. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 510.01/FFF1

Topic: H.01. Animal Cognition and Behavior

Support: NIH/NINDS NS023945
NIH/NHLBI HL028785

Title: Glutamatergic and GABAergic sources of synaptic input to septohippocampal cholinergic projections

Authors: *M. R. GIELOW[1], R. L. STORNETTA[2], L. ZABORSZKY[3]
[1]Rutgers Univ., Newark, NJ; [2]Pharmacol., Univ. of Virginia, Charlottesville, VA; [3]Rutgers The State Univ. of New Jersey, Newark, NJ

Abstract: Acetylcholine is a neuromodulator (neurotransmitter) critical to normal function of hippocampal and entorhinal cortical circuits. Control of medial temporal cholinergic efflux is achieved by cholinergic cell bodies located in the medial septum and diagonal bands (VDB and HDB) of the basal forebrain. We previously showed that, depending on projection target, different populations of cholinergic basal forebrain cells enjoy different inputs (Chavez & Zaborszky 2017; Gielow & Zaborszky 2017). The location of cells supplying excitatory and inhibitory inputs onto cholinergic neurons specifically projecting to the hippocampus remains unknown, and defies estimation based on retrograde tracing from the anterior basal forebrain itself, as a given nucleus in the basal forebrain contains multiple different populations of cholinergic cells projecting to disparate corners of the brain. Monosynaptic retrograde replication-deficient rabies vectors delivered to cholinergic terminals in hippocampus, coupled with cre-dependent helper virus transfection in choline acetyltransferase-positive cells of the rat basal forebrain presently allows us to map the whole brain atlas of GFP-tagged inputs to the hippocampal cholinergic projection in particular, verifying exact location of cells subsequently via same-section thionin nissl stain. We additionally employ fluorescent in situ hybridization of glutamatergic and GABAergic markers in the same tissue and map the resulting double-labeling of inputs. This DNA-tagged connectome of the cholinergic septohippocampal system enables novel and testable hypotheses regarding monosynaptic control of cholinergic tone in the hippocampus, and together with previous studies, allows a glimpse of the actors able to control local vs global cholinergic activity.

Disclosures: M.R. Gielow: None. **R.L. Stornetta:** None. **L. Zaborszky:** None.

Poster

510. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms II

Location: SDCC Halls B-H

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Program #/Poster #: 510.02/FFF2

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant NS023945
NVIDIA Academic Program

Title: Contribution of the basal forebrain to fine-tuned cortical states during a visual discrimination task in rats

Authors: *P. GOMBKOTO, P. VARSANYI, L. ZABORSZKY
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Abstract: The basal forebrain (BF) contains a diverse population of neurons, including cholinergic and non-cholinergic corticopetal cells that play a crucial role in the regulation of cortical synchronization and desynchronization of different cortical regions. The basal forebrain's activity, through its projection patterns, provides a key functional involvement in cortical activation, attention, and memory. Cortical activity is defined through an interaction of external stimuli with spontaneous patterns that are produced endogenously. Spontaneous cortical population activity in an awake animal does not simply switch between discrete synchronized and desynchronized states but forms a continuum of states characterized by fluctuation depth of oscillations that correlate at least partially to ongoing behaviors (Harris and Thiele, 2011). We hypostatized that the BF, via its projection patterns, participates in the coordination of distinct cortical areas based on behavioral demands.We examined cortical state changes in V2, VO/VL, and from multiple locations of the BF simultaneously in freely moving awake rats. We determined the beginning of up-phases in V2 and VO/VL separately, and we distinguished the up-down states for global (phase locked) and local state changes. These time points were used as cross trigger sources for observing modulation of cellular activity within these cortical regions and in the BF.During cross triggered local cortical states, Cholinergic and noncholinergic cells of the BF, showed either agonist modulations, antagonist modulations, or their activity ignored the cortical state change. On the other hand, during task related activity of the animals, the LFPs from BF and both cortical regions were in highly active desynchronized state. The energy content of continuous wavelet transformation between 45-100Hz of LFPs fluctuated along the frequency domain. We introduced Topic Model Analyses (LDA) on the clustered Principal Component Analysis of the data that reflect combination of gamma band compartments in order to define "micro" cortical state changes which selectively correlated with the BF activity. We localized those cells from the BF which were involved in the modulation of local changes in the cortex. Our study suggests that the BF may contribute to changes of local synchronized states. This in turn, can represent a 'power save' mode of the local cortical region that is independent from specific states in other cortical regions. In contrast, during tasks, the BF neuronal activity participates in the fine-tuned pattern of micro gamma band changes of cortical regions and synchronize distinct cortical areas to the behavioral demands.

Disclosures: P. Gombkoto: None. **P. Varsanyi:** None. **L. Zaborszky:** None.

Poster

510. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms II

Location: SDCC Halls B-H

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Program #/Poster #: 510.03/FFF3

Topic: H.01. Animal Cognition and Behavior

Support: NIH(NINDS)R01 NS023945
NIH(NIDCD)R03 DC-014753
Brain Health Institute (Rutgers) Pilot Grant in Neuroscience

Title: Striatal activity during early acquisition and later habit formation of an auditory operant task

Authors: *C. M. CHAVEZ[1], D. NOOFOORY[1], K. BIESZCZAD[2], L. ZABORSZKY[1]
[1]Ctr. for Mol. and Behavioral Neurosci., Rutgers, The State Univ. of New Jersey, Newark, NJ; [2]Psychology, Rutgers, The State Univ. of New Jersey, Piscataway, NJ

Abstract: The basal forebrain cholinergic (BFC) projection system plays a critical role in learning and memory processes including the induction of experience-dependent neural plasticity in the cerebral cortex. Monosynaptic viral tracing of cholinergic projection cells, including those that target the primary auditory cortex (A1), revealed that the BFC receives a large proportion of its input from the striatum (Chavez & Zaborszky, 2017; Gielow & Zaborszky, 2017). While the role of the striatum in learning, habit formation, and memory has been well established, it has not been considered in relation to the BFC-A1 circuit. The proposed function of striatal projection cell activity during learning and later habit formation vary depending on their affiliation with the direct or indirect pathway as well as their localization within the striatum (Macpherson et al., 2014; Natsubori et al., 2017). We hypothesize that striatal cells that specifically project to the BFC-A1 circuit exert their influence differentially during early vs. late stages of auditory task performance. Using monosynaptic viral tracing with EnvA g-deleted rabies virus coding for channelrhodopsin (ChR2) in ChAT::Cre rats, we restricted ChR2 expression to cholinergic projection neurons that target A1 and their specific input cells within the striatum. This technique enabled selective optogenetic control over the striatal-BFC-A1 circuit allowing us to identify and determine striatal cell activity during an auditory-based behavioral task dependent on A1 plasticity (Elias et al., 2015; Bieszczad & Weinberger 2010). We recorded from the striatum and the basal forebrain throughout daily behavioral training sessions using a 64-channel 8-shank silicone optrode. Striatal inputs to A1-projecting BFC neurons were identified by brief optical stimulation following each training session. The behavioral training consisted of an operant task where a pure tone stimulus (S+) signaled the availability to bar-press for a water reward for water deprived rats. Preliminary data provide evidence for a diverse range of S+ tone driven activity in the striatum and BF that suggests a changing profile of characteristic responses expressed early or late in training. These findings may show that the striatum dynamically alters its inputs to the auditory projecting BFC neurons as behavioral performance improves in auditory tasks.

Disclosures: C.M. Chavez: None. **D. Noofoory:** None. **K. Bieszczad:** None. **L. Zaborszky:** None.

Poster

510. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 510.04/FFF4

Topic: H.01. Animal Cognition and Behavior

Title: Lateral hypothalamic area projection neurons contribute to an innate freezing response

Authors: *J. HAZEN[1], M. WIGESTRAND[1], I. AASEBØ[1], A. TULLY[1], T. DINH[2], M. LEPPERØD[2], T. HAFTING[2], M. FYHN[1]
[1]Dept. of Biosci., [2]Inst. of Basic Med. Sci., Univ. of Oslo, Oslo, Norway

Abstract: Rodents display innate defensive responses to a range of visual stimuli mimicking the hunting behavior of aerial predators. In the looming assay, an expanding dark circle simulates overhead attack. In response, rodents make an informed choice about the appropriate response. If shelter is available, they rapidly flee. If no shelter exists, animals engage in extended freezing. For each type of response (freezing/escape), much of the circuitry linking visual perception areas to integrative/affective areas to motor output areas has been roughly outlined. Importantly, how pro-freezing signals reach output areas remains unresolved. The medial hypothalamus is well known for its role in innate defensive responses, while the lateral hypothalamic area (LHA) is viewed as chiefly responsible for arousal and feeding. However, electrical stimulation of the LHA elicits defensive behaviors. Based on this, we hypothesized the LHA may play an important role in innate defensive behaviours. Using optogenetic excitation, we show that activation of anterior LHA induces avoidance/escape behavior, while activation of posterior LHA induces freezing. Furthermore, posterior LHA neurons project to the periaqueductal gray (PAG) motor output area and optogenetic stimulation of LHA terminals in PAG induces freezing. Interestingly, we observe that chemogenetic silencing of the LHA does not block conditioned freezing but does significantly impair looming induced freezing. Based on these observations, we hypothesize that LHA plays an important role in transmitting looming induced pro-freezing signals to the PAG motor output area. To further elucidate the neural network and computations in the LHA underlying looming induced freezing, we are performing calcium imaging on behaving rats.

Disclosures: J. Hazen: None. **M. Wigestrand:** None. **I. Aasebø:** None. **A. Tully:** None. **T. Dinh:** None. **M. Lepperød:** None. **T. Hafting:** None. **M. Fyhn:** None.

Poster

510. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 510.05/FFF5

Topic: H.01. Animal Cognition and Behavior

Support: UIO:Life Science summer project

Title: Social memory processing and plasticity in hippocampus CA2

Authors: *A. CHRISTENSEN[1,2], T. STÖBER[4,3], S. K. NOSSEN[2], M. FYHN[2], T. HAFTING-FYHN[1,2]
[1]Inst. of Basic Med. Sci., [2]Dept. of Biosci., [3]Dept. of Informatics, Univ. of Oslo, Oslo, Norway; [4]Simula Res. Lab., Oslo, Norway

Abstract: Emerging evidence suggests that CA2 plays an essential role in social memory as blocking activity in CA2 neurons impairs social memory in mice without affecting other hippocampus-dependent memory tasks. A striking feature of CA2 is its seemingly low levels of plasticity, both in terms of resistance to undergo LTP by stimulation of input from CA3, as well as high calcium buffering capacity and dense expression of perineuronal nets (PNNs). Plasticity in CA2 may be facilitated however by removal of the PNNs or application of neuromodulatory agents suggesting that a salient cue, such as a social encounter, may cause learning of important events. The CA2 is uniquely positioned for integrating social information into complex representations. Through direct projections, CA2 receives sub-cortical inputs from vasopressinergic neurons in the paraventricular nucleus, stored associative, contextual information from DG and CA3 as well as online sensory information from layer II of the entorhinal cortex. Indeed, local stimulation of vasopressin terminals in CA2 is shown to increase social memory in mice, indicating that heightened plasticity induced by the modulatory effects of vasopressin helps to strengthen social memories. Here, we first test if heightened plasticity of CA2 neurons is enough to elicit a similar effect on social memory. For this, we selectively delete the ACAN gene from CA2 neurons to permanently remove PNNs in CA2 of adult mice, which is shown to cause potentiation of excitatory signal transmission in vitro. We have then tested social memory in mice with and without PNNs in CA2.
In contrast to the stable spatial representations of the CA3 and CA1, place fields of CA2 neurons are unstable over time. In fact, they have been shown to change their location of firing (global remapping) in response to a social stimulation. We hypothesize that the the social encounter causes vasopressin release from paraventricular nucleus into the CA2 which facilitate plasticity necessary for global remapping to occur. Using guide cannulas to infuse vasopressin in CA2 of

rats, we examine the effect of modulatory neurotransmitter vasopressin on spatial representations in CA2 and on social memory.

Disclosures: A. Christensen: None. **T. Stöber:** None. **S.K. Nossen:** None. **M. Fyhn:** None. **T. Hafting-Fyhn:** None.

Poster

510. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 510.06/FFF6

Topic: H.01. Animal Cognition and Behavior

Support: FRIPRO toppforsk 250259

Title: A CRISPR-Cas9 platform for genetic perturbation of brain extracellular matrix regulators in-vivo

Authors: *S. GRØDEM, G. SANDVIK, K. LENSJØ, J. HAZEN, T. HAFTING, M. FYHN
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Abstract: Perineuronal nets (PNNs) are lattice-like extracellular matrix structures surrounding the soma and apical dendrites of a subset of inhibitory neurons in the mammalian cortex. These specialized structures are posited to be critical regulatory elements of synaptic plasticity through structural control and stabilization of synaptic connections. The development of PNNs in the juvenile brain coincides with the maturation of Parvalbumin-positive (PV+) inhibitory neurons and the closure of critical phase plasticity, and it was recently demonstrated that the nets are required for long-term memory in the visual cortex.
While the structural components of the PNNs are well characterized, the principal regulators of the nets remain obscure. Several candidate proteases from the ADAMTS and MMP families have been implicated in attenuation of the nets, but their expression is heterogenous and they also act on other ECM components outside the nets, making it difficult to determine which protease is specifically concerned with regulating the PNNs. In order to identify and characterize the function of the genes regulating the PNNs in various cell-types and brain regions in-vivo we are developing a CRISPR-Cas9 gene perturbation platform for both gain and loss of function control of candidate genes. This involves AAV delivered single- or multiplex-targeted CRISPRko, transcriptional activation using dCas9-HSF, and transcriptional inhibition using dCas9-KRAB.
Furthering our understanding of PNN regulation could not only provide a more physiological route for studying the function of the PNNs, but also reveal promising therapeutic targets.

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Poster

510. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms II

Location: SDCC Halls B-H

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Program #/Poster #: 510.07/FFF7

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant NS097772
HHMI International Student Fellowship

Title: Layer specific characterization of local projections within the medial entorhinal cortex

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Abstract: The superficial layers (LII and LIII) of the medial entorhinal cortex (mEC) are the primary source of excitation to the hippocampus and the hippocampus, in turn, projects back to the deep layers (LV and LVI) of the mEC. The loop through hippocampus is closed by extensive projections from the deep to the superficial mEC layers, but there are also shorter recurrent loops that consist of local projections within and between mEC cell layers. These local connections become particularly relevant based on the observation that mEC cells have unique functional properties corresponding to combinations of grid, head direction, border, speed, and other context-dependent spatial tuning. Moreover, the spatial scale of some of these functional cell types, such as grid and head direction cells, increases in modular steps along the dorso-ventral axis of the mEC (Giocomo et al., 2014; Stensola et al., 2012), suggesting some degree of topographical organization within the mEC. Several studies have previously examined local projections between layers (Beed et al., 2010; Sürmeli et al., 2015) and within LII (Couey et al., 2013; Fuchs et al., 2016; Winterer et al., 2017) using patch recordings from multiple cells, but this method is only feasible in sampling cells in proximity to each other and does not capture the topographical organization of projections within the mEC. In our study, we took advantage of a wide range of layer specific mouse lines, corresponding to the two major excitatory cell types in layer II - pyramidal (LIIP) and stellate (LIIS) cells, and to cells in LIII, LVa and LVI, and utilized cell type specific anterograde and retrograde viral tracing strategies to dissect and quantify local projections between the mEC layers. Surprisingly, neurons from both LVa and LVI only weakly projected to the superficial layers of the mEC, suggesting that LVb neurons act as the primary source of projections from the deep to superficial layers. By performing retrograde tracing of inputs to sub-populations of LIIP cells at various depths along the mEC, we

found that projections originate predominantly from LII and LIII cells at the same dorso-ventral level, which is consistent with a modular organization. We are currently performing similar experiments to determine the organization of local projections to LIIS and LIII cells. We propose that a comprehensive characterization of deep to superficial layer projections, as well as of recurrent superficial layer projections, will provide a foundation for identifying circuit computations that give rise to the diverse functional cell types in the mEC.

Disclosures: M.L. Fu: None. **I. Zutshi:** None. **S. Liu:** None. **J.K. Leutgeb:** None. **B.K. Lim:** None. **S. Leutgeb:** None.

Poster

510. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 510.08/FFF8

Topic: H.01. Animal Cognition and Behavior

Support: NS102915

Title: Coordination of theta and slow oscillations across medial septum, hippocampus, olfactory bulb and prefrontal cortex

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Abstract: It has been proposed that communication between the sensory cortices and the hippocampus during memory acquisition and retrieval is coordinated by oscillations (Buzsáki, 1996). Furthermore, hippocampal oscillations are thought to be synchronized by subcortical inputs from the medial septal area (MSA). To investigate whether MSA may coordinate oscillations across a larger cortical network, we recorded local field potentials (LFPs) across brain regions with prominent oscillations in the theta range. These regions not only include the hippocampus and prefrontal cortex, but also the olfactory bulb (OB) where oscillations in the theta band (3-12 Hz) closely follow the respiratory frequency (Rojas-Líbano et al., 2014). In particular, the respiration rhythm and the dorsal and ventral hippocampal theta rhythms are coherent during odor learning and discrimination tasks (Macrides et al., 1982; Kay, 2005). The olfactory respiration rhythm may thus couple to theta band rhythms in the limbic-cortical network and contribute to sensory processing. To begin to understand the mechanisms for theta coupling, we simultaneously recorded LFP signals from the OB, MSA, dorsal hippocampus (dHpC), ventral hippocampus (vHpC), and medial prefrontal cortex (mPFC). We compared these

signals between different periods when mice were running on a figure 8 maze, actively sniffing a neutral odor presented at an odor port, or sleeping in the home cage following behavior. As expected, we found that the oscillations in the MSA and dHpC were coordinated in the theta range (7-9 Hz) throughout all the phases of behavior (odor sniffing, running and sleep). However, septal oscillations were coherent with the vHpC only during sleep and odor presentation, but not during running. During sleep, the OB and mPFC oscillations were highly coherent to each other and to the other three regions in the 3-5 Hz range, but this coherence shifted to higher frequencies (5-7 Hz) during odor presentation. Oscillations are thus differentially coordinated between these regions during each behavioral epoch, such that task-dependent functional subnetworks emerge, which can each use frequencies in the theta range for coupling.

Disclosures: S. Srikanth: None. **J.K. Leutgeb:** None. **S. Leutgeb:** None.

Poster

510. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms II

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 510.09/FFF9

Topic: H.01. Animal Cognition and Behavior

Support: NS102915

Title: Effects of manipulating theta frequency on medial entorhinal cells

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Abstract: Computational models for generating medial entorhinal cortex (mEC) grid cells all require a running speed signal in the form of either an oscillatory or firing rate signal. Theta oscillations are prominent in the hippocampus and in mEC and increase in frequency and amplitude with faster running speeds. It has therefore been hypothesized that theta oscillations could be the speed signal to grid cells. Previous work has demonstrated that inactivating the medial septum results in a substantial reduction of theta power and disrupts the spatial periodicity of grid cells while border, head direction, and place cells are retained. However, it remains unclear whether disrupted grid patterns selectively emerge from effects on theta oscillations or, more generally, from the decreased excitation after septal inactivation. To specifically examine the influence of theta oscillation frequencies on grid cell generation, we took advantage of the role of medial septal parvalbumin-expressing GABAergic (PV) cells in generating theta oscillations and selectively expressed channelrhodopsin (ChR2) in PV cells in

the medial septum. We established that rhythmic stimulation of PV cells in the medial septum could be used to reliably control the frequency of theta oscillations in freely moving mice within the endogenous theta frequency range (e.g., 8 Hz) as well as outside the normal range (e.g., 10 and 12 Hz). We then recorded mEC cells in an open field and found that shifting theta to frequencies of 8 Hz, 10 Hz, and 12 Hz had no effect on the average firing rate of principal cells but significantly lowered the firing rate of interneurons relative to their baseline firing rates. We also found that pacing theta at 8 Hz and at 10 Hz reduced the spatial precision of mEC cells. These findings are consistent with the notion that theta oscillations are essential for spatial processing in the medial entorhinal cortex but they do not reveal a direct relation between theta frequency and spatial scaling.

Disclosures: C.R. Quirk: None. **N. Devico Marciano:** None. **J.K. Leutgeb:** None. **S. Leutgeb:** None.

Poster

510. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms II

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Topic: H.01. Animal Cognition and Behavior

Support: HHMI International Student Fellowship
NS097772

Title: Modulation of CA1 and CA3 hippocampal cell oscillation frequencies by optogenetically paced theta oscillations from the medial septal area

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Abstract: Oscillations in the brain organize the temporal firing of neurons, facilitating information flow and supporting cognitive functions. The 6- to 9-Hz theta band is one such local field potential (LFP) oscillation that coordinates the rhythmic firing of hippocampal neurons. GABAergic neurons in the medial septal area (MSA) act as pacemaker neurons that control the frequency of theta oscillations by projecting to local interneurons in the hippocampus. While these projections from the MSA to hippocampal GABAergic cells terminate in all the sub-regions of the hippocampus, interneurons in the CA3 and DG are more densely targeted compared to CA1 (Freund and Antal, 1988). A recent study further described a distinct sub-

population of highly rhythmic parvalbumin (PV+) cells that extensively project to basket cells and axo-axonic cells in CA3 but bypass CA1 (Joshi et al., 2017). These anatomical projections are consistent with the observation that CA3 pyramidal cells are more tightly phase locked and phase precess to a lesser extent than CA1 pyramidal cells (Mizuseki et al., 2012). Furthermore, on controlling the frequency of LFP oscillations using optogenetic activation of PV neurons in the MSA, we recently demonstrated that the cellular oscillation frequency of CA1 neurons remained broadly distributed and that interneurons in the CA1 pyramidal cell layer oscillated faster than the stimulation frequency (Zutshi et al., 2018). Based on these physiological studies and the anatomical projections, we hypothesized that CA1 principal cells and interneurons in the CA1 cell layer are not directly controlled by septal PV neurons but rather by local feedback loops within CA1. To allow for the observed control of the LFP at the frequency of the septal pacemaker, we tested whether interneurons and principal cells that target the CA1 dendritic region, such as CA3 pyramidal cells, are more directly controlled by the septal pacemaker. Consistent with this hypothesis, we found interneurons outside of the CA1 cell layer that were phase locked to the septal stimulation frequency and we are currently testing whether optogenetic pacing of theta oscillations more directly controls the oscillation frequency of CA3 pyramidal cells and interneurons. Together, the variety of responses of CA1 and CA3 pyramidal cells and interneurons can be combined to generate a model to describe how local hippocampal circuits can generate oscillations that are directly paced by the medial septum while simultaneously generating accelerated cellular oscillation frequencies.

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Poster

510. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms II

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Title: Distinct and complementary roles of medial entorhinal cortex and dentate gyrus inputs for hippocampal CA3 phase precession

Authors: *S. AHMADI[1], M. SABARIEGO[1], T. SASAKI[1], C. LEIBOLD[2,3], S. LEUTGEB[1,4], J. K. LEUTGEB[1]
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Abstract: The temporal order of events is a defining characteristic of episodic memory which critically depends on the hippocampus (HPC). Theta phase precession (PP) organizes the order of place cell spikes in relation to behavior and can be thought of as consisting of "prospective and true-field" portions (Sanders et al., 2015). How the inputs, intrinsic cellular and network properties combine in HPC to compute current location and future choices on an ensemble level is not well understood. To understand the network mechanisms supporting PP in HPC CA3, we trained rats to perform a HPC-dependent task and disrupted the primary theta-modulated inputs of HPC, either the medial entorhinal cortex (MEC) or the dentate gyrus (DG), by selective lesions. We then recorded single unit activity (n = 101, 158, 84, and 68 for MEC^{CTRL}, MEC^{LESION}, DG^{CTRL}, and DG^{LESION}) in the CA3 area. Lesions of the MEC or the DG resulted in significant reductions in the fraction of phase precessing cells in CA3 (DG: C 67%, L 40%, p = 0.001; MEC: C, 59%, L 35%, p = 0.0001; Fisher's exact) and the average slopes (DG: C = -0.33, L = -0.02, $p < 0.05$; MEC: C = -0.29, L = -0.07, $p < 0.05$; Mann-Whitney; units cyc/field). Despite the reduction after loss of either input, the effects were nonetheless qualitatively different. In control animals, the onset phase of spikes showed a preference for late theta (DG: $\Phi_0^C = 243°$, MEC: $\Phi_0^C = 236°$). This preference diminished and shifted to earlier phases only when the DG, but not MEC, input was disrupted (DG: $\Phi_0^L = 202°$, w.r.t. C $p < 0.001$; MEC: $\Phi_0^L = 237°$, w.r.t. C p = 0.84; non-parametric test for equal circular median). The offset phase of PP was unaffected by the manipulations (DG $\Phi_f^C = 144°$, $\Phi_f^L = 132°$; MEC $\Phi_f^C = 133°$, $\Phi_f^L = 135°$; $p > 0.05$). These observations suggested that the DG is responsible for the prospective portion of CA3 place field firing while the MEC input controls the precise temporal code and the true-field representation. A computational model is proposed, consisting of two multiplicatively combining oscillatory inputs modulated by both theta and the local gamma inputs. The interaction of the inputs generates a suprathreshold total drive onto CA3 cells, providing short windows during which the CA3 cells emit spikes by a Poisson process. The intact model reproduced PP similar to that of the experimental data. A degraded MEC input reduced overall PP and increased the "burst weight" of firing. In contrast, a degraded DG input reduced the onset phase and PP, analogous to the effects observed in animals with DG lesions. Taken together, these observations support the notion that PP is supported at the network level and provide insight into the mechanisms by which these effects are produced.

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Poster

510. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms II

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Topic: H.01. Animal Cognition and Behavior

Support: NIMH Grant R01 MH-102841
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Ray Thomas Edwards Foundation
Walter F. Heiligenberg Professorship

Title: Dentate dependent-CA3 network pattern separation can occur in the absence of neurogenesis

Authors: *A.-L. SCHLENNER[1], V. C. PIATTI[1,2], L. A. EWELL[1], Y. AN[1], O. HON[1], H. A. CAMERON[3], S. LEUTGEB[1,4], J. K. LEUTGEB[1]
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Abstract: In the dentate gyrus (DG) neurons are born and integrated into the DG network throughout the lifespan, which implies that a proportion of dentate granule cells is immature. The increased excitability of immature cells has been proposed to sparsify dentate network activity such that adult dentate neurogenesis is essential for supporting network discrimination of novel or overlapping network patterns. To determine how immature granule cells in the DG influence network processes of pattern separation in the downstream CA3, we recorded CA3 single unit activity in rats with and without neurogenesis. We used a task where dentate network activity was shown to be necessary for CA3 principal neurons to discriminate between novel sensory cues (McHugh et al., 2007). In this paradigm, rats were allowed to explore a novel environment over four 10-minute sessions. The walls of the environment were switched in each session from black (A) to white (B) in an A-B-B-A order. The experiment was repeated across multiple days. CA3 pyramidal cells were recorded in the transgenic GFAP-TK rat strain in which adult neurogenesis can be completely ablated by daily administration of the drug Valganciclovir. By performing doublecortin and bromodeoxyuridine immunohistochemistry, we confirmed that neurogenesis was ablated (99 ± 0.5%) in GFAP-TK^{+} rats (n = 6) 6-8 weeks after continuous drug administration compared to GFAP-TK^{-} control animals (n = 8). In animals with confirmed ablation of dentate neurogenesis in comparison to controls we did not observe significant differences in the degree of CA3 network discrimination for novel sensory cues, a dentate-dependent computation, or the pattern separation of the same cues once familiar. Although we observed a decrease in firing rate with increasing familiarity of the environment in control rats,

the firing rates stayed the same across days in animals without neurogenesis. This resulted in a significantly lower firing rate in control animals already on the second, more familiar day ($p=0.0011$, Kolmogorov-Smirnov test). The difference in CA3 network firing rate between GFAP-TK^{+} rats and GFAP-TK^{-} controls was not accompanied by a significant difference in field size, number of fields per cell or spatial information. Our results suggest that adult born neurons modulate the excitability of the downstream CA3 network, but are not critical for dentate-dependent CA3 network pattern separation.

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Poster

510. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms II

Location: SDCC Halls B-H

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Program #/Poster #: 510.13/FFF13

Topic: H.01. Animal Cognition and Behavior

Support: NS086947

Title: Hippocampal sequential firing during delay intervals is not required for working memory performance

Authors: *M. SABARIEGO, D. T. ZIMMERMAN, A. SCHONWALD, V. ALLURI, N. GONZALEZ, B. L. BOUBLIL, J. K. LEUTGEB, S. LEUTGEB
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Abstract: The hippocampus is critical for remembering the flow of events in distinct experiences and, in doing so, bridges temporal gaps between discontinuous events (MacDonald et al., 2011). In order to temporally organize experiences, it has been suggested that hippocampal neural activity patterns represent sequential time points in support of episodic memory (Robinson et al., 2017). This type of sequential cell firing has been observed in both CA1 and CA3, although in tasks with no episodic memory demand and hence during tasks that are not dependent on hippocampus (Salz et al., 2016; Wood et al., 2000). Therefore, the functional significance of discrete serial firing patterns observed during delay periods in behavior remains unclear. We used a spatial working memory (WM) task in which animals needed to alternate between left and right sides of a figure-8 maze on a trial-by-trial basis to receive a reward. On each trial the rat had to remember the last episode and turn in the opposite direction compared to the previous trial. We manipulated the WM load by introducing delays of various lengths (10s and 60s) between trials. Recordings of hippocampal CA1 and CA3 single units and local field

potentials were performed to investigate the neuronal firing patterns that characterize WM processing throughout delay periods. In CA1 and CA3, WM maintenance was not accompanied by an unbroken chain of persistent delay activity. In addition, the order of sequential firing was not maintained across repetitions of equivalent trials so that right versus left trials could not be distinguished by analyzing neural activity at precise temporal intervals. Together with performance levels that were consistently above chance in all delay conditions, sequential hippocampal delay activity was therefore not associated with accurate WM-guided behavior. Rather, differential trial dependent activity re-emerged right before the animals turned to retrieve the next reward and persisted until the entrance to the delay site. Thus, during the delay, trial-related information could be maintained as a pattern of synaptic weights, analogous to long-term memory. Our results are consistent with the interpretation that temporally organized sequences between encoding and response preparation are not necessary, at least in the hippocampus, for the continuity of the mental representation during WM performance.

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Poster

510. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms II

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Program #/Poster #: 510.14/FFF14

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 NS084324

Title: Genetically targeted expression of APP to the hippocampal CA3 subpopulation of principal neurons leads to neuronal network dysfunction and memory impairment

Authors: *S. VIANA DA SILVA[1], M. G. HABERL[1], K. GAUR[1], M. L. FU[1], J. K. LEUTGEB[1], E. H. KOO[2], S. LEUTGEB[1,3]
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a striking loss of episodic memory. We developed transgenic mice that express human amyloid precursor protein (APP) selectively in CA3 pyramidal cells as models to investigate how amyloid beta (AB) peptide induced synaptic toxicity leads to hippocampal circuit and memory dysfunction during early phases of AD. CA3-APP mice have normal basal synaptic transmission but impaired synaptic plasticity at Schaffer collateral synapses from 2 months of age. To test for

hippocampal memory deficits, we performed a spatial alternation task on a figure-8 maze with either no delay or brief delays (i.e., 2 s or 10 s) at the beginning of the center arm. Introducing a delay period is known to make the task hippocampus-dependent, in contrast to the continuous version. Aged CA3-APP mice (16-19 months) show deficits in hippocampus-dependent memory while younger mice (4-6 months) display only a transient deficit during the initial days of testing, reaching control levels after 5 days of behavioral testing. To understand changes in network function that may underlie the behavioral phenotypes, we recorded local field potentials (LFP) and single units before, during, and after the mice performed the spatial alternation task. Despite the limited expression of APP, we found extensively altered hippocampal physiology. In LFP recordings performed in the CA1 region of aged CA3-APP mice we observed a decrease in the frequency of theta and gamma oscillations in transgenic mice both in the return and central arms. Younger CA3-APP mice also show a decrease in theta (6-12Hz) and gamma frequencies (40-120Hz), but less pronounced when compared with the aged CA3-APP. No difference in the velocity modulation of these oscillations was found between genotypes. We further identify a transient peak in the LFP at the Beta range (15-30Hz) in the central arm, close to the point where the mice need to turn right or left. No statistical difference was found in the amplitude of this peak between genotypes. Additionally, we are currently investigating spatial and temporal firing patterns of hippocampal CA1 neurons in order to complete our understanding of whether AB-induced synaptic impairment alters interneurons and principal cell's activity and their modulation by the different oscillations in the LFP. Overall, our data indicate that local synaptic plasticity deficits may lead to network dysfunction, and the results strengthen the idea that memory in AD could be improved by restoring brain oscillations. Research supported by NIH grant R01 NS084324

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Poster

511. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 511.01/FFF15

Topic: H.01. Animal Cognition and Behavior

Title: Optogenetic expression of situation-specific behavior to a cue composing multiple memory traces

Authors: *C. A. COELHO, A. RASHID, S. JOSSELYN, P. FRANKLAND
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Abstract: A number of studies have employed viral and transgenic approaches to 'tag' neuronal populations expressing c-fos (a proxy for activation) during encoding, and later optogenetically manipulate these neurons to artificially induce recall in the absence of reminder cues. In most of these studies, freezing behavior was used as the readout of memory. Here we ask whether similar engram reactivation can drive active, situational-specific behaviors for stimuli that have different meanings in different contexts. To do this we used a discriminative context-odor pair associates paradigm in which mice learn that in one context (A), digging in a peppermint-scented (odor 1), but not carvone-scented (odor 2), bedding is reinforced. Concurrently, these mice learn in a second context (B) that digging in carvone-scented (odor 2) but not peppermint-scented (odor 1), bedding is reinforced. Following training, mice underwent unrewarded memory probes in either context A or B, where they were presented with odor 1 and odor 2, and we assessed where mice dug for food. In order to tag neurons during the learning experience, we first infected wild type mice under doxycycline (dox) food diet with an AAV(DJ)-RAM-ChR2-EYFP virus in the dentate gyrus (DG). After recovery, mice were trained as above. Once mice reached asymptotic performance, DOX was removed in order to tag a single learning session (either in context A or in context B, counter-balanced). After two more intermixed sessions, mice underwent two unrewarded probe sessions (10 trials each) in the novel context C. Remarkably, opto-stimulation in the neutral context biased animals toward situation specific responding (i.e., responding as if they were in context A when context A tagged neurons were reactivated, or responding as if they were in context B when context B tagged neurons were reactivated). This result suggests that engram stimulation is not only able to drive complex memory-specific behaviors, but also circumstance-specific.

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Poster

511. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms III

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Program #/Poster #: 511.02/FFF16

Topic: H.01. Animal Cognition and Behavior

Support: CIHR
NSERC

Title: Relaxing the rules of memory allocation in the lateral amygdala attenuates fear memory strength and specificity

Authors: *A. J. RASHID[1], C. YAN[2], J. YU[3], P. W. FRANKLAND[4], S. A. JOSSELYN[5]
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Abstract: Increasing neuronal excitability in a small, random population of principal neurons in the lateral amygdala (LA) via overexpression of CREB drives allocation to a fear memory engram and enhances memory strength in mice. A similar effect can be induced by increasing neuronal excitability via expression of ChR2 in a population of LA neurons and brief activation of these neurons with blue light just prior to auditory fear conditioning. This increase in excitability is accompanied by concomitant inhibition of surrounding principal neurons, likely through activation of parvalbumin-positive interneurons, suggesting a form of feedforward inhibition from more-excitable to less-excitable principal neurons that may serve to constrain the overall size of an LA engram. To investigate the rules of allocation, we virally co-expressed CREB and tetanus toxin light chain (TetTx) in a random subset of principal LA neurons (~20%) to prevent neurotransmission from neurons with increased excitability without interfering with their ability to receive input. Compared to the enhanced fear memory in mice microinjected with CREB alone, mice microinjected with CREB+TetTx showed control levels of memory. A similar lack of memory enhancement was observed in mice microinjected with ChR2+TetTx compared to mice microinjected with ChR2 alone. Since neurons expressing TetTx could not provide output to contribute to the behavioral response (freezing), this suggested that control levels of freezing in mice microinjected with CREB+TetTx (or ChR2+TetTx) was mediated by non-infected neurons in the LA. This was supported by examining the overall size of the engram after fear conditioning using nuclear mRNA levels of the neuronal activity marker Arc. The Arc+ engram was larger in mice microinjected with CREB+TetTx as there was an increase in Arc expression in non-infected neurons. To further examine the behavioral consequences of disrupting the rules of neuronal allocation in the LA, we also examined memory specificity. Mice were fear conditioned such that a 2.8 kHz tone (CS+) was paired with foot-shock. Generalization was assessed by measuring freezing both to the CS+ tone and to a novel, distinct tone (7.5 kHz, CS-). While mice microinjected with vectors expressing CREB, GFP or TetTx alone showed high discrimination between CS+ and CS-, mice microinjected with CREB+TetTx displayed increased freezing to CS-. Collectively, our findings suggest that, within the LA, local interactions between excitatory and inhibitory neurons help establish the rules of neuronal allocation to a fear memory engram and that this mechanism plays a key role in regulating memory strength and memory specificity.

Disclosures: A.J. Rashid: None. **C. Yan:** None. **J. Yu:** None. **P.W. Frankland:** None. **S.A. Josselyn:** None.

Poster

511. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms III

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 511.03/FFF17

Topic: H.01. Animal Cognition and Behavior

Support: CIHR
NSERC

Title: Active myelination is required for spatial learning and memory consolidation

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Abstract: The mechanisms for memory encoding and consolidation have focused on neuronal and synaptic modifications. Recent discoveries have shown oligodendrocyte precursor cells (OPCs) are highly responsive to experience and may represent another form of plasticity in the adult brain. Research over the last decade converges on the idea that experience-dependent myelination represents an important aspect of functional plasticity underlying behaviour. However, the relevance of white matter plasticity in learning and memory remains to be explored. In this study, we ask how acquisition and consolidation of a spatial memory influence oligodendrogenesis in distinct neural circuits, and whether adaptive myelination is needed for learning and consolidation in the adult brain. We find that acquisition and consolidation of a memory for a spatial task induces oligodendrogenesis in functionally-relevant regions of the brain. Furthermore, active myelination is required for learning and consolidation of a spatial memory. These findings suggest that adaptive myelination is an important facet of neuroplasticity supporting learning and memory beyond the neuron.

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Poster

511. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms III

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Program #/Poster #: 511.04/FFF18

Topic: H.01. Animal Cognition and Behavior

Support: CIHR
NSERC

Title: Maturation of hippocampal perineuronal nets underlies the ontogeny of memory specificity

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Abstract: Compared to memories in adults, memories in infants and young children are more prone to forgetting over time (i.e., infantile amnesia; IA) and expressed less specifically (i.e., infantile generalization; IG). While biological mechanisms have been identified for IA, the neurobiology of IG remains unknown. We hypothesized that the maturation of perineuronal nets (PNNs), late-developing extracellular matrix structures known to inhibit juvenile plasticity in sensory systems, may regulate memory specificity across development. To test this, we first performed contextual fear conditioning (CFC) in mice from infancy (P16) through adulthood (P60). Fear memory was generalized in mice tested before P21 whereas fear expression was specific in mice tested after P24, indicating that IG drastically decreases during the fourth postnatal week. To examine whether this shift in memory expression was related to PNN development, we next characterized the distribution of PNNs in the dorsal hippocampus. Consistent with previous reports, we found that PNNs in the adult hippocampus varied in density, laminar organization, and co-localization with inhibitory and excitatory cell populations across subfields. Across development, we found that PNNs in CA1 rapidly accumulated around parvalbumin interneurons between P20 and P24, which tracked the behavioral transition from memory generalization to specificity. These experiments suggested that the maturation of PNNs in the hippocampus may regulate the switch from memory generalization to specificity during the fourth postnatal week. Accordingly, we predicted that disrupting PNNs in adult mice would reinstate juvenile-like memory generalization. To this end, we performed intracranial injections of chondroitinase ABC (ChABC) to digest PNNs in CA1 of adult mice. Local injections of ChABC drastically reduced the density of PNNs in CA1 3- and 7-days post-injection, but PNNs regenerated in CA1 to control levels by 14-days after surgery. In line with these results, we

observed fear memory generalization in adult mice that received injections of ChABC into CA1 3- and 7-days prior to CFC (i.e., when PNNs were reduced in CA1), but not 14-days prior to CFC (i.e., after PNNs regenerated in CA1). Thus, PNNs in CA1 were necessary for adult-like memory specificity and reducing PNNs in CA1 was sufficient to reinstate juvenile-like memory generalization in adult mice. Our findings support a role for PNNs in the development of the hippocampal memory system, and we demonstrate for the first time that the maturation of PNNs in the hippocampus underlies the switch from memory generalization to memory specificity.

Disclosures: A.I. Ramsaran: None. **B.A. Yeung:** None. **M. Ahmed:** None. **S.A. Josselyn:** None. **P.W. Frankland:** None.

Poster

511. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms III

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Program #/Poster #: 511.05/FFF19

Topic: H.01. Animal Cognition and Behavior

Support: NSERC
CIHR

Title: A two colour system for *in vivo* calcium imaging of engram populations

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Abstract: Understanding the contributions of neuronal populations to memory encoding and retrieval remains an important question in neuroscience. Previous work has identified a subpopulation of cells - termed the engram - whose activity is both necessary and sufficient for memory recall. To date, most investigations of the engram have used immediate early genes (IEGs) as a marker of this cell population. However, these IEG-based approaches do not provide information concerning the temporal dynamics of the engram population during mnemonic tasks. Miniaturized fluorescence microscopes offer the possibility of examining these dynamics by allowing for the simultaneous recording of activity from hundreds of neurons stably across days. While promising, current iterations of this technology only allow for imaging in a singe channel. As a result, identification and analysis of sparse neuronal subpopulations like the engram remains difficult using current calcium imaging techniques.
To address this issue, we developed a novel two-channel calcium imaging system based on our previously published compact head-mounted endoscope (CHEndoscope). This system allows for

imaging of dynamic activity in genetically defined neuronal populations in vivo during unrestrained behaviour. The system utilizes a green calcium reporter and a red fluorophore whose expression is activity dependent. Using red/green overlap, it is possible to distinguish between activity patterns in a relevant subpopulation compared with the overall population. We describe the construction and use of this system, as well as its potential application in analysing activity of an engram population or other genetically-defined subpopulation.

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Poster

511. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms III

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Program #/Poster #: 511.06/FFF20

Topic: H.01. Animal Cognition and Behavior

Support: NSERC PGS-D

Title: Modeling the impact of neurogenesis on memory formation and stability

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Abstract: In neural networks, the stability of stored information may be compromised by a) changing the neural architecture (e.g., adult neurogenesis) and b) adding new memories. Furthermore, these processes may also effect the ability to learn new memories. We tested these ideas in a three layer feedforward neural network. In this network the input, middle and output layers represent the entorhinal cortex, DG and CA3 regions, respectively, with neurogenesis occuring only in the DG layer. We generated input patterns, drawn from two partially overlapping distributions, A and B. The network was trained to recognize A and B input patterns and produce one of two discrete output patterns. The networks ability to generalize was assessed by presenting novel input patterns that were either drawn from the A and B distributions, and measuring accuracy of the output pattern produced. Following training, we either a) added new neurons to the middle layer, or b) trained the network on two new distributions C and D. Both a) new neuron addition and b) new learning impaired AB categorization, consistent with previous modeling and experimental data. Moreover, increasing plasticity, excitability and input and output connectivity of the new neurons exacerbated these categorization impairments. Next, we studied the impact of neurogenesis on subsequent learning. In this experiment, we trained the

network on AB and then added new neurons, as above. We then retrained the network on a) new distributions C and D, or b) a reversal condition where expected outputs of A and B are flipped (A'B'). The addition of new neurons enhanced reversal learning as well as new learning (albeit to a lesser extent). We found that with neuron addition, the degree to which networks forgot AB was correlated with enhancements and overall performance in reversal learning (A'B'), but not with new learning (CD), and not in the absence of neurogenesis. Next, we explored the consequences of varying both the rate of neuronal addition and the rate of neuron replacement relative to number of new neurons added (i.e. rate of turnover) on these observed effects. The network learned reversal categories best when turnover is zero (full addition). However, as the turnover ratio increased to one (balanced addition/loss) and beyond (net loss), the reversal enhancement decreased while the neurogenesis-mediated forgetting significantly increased. By exploring how new neurons impact stored memories and new memory storage, and the differential impact of various parameters governing these processes, our results begin to help us understand how adult neurogenesis in the hippocampus influences cognition.

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Poster

511. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms III

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Title: Ptchd1 exon 3 truncating mutation mice: More clinically relevant mouse model of autism spectrum disorder

Authors: *S.-Y. KO[1,2], J. R. EPP[1], K. MITTAL[6], T. I. SHEIKH[3,6], V. N. HA[1], B. DEGAGNE[1,3], A. MIKHAILOV[6], L. FRENCH[7], S. A. JOSSELYN[1,2,3,4], J. B. VINCENT[3,5,6], P. W. FRANKLAND[1,2,3,4]
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Abstract: *Ptchd1* is a gene located on chromosome Xp22.11, where genomic deletions or loss-of-function coding mutations has been reported in autism spectrum disorder (ASD) patients[1-5]. In order to determine the significance of *Ptchd1* mutations for ASD, *Ptchd1* knockout mice have been generated through excision of exon 2 (*Ptchd1*$^{\Delta exon2}$)[6-8]. Various autistic-like behavioral phenotypes - hyperactivity, learning deficits, motor coordination abnormalities - are characterized in the *Ptchd1*$^{\Delta exon2}$ mice, but no alterations in social behaviors have been identified, which is one of key features of ASD[9-10]. Here, we note that Ptchd1 frameshifting/prematurely truncating mutations are identified within exon 3 in patients, but not in exon 2, probably leading to PDZ-containing C-terminal truncation for both Ptchd1_a and Ptchd1_c transcript isoforms. In an attempt to recapitulate more clinically relevant *Ptchd1*-related ASD traits, we generated an alternative *Ptchd1* knockout mouse model where frameshifting/truncating mutations are introduced to the exon 3 using CRISPR/Cas9 technology (*Ptchd1*^{exon3} mice). As a result, male hemizygous from two *Ptchd1*^{exon3} lines (*Ptchd1*^{G387Ifs*29}: *Ptchd1*^{exon3} line1; *Ptchd1*^{G387Vfs*2}: *Ptchd1*^{exon3} line2) exhibit previously reported ASD-related behavioral phenotypes including hyperactivity, decreased learning, and motor deficits. In contrast with the *Ptchd1*$^{\Delta exon2}$ mice, however, our both *Ptchd1*^{exon3} line1 and *Ptchd1*^{exon3} line2 show striking deficits in social behaviors as well as repetitive behavior. Additionally, application of unsupervised data-driven analysis of human speech[11] reveals that *Ptchd1*^{exon3} mice produce significantly altered ultrasonic vocalizations (USVs) (i.e., spectro-temporal features of individual syllables and diversity of syllable repertoire). Unexpectedly, using both gene expression microarray and RT-PCR, our analysis of mRNA from the *Ptchd1*$^{\Delta exon2}$ mice reveals a modest elevation in overall *Ptchd1* transcriptional levels. Consistent with excision of exon 2, this appears to be due to loss of the *Ptchd1_a* transcript (exons 1 to 3, encoding and 888 amino acid open reading frame), but homeostatic activation of *Ptchd1_c* (exons 1 and 3, encoding open reading frames up to 542 amino acids long), suggesting that compensatory upregulation of *Ptchd1_c* in the *Ptchd1*$^{\Delta exon2}$ mice rescues social deficits.
Collectively, our results suggest that mutations on the exon 3 site of *Ptchd1* and resultant impairment of *Ptchd1_c* transcript are related with autistic-like social deficits and repetitive behaviors, providing more clinically relevant behavioral phenotypes compared to previously reported *Ptchd1* mouse models.

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Poster

511. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms III

Location: SDCC Halls B-H

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Title: Role of sleep spindles in consolidation of competing memories

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Abstract: Previously encoded memories can be damaged by encoding of new memories, especially when they are relevant to the new data and hence can be disrupted by new training. Sleep can prevent the damage by replaying recent memories along with the old relevant memories. Though multiple evidences point to the role of sleep in memory consolidation, exact mechanisms remain to be understood. In this new study, we explored the role of stage 2 (N2) sleep spindles in protecting against memory degradation in response to encoding new memories. We used previously developed computational model of the thalamocortical network which exhibits transitions between awake, stage 2 (N2), and stage 3 (N3) sleep by modeling changes in neuromodulator concentrations. The model was able of generating characteristic sleep spindles in N2 and slow oscillations in N3. Spike-time dependent plasticity (STDP) was implemented on excitatory connections between cortical neurons to model synaptic weight changes associated with training and memory consolidation. When N3 sleep was presented alone, consolidation resulted in replay and improved performance for the newly encoded strong memory, while performance for the weak old memory was reduced. In contrast, a presence of N2 prior to N3 sleep resulted in improved consolidation of both strongly and weakly encoded memories. This difference arose from the local and asymmetric changes in synaptic weights, through local memory replay in N2. The local changes in synaptic weights were then further amplified during following N3 sleep. Together, this study provides evidence for the role of N2 sleep spindles in protecting pre-existing weak memories from undergoing degradation and interference in response to newly encoded memories.

Disclosures: O.C. Gonzalez: None. **G.P. Krishnan:** None. **M.V. Bazhenov:** None.

Poster

511. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms III

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Topic: H.01. Animal Cognition and Behavior

Support: ONR (MURI: N000141612829)
National Science Foundation (IIS-1724405)
DARPA (HR0011-18-2-0021)

Title: Reactivation in network motifs during NREM and REM sleep in thalamocortical model

Authors: *G. P. KRISHNAN[1], R. RAMYAA[3], M. V. BAZHENOV[2]
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Abstract: Reactivation or replay of the memory traces during sleep is critical for memory consolidation. However, very little is known about the neural mechanisms that result in memory replay during sleep. Empirical studies have shown that memories are represented in a distributed fashion widely across the brain. Thus, memory reactivation during sleep requires precise large-scale interaction and coordination of activity in the distributed neuronal ensembles. In this study, we examined how reactivation occurs in various network motifs during NREM and REM sleep in a biophysical thalamocortical network model. Each node in the network motif consisted of the biophysically realistic pyramidal neurons and interneurons with high probability of recurrent AMPA, NMDA and GABA connections within a node and sparse connections between nodes mediated by AMPA and NMDA synapses. Changes in the level of neuromodulators were modeled to obtain NREM and REM like states in the computational model. We examined network motifs (sizes 3, 4 and 5) which have previously observed in high frequency structural and functional imaging studies during awake. During NREM sleep, motifs which are cyclic were reactivated at higher frequency compared to REM sleep. We developed a simplified probabilistic neuron model which could be analytically analyzed within a framework of Markovian dynamics that explains the differences in reactivation during NREM and REM sleep. Our results suggest a differential role of NREM and REM sleep in shaping long-range interaction in cortical networks that is specific to the type of the network motifs.

Disclosures: G.P. Krishnan: None. **R. Ramyaa:** None. **M.V. Bazhenov:** None.

Poster

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Title: Continuous learning in a multi-layer network with rewarded spike-timing-dependent plasticity

Authors: *M. V. BAZHENOV[1], R. GOLDEN[2], E. DELANOIS[1], P. SANDA[3]
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Abstract: Neural networks with multiple plastic layers equipped with rewarded spike-timing-dependent plasticity (R-STDP) and homeostatic regulation mechanisms are capable of learning advanced foraging tasks which have a pattern discrimination component as a sub-goal. However, if the networks are subsequently trained on a second foraging task which has different reward contingencies, memory of the first task will be overwritten - a phenomenon called “catastrophic forgetting” - and relearning must occur. In other words, these networks do not have flexible reward revaluation. In contrast, human and animal brains are fully capable of new learning without erasing old knowledge. We now believe this is accomplished by replaying both new and old knowledge during periods of off-line processing such as sleep. Here we used our previously developed computer model of reinforcement learning [Skorheim at al. PLoS One 2014; Sanda et al. PLoS Comp Bio 2017] to explore the idea that simulated replay can help preserve memories for multiple tasks. The network utilized reward modulated and non-reward modulated STDP and implemented multiple mechanisms for homeostatic regulation of synaptic efficacy. A basic convolution driven by unsupervised STDP occurred between input and hidden layers to learn input features. The network allowed for decorrelated subsets of middle-to-output layer synapses to develop for each task. Memory replay ensured that the output layer neurons maintained functional synaptic traces for tasks that had not been experienced in the recent past. The study predicts a critical set of properties for spiking neuronal networks with STDP that can continuously learn to solve complex foraging tasks without catastrophic forgetting.

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Poster

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Title: Surround inhibition and memory replay support sequential encoding of multiple stimulus-response associations without catastrophic forgetting

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Abstract: Stimulus-response associations are learned through a neurobiological implementation of reinforcement learning (RL) which uses dopamine (DA) signaling to represent reward-prediction errors (RPEs). While computational models of dopamine-mediated reinforcement learning have previously been implemented in spiking neural networks using a reward-modulated spike-timing-dependent plasticity (R-STDP) rule, these models have some major pitfalls. For example, if trained on a second task, these models will generally undergo catastrophic forgetting (i.e. they overwrite the stimulus-response associations they had learned for the first task). In this new study, we tested whether memory replay during stage 3 (N3) sleep can allow the model to overcome catastrophic forgetting. To do so, we used our computational model of a thalamocortical network which exhibits transitions through awake and N3 sleep by modeling changes in neuromodulator concentrations and can generate Up and Down states during slow oscillations in N3. Additionally, we implemented the R-STDP rule as a model of neurobiologically plausible RL. We found that memory replay is sufficient to overcome catastrophic forgetting only if the input patterns for the stimuli have low mutual information. As the mutual information between the input patterns increased, a broader radius of inhibition to implement surround inhibition was needed to ensure that the initial encodings are decorrelated enough to circumvent catastrophic forgetting. This study provides evidence for the crucial roles of surround inhibition and memory replay during the encoding and consolidation phases of continuous learning.

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Poster

511. Animal Cognition and Behavior: Learning and Memory: Neural Circuit Mechanisms III

Location: SDCC Halls B-H

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Program #/Poster #: 511.12/GGG2

Topic: H.01. Animal Cognition and Behavior

Support: RSF #16-15-00300
RSF #14-15-00685

Title: Cellular resting-state network activity depends on previous experience of a mouse

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Abstract: The brain activity in a resting state is often interpreted in terms of background replay of neural networks of prior experience. Here we show that past traumatic experience can shape the resting-state neuronal networks of a mouse. The c-Fos activity of sensory and motor cortices, hippocampus, parahippocampal cortex, amygdala, basal nuclei, associative and sensory thalamic nuclei, hypothalamic nuclei and midbrain was investigated in mice that underwent post-traumatic stress disorder (PTSD) inducing footshock stress 7 days earlier and naive (non-stressed) mice. PTSD induction strongly affected subsequent resting-state brain activity: mice with prior traumatic experience had significantly more c-Fos+ cells in cingulate, retrosplenial, parietal associative and entorhinal cortices, basolateral and lateral amygdala, paraventricular thalamic nucleus and periaqueductal gray. We used graph theory approach to reconstruct resting-state network connectivity of naive and PTSD mice and compared experimentally identified networks with model networks: random, scale free and small world. In both groups of mice, the clustering was at the random network level. These clusters had weak interactions with each other: global efficiency of experimental networks was at the same level as of a random network. At the same time, PTSD network was less clustered and the clusters were divided by longer routes than in naive mice. PTSD induction caused global changes in the resting-state network structure, which affected all studied brain areas. While naive mice had most of the connections between the cortical areas, in PTSD mice the majority of connections were subcortical. PTSD induction eliminated almost all functional connections present in naive mice; the only cluster to survive was the closely connected cluster of visual and auditory cortical areas. Furthermore, while cingulate and retrosplenial cortices were the main network hubs in naive mice, functional connectivity between those areas was lost in PTSD mice, and paraventricular thalamic nucleus

became a hub. Conversely, while functional connections of amygdala were almost absent in naive mice, in PTSD mice there was a substantial number of connections between amygdala, cortical associative areas and striatum. Our data suggest that experience of stressful event can change both resting-state spontaneous activity and resting-state functional connectivity patterns in the mouse brain long after the traumatic episode. We hypothesize that these changes reflect a replay of neuronal assemblies involved in the states of past subjective experience. We plan to test this hypothesis by using TRAP technique.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: RSCF 14-15-00685
RFBR 16-04-01545

Title: Application of TRAP strategy to investigate engram dynamics: Genetical tagging and *in vivo* calcium imaging of cognitively indexed neurons

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Abstract: Numerous evidence suggest that memory engram is not static, however, not much is known about cellular mechanisms of engram reorganization over time. In this study we describe a novel application of targeted recombination in active populations (TRAP) strategy to investigate short-term and long-term engram dynamic at the cellular level. TRAP strategy uses a tamoxifen-inducible Cre-recombinase system under control of immediate-early genes promotors and allows to compare neuronal populations which were activated in two episodes of activity spaced for at least 72 h. To study long-term changes in cellular engram over time Fos-Cre-tdTomato mice were trained in contextual fear conditioning. Tamoxifen was injected 24 h before retrieval of the recent memory (3 days) to tag activated neurons with tdTomato. 30 days later we performed a remote memory retrieval and used double immunostaining for endogenous c-Fos and tdTomato to compare neuronal populations which were active during retrieval of recent and remote memory. To investigate short-term engram changes we developed a variation of TRAP

strategy based on double immunostaining for endogenous c-Fos and Cre-recombinase expressed under c-fos promotor. Tamoxifen was injected to Fos-Cre mice 24 h before the contextual fear conditioning, and immunostaining for c-Fos and Cre was performed at different time points after training. We show that the total number of Cre-positive neurons was maximal at 3-8 h and decreased by 16 h after the training. Thus, this strategy allows to compare neurons that were activated in two cognitive episodes spaced for 3-8 h. Next we employed Fos-Cre-GCaMP transgenic mouse strain to image calcium activity in cognitively indexed neurons. To this end we used TRAP strategy to introduce GCaMP3 sensor into engram neurons of conditioned fear to auditory stimulus. Tamoxifen was injected 24 h before the training, so that the neurons that expressed c-fos during fear conditioning also expressed the GCaMP3. The total number of GCaMP3 positive neurons reached maximum 72 h after the tamoxifen injection and remained stable for at least two months. We performed two-photon calcium imaging of TRAPed neurons in the mouse parietal cortex during presentation of the conditioned sound (CS) and found neurons which responded during CS and neurons which responded between CS. Additionally, the use of Fos-Cre-GCaMP mice reveal calcium dynamic in dendritic spines of TRAPed neurons. Thus, in vivo calcium imaging in the brain of conditioned Fos-Cre-GCaMP mice allows to investigate dynamic of calcium activity in the engram neurons.

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Poster

512. Age-Related Cognitive Deficits and Treatments

Location: SDCC Halls B-H

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Title: Epigenetic regulation of the circadian gene Per1 contributes to age-related impairments in long-term memory

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Abstract: Aging is accompanied by impairments in both long-term memory and circadian rhythmicity. Although it is clear that memory is affected by circadian cycling, it is unknown whether age-related disruption of the circadian clock causes impaired hippocampal memory or whether these biological processes simply share a common mechanism that is altered with age. Here, we tested whether dysregulation of a key epigenetic mechanism, histone deacetylase 3 (HDAC3) in the aging hippocampus might contribute to impairments in long-term memory formation. HDAC3 typically represses gene expression by removing acetyl groups from histone tails and has previously been shown to be a key negative regulator of long-term memory formation. Here, we hypothesized that dysregulation of HDAC3 activity in the aging brain contributes to an unusually repressive chromatin structure that limits synaptic plasticity and memory formation. To test this, we disrupted HDAC3 in the dorsal hippocampus of 18-month-old mice with two different manipulations: focal genetic deletion with HDAC3$^{flox/flox}$mice and activity-specific disruption with a dominant-negative point mutant virus (AAV-HDAC3(Y298H)). We found that deletion or disruption of HDAC3 ameliorated age-related impairments in both long-term memory and synaptic plasticity. To identify the mechanism through which HDAC3 deletion ameliorates age-related memory impairments, we ran RNA sequencing on hippocampal tissue from young mice, aging mice, and aging mice with focal HDAC3 deletion in the dorsal hippocampus. We identified a subset of genes, including the circadian gene Period1 (*Per1*), that is restricted in the aging hippocampus by HDAC3. Using siRNA-mediated knockdown of PER1 protein, we show that hippocampal PER1 is critical for long-term memory formation in young mice. Finally, to determine whether overexpression of *Per1* is sufficient to ameliorate age-related memory impairments, we locally upregulated *Per1* in the dorsal hippocampus using two methods: lentivirus-mediated overexpression of wildtype *Per1* (pLVX-Per1) or transcriptional activation of *Per1* using the CRISPR/dCas9 SAM system. Both methods demonstrate that overexpression of *Per1* in the dorsal hippocampus can ameliorate age-related impairments in long-term memory formation. Together, our data suggest that HDAC3-mediated repression of *Per1* contributes to age-related impairments in long-term memory formation. More broadly, this age-related disruption of *Per1* might connect age-related impairments in both long-term memory and circadian rhythmicity, depending on the structure.

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Poster

512. Age-Related Cognitive Deficits and Treatments

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Topic: H.01. Animal Cognition and Behavior

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Title: Cilostazol, a phosphodiesterase 3 inhibitor, maintains and improves memory function in aged mice

Authors: *S. YANAI[1], T. ARASAKI[2], S. ENDO[2]
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Abstract: The cAMP pathway mediates a variety of physiological functions including learning and memory. Intracellular concentration of cAMP is achieved by the balance between its synthesis by adenylate cyclase and hydrolysis by phosphodiesterases (PDEs). Therefore, inhibitors of PDEs, which elevate intracellular concentration of cAMP, are promising targets for the development of cognitive enhancement drugs by upregulating cAMP functions such as the activation of PKA-CREB pathway. Among several PDE inhibitors, we have been focused on cilostazol, a PDE3 selective inhibitor, as potential therapeutic intervention for age-related cognitive impairment in human. In the present study, we examined the effect of cilostazol administration on age-related memory impairment in the standard mice model of aging, C57BL/6J mice. To examine whether long-term cilostazol administration maintain cognitive function in aged mice, cilostazol (0, 0.3%, or 1.5%) had been administered by mixing it in the feed starting from 13 months of age, when their cognitive function starts to decline. At 23 months of age, the mice were subjected to the behavioral battery of tests. The 1.5% cilostazol-administered mice performed significantly better in the object recognition task and the Morris water maze task compared to the non-cilostazol-administered control mice, suggesting that long-term cilostazol administration maintain the hippocampus-dependent memory in aged mice. Separate groups of mice were administered cilostazol starting from 22 months of age, when they show major impairment in cognitive functions. After relatively short-term administration period for 1 month, the behavioral battery of tests were conducted at 23 months of age. Consistent with long-term administration, performance of the 1.5% cilostazol-administered mice in two hippocampus-dependent memory tasks were significantly better than that of the non-cilostazol-administered control mice. These results suggest that cilostazol can improve the age-related memory impairments. Regardless of the administration period (10 or 1 months), no apparent influences of cilostazol were observed in the open field test, suggesting that cilostazol have no significant effects on locomotor activity and anxiety. Based on these findings that cilostazol is effective for the prevention and treatment of age-related memory impairment, a clinical trial is now underway in Japan to treat mild cognitive impairment. Because the safety evaluation of cilostazol is well established, cilostazol is a potentially promising target for the maintenance and treatment of cognitive impairment in the aging human population.

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Poster

512. Age-Related Cognitive Deficits and Treatments

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Program #/Poster #: 512.03/GGG6

Topic: H.01. Animal Cognition and Behavior

Support: L.I.F.E. Foundation Award

Title: DEK loss is associated with cellular, molecular, and clinical features of dementia

Authors: *A. GREENE[1], N. J. BALMER[2], V. GHISAYS[3], L. PRIVETTE VINNEDGE[4], M. B. SOLOMON[2]
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Abstract: DEK, a chromatin-remodeling phosphoprotein, is well-known to have a role in cancer and autoimmune diseases; however, we have accumulated compelling data suggesting that DEK deficiency is linked with cognitive dysfunction. Our laboratory was the first to characterize the neuroanatomical distribution of DEK in the male and female murine brain, where it is prominently expressed in cognitive-relevant brain regions including the prefrontal cortex, amygdala, and hippocampus. Behavioral consequences of DEK loss in female knockout mice include impaired object recognition relative to wild-type mice, which was not due to increased anxiety-like behavior or deficits in locomotion. In addition, we have determined that cortical DEK protein expression decreases with dementia severity (Clinical Dementia Rating >2.0) in elderly women, but not men. This is notable because DEK is an estrogen receptor-α target gene, and these findings suggest a sex-specific functional role for DEK in learning and memory, and perhaps dementia. Further, a Topp-Gene analysis identified Alzheimer's disease (AD) and age-related cognitive decline as candidate DEK loss-associated diseases.
In an effort to elucidate how DEK loss may contribute to AD-related pathology or cognitive dysfunction, we employed *in vitro* and *in vivo* methodology. We report that DEK loss in neuronal cell lines (HT22; immortalized mouse hippocampal cells or differentiated SH-SY-5Y cells) induces cellular and molecular signatures of dementia or cognitive dysfunction including: DNA damage (phosphorylated-p53), apoptosis (cleaved caspase 8), decreased β-catenin levels, and increased tau accumulation. Further, female DEK KO mice exhibit decreased hippocampal MAP-2 protein expression compared with wild-type mice, indicative of decreased dendritic

density. This observed decrease in hippocampal MAP-2 expression may partly explain our previously observed cognitive impairment in female DEK KO mice. Together, these data suggest a critical role for DEK in cellular and behavioral markers of learning and memory.
We are currently exploring the role of DEK in other cellular and behavioral features of learning and memory (e.g., spatial and social) and in males to determine if these cognitive effects are limited to females.

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Poster

512. Age-Related Cognitive Deficits and Treatments

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Topic: H.01. Animal Cognition and Behavior

Support: This research was supported by the Intramural Research Program of the NIH, National Institute on Aging

Title: Surveying the epigenetic landscape of Arc-mediated age-related cognitive decline

Authors: *C. MYRUM, B. R. FLETCHER, S. DE, K. G. BECKER, P. R. RAPP
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Abstract: Pinpointing the molecular basis of age-related cognitive decline is critical for early detection, treatment, and slowing age-related memory loss. The protein Arc (activity-regulated cytoskeleton-associated protein) has been dubbed the "master regulator" of memory-related synaptic plasticity, and several aspects of Arc regulation are altered in aged rats with cognitive impairment. In the current study, we examined whether altered epigenetic control (a hallmark of aging) is coupled with cognitive outcome. Utilizing a well-characterized rat model of neurocognitive aging, young and aged animals' spatial memory capacities were assessed in a water maze. Aged rats were then classified as either unimpaired (AU) or impaired (AI) relative to young (Y). The hippocampal CA3 subfield—a key site of altered plasticity in age-related memory impairment—was then microdissected and processed for analysis. We surveyed three key epigenetic mechanisms of Arc gene regulation: (A) DNA methylation examined by bisulfite conversion and analyzed using a next-generation sequencing (NGS) MiSeq platform; (B) histone modification analyzed via chromatin immunoprecipitation (ChIP) followed by RT-qPCR; and (C) nucleosome positioning assessed via micrococcal nuclease digestion followed by Ion Torrent NGS. Bisulfite experiments identified seven bases that were differentially methylated between Y, AU, and AI rats (p's < 0.05). One particularly noteworthy base was significantly elevated in AI rats compared to Y and AU under basal conditions (p's < 0.05), but became significantly

demethylated (and thus non-significant compared to Y and AU) following exploratory behavior ($p < 0.05$). This active demethylation may represent an unsuccessful compensatory mechanism to enhance Arc expression following exploratory behavior. ChIP experiments revealed two histone markers for active transcription (H3K9AcS10p and H3K9Ac) and one repressive marker (H3K9me2) that were more enriched in AI animals than in Y or AU animals (p's < 0.05), while Y vs AU comparisons showed no difference ($p > 0.05$). Available results from nucleosome positioning experiments suggest that Arc nucleosome occupancy and fuzziness are strikingly stable between Y, AU, and AI rats. Together these data identify important neuroepigenetic signatures that distinguish impaired and successful cognitive aging, and represent novel, potential drug targets for treating age-related memory decline.

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Poster

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Program #/Poster #: 512.05/GGG8

Topic: H.01. Animal Cognition and Behavior

Support: NIFA Hatch grant

Title: Lifespan and cholinergic changes in cognitive flexibility in rats

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Abstract: The ability to update one's mental schemas in order respond flexibly and adaptably - i.e. cognitive flexibility - is crucial to navigating a dynamic environment. Proactive interference (PI) is a phenomenon wherein prior memory impedes the formation of new memories for similar information, biasing behavior toward no-longer-relevant schemas. Thus, overcoming PI is an important aspect of cognitive flexibility. PI is exacerbated during aging, and in turn contributes to age-related deficits in cognitive flexibility. In young animals and young adult humans, resolution of PI has been found to rely on neuromodulatory activity via Acetylcholine (ACh), and ACh levels are known to decline in aging, however it has yet to be demonstrated whether these age-related changes in ACh directly contribute to age-related increase in PI. Here, we first compared PI resolution in middle-aged (13 months, n = 8) and old (23 months, n= 11) male Long Evans rats, finding that old animals were more inefficient in resolving PI when compared to the middle-aged animals. Furthermore we performed cholinergic deafferentation, with the immunotoxin 192-IgG saporin (SAP; 0.2 µl of 0.3 µg/µl dissolved in sterile phosphate buffered

sale in each of four locations targeting bilateral anterior and posterior basal forebrain), in our older rats (N= 5 SAP and N=6 Sham) which had no effect on the floor performance of older rats. This suggests that the inability to resolve PI seen in the aged rats may be due to already-depleted levels of ACh. We are currently collecting local field potential data in the prelimbic and posterior parietal cortices in behaving older and younger rats and will combine this with central administration of muscarinic cholinergic pharmacology to continue to examine age-related changes in the cortical dynamics that support cognitive flexibility. Based on prior findings in our laboratory examining similar attentional flexibility, we predict the young animals will demonstrate increased beta band LFP activity in the posterior parietal cortex, and potentially increased beta coherence between prefrontal and posterior parietal cortices, related to successful resolution of PI. We expect such activity to be mitigated by cholinergic antagonists and in the older animals.

Disclosures: C. Cammarata: None. **E.D. De Rosa:** None. **A.K. Anderson:** None.

Poster

512. Age-Related Cognitive Deficits and Treatments

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 512.06/GGG9

Topic: H.01. Animal Cognition and Behavior

Title: The dissociation of normal aging from Alzheimer's disease in mouse models of tauopathy and amyloidosis

Authors: *I. MORGANSTERN[1], D. HE[1], R. ZENOWICH[1], L. THIEDE[1], D. HAVAS[1], A. AMBESI[2], M. BANSAL[2], T. HANANIA[1]
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Abstract: Aging is the leading risk factor for the chronic diseases that account for the bulk of morbidity, mortality, and health costs. Although there's been a tremendous progress in understanding the underlying molecular processes important in the aging cascade, much remains unknown specifically with regard to the relationship of normal aging to more advanced pathological states such as Alzheimer's disease (AD). In order to better understand this critical relationship and provide more robust pre-clinical models for drug development, the goal of the current study was two-fold; 1) to identify the prominent behavioral features related to standard aging in C57BL/6 mice using both standard and computational analyses; 2) to examine the behavioral similarities and distinctions of normal aging from that of two mouse models of AD, namely rTg4510 (Tauopathy) and APP/PS1 (Amyloidosis). The test battery consisted of commonly used metrics for motor function (Open Field, Rotarod), depression (Forced Swim, Tail Suspension), anxiety (Marble Burying) as well as cognition (Y-maze, Fear Conditioning, Odor Habituation). Additionally, more complex behavioral patterns profiled using proprietary

platforms such as SmartCube®, combined with computational analyses were utilized in order to identify an age-related behavioral signature. We tested three age-groups of wild type C57/BL6 mice, young (7-10 weeks), middle-age (16-20 weeks) and old-age (39-43 weeks) and AD mutant lines, rTg4510 and APP/PS1, at similar ages. The behavioral findings demonstrate age and line-dependent similarities and distinctions from normal aging mice. While behaviors related to motor function and depression were distinct in both AD lines compared to aging mice; behaviors related to cognition and anxiety demonstrated some similarity with that of normal aging. Using SmartCube® technology we identified distinct behavioral features that are directly-related to aging and progressed over time. Comparison of these age-related features to that of the two AD lines (rTg4510 and APP/PS1) demonstrated a clear relationship between aging and AD as well as pointed to several unique features that are specific to AD. In summary, we demonstrate here the common and distinct features of aging and AD phenotypes using both standard and algorithm-based behavioral tests. More importantly, we are able to dissociate aging-specific behavioral features from mutant lines of Tauopathy and Amyloidosis and identify, more precisely, AD-specific features using advanced and un-biased computer vision systems. Such an approach would be extremely valuable when assessing novel potential therapeutic approaches for AD and aging.

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Poster

512. Age-Related Cognitive Deficits and Treatments

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Program #/Poster #: 512.07/GGG10

Topic: H.01. Animal Cognition and Behavior

Title: Paramylon improves age-dependent impairment of spatial memory of the senescence-accelerated mouse prone 8

Authors: K. YASUDA[1], M. OGURA[2], S. TANIGUCHI[2], A. NAKASHIMA[1], *S. KENGO[1,3], K. ITO[2]
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Abstract: *Euglena gracilis*, a single celled microalga, is used as natural sources to obtain a whole variety of compounds, such as vitamins, minerals, amino acids, and unsaturated fatty acids. Euglena cells also accumulate β-1,3-glucan (paramylon), a Euglena-specific novel polysaccharide. Recent studies revealed that paramylon improves not only intestinal regulation or immune function but also antioxidant activity which is involved in the learning and memory. However, the effects of Euglena and the extract of Euglena on cognitive function are poorly

understood. Here, we aim to evaluate the potency of Euglena and paramylon on age-related decline of learning and memory in the senescence-accelerated mouse prone-8 (SAMP8) which exhibits age-dependent cognitive deficit at around 6 months old. We used 6-month-old SAMP8 fed 2% Euglena or paramylon for 5 weeks and adopted Morris water maze test and Y-maze spontaneous alternation test for the assessment of spatial learning and short-term memory, respectively. On day 4 of the learning phase in Morris Water maze test, paramylon-supplemented SAMP8 required significantly shorter escape latency compared to control and euglena-supplemented group although there was no difference between the Euglena-supplemented group and the control group. In contrast, we could not find any significant differences among the groups in the probe test. The swimming velocity of paramylon-supplemented SAMP8 was comparable with other groups. Y-maze spontaneous alternation task showed no significant differences in alteration behavior rate among the groups. These data suggest that 2% paramylon treatment attenuates the age-related spatial learning deficits, while it does not influence on memory consolidation or acquisition of short-term memory in SAMP8. Although the underlying mechanism of paramylon on the hippocampus are yet unclear, paramylon has potentiality for therapeutic application on cognitive decline.

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Poster

512. Age-Related Cognitive Deficits and Treatments

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Topic: H.01. Animal Cognition and Behavior

Support: R01-AG043478-02
R01-AG043640-05

Title: The effects of chronic curcumin treatment in a non-human primate model of aging

Authors: ***A. UPRETY**[1], M. MEDALLA[1], B. G. BOWLEY[1], P. L. SHULTZ[1], S. M. CALDERAZZO[1], E. J. SHOBIN[2], D. L. ROSENE[1], M. B. MOSS[1], T. L. MOORE[1]
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Abstract: Studies of both humans and non-human primates have demonstrated that aging is typically characterized by a decline in cognition specifically in the domains of executive function and memory starting as early as midlife. While the underlying cause of age-related cognitive

decline is unclear, there is significant evidence for age-related pathology in the white matter associated with an increase in age-related inflammation. Nutraceuticals that are rich in polyphenols, have received considerable attention as possible treatments to slow or potentially mitigate age-related cognitive decline by virtue of their anti-inflammatory and antioxidant effects. Of these, curcumin (CUR), has been shown to produce significant anti-inflammatory and antioxidative effects in humans and rodents. Accordingly, using the rhesus monkey well-established model of normal aging, we assessed for the first time the efficacy of dietary supplementation of CUR as an intervention to reduce the effects of aging on cognitive function and markers of inflammation. Daily oral doses (500mg) of CUR or a vehicle control were given to 17 monkeys over an 18-month period during which they completed tasks of visual recognition memory spatial working memory, and reversal learning. To date, we have demonstrated that CUR treated monkeys evidenced enhanced performance on spatial working memory and reversal tasks compared with monkeys that received vehicle control. No differences were seen between groups on recognition memory or object discrimination tasks. In addition, we have preliminary data demonstrating that CUR treatment significantly alters the morphology and antigen presentation of microglia, the resident macrophages and mediators of inflammation in the brain. Specifically, there is a reduction in LN3+ expression in the frontal white matter and corpus callosum of CUR treated monkeys. Additionally, compared to vehicle controls, microglia in the cingulate cortex (BA 25) of CUR subjects had longer distal processes with increased branching characteristic of a 'surveying' state morphology, typically associated with a reduced inflammatory state. Together these findings are consistent with the anti-inflammatory properties of CUR and its potential for reducing age-related cognitive decline in normal aging monkeys.

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Poster

512. Age-Related Cognitive Deficits and Treatments

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Program #/Poster #: 512.09/GGG12

Topic: H.01. Animal Cognition and Behavior

Title: Age dependent effect of testosterone on the spatial memory in the male rat

Authors: *G. JIMENEZ RUBIO, H. A. MARTINEZ BECERRIL, M. S. MARQUEZ BALTAZAR, J. J. HERRERA PEREZ, L. A. MARTINEZ MOTA
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Abstract: Old people present substantial declines in spatial memory, it has been proposed that gonadal or stress-related hormones may contribute to these changes in cognition. The aim of our

study was to identify in male rats the role of testosterone (T) in age-related differences in the performance of spatial memory. Young (3 months old) and aged (21 months old) Wistar rats were assigned to one of three independent groups: intact, orchidectomized or orchidectomized treated with T (pellets with 9 mg of T propionate). Spatial memory was evaluated using the Barnes maze, this test elicits low levels of stress respect to other paradigms. The phases of acquisition and retention of spatial memory were evaluated. The open field test was carried out in the animals in order to investigate whether changes in general motor function could interfere with the performance in the Barnes maze. It was found that, compared with young, the aged intact animals took more time to find goal, made more mistakes and did not improve the performance in the Barnes maze across the acquisition period. Orchidectomized young animals did not improve their performance across the acquisition phase in comparison to intact young animals, which increased the search in the goal sector and decreased the number of errors in comparison with the first day. Additionally, hormonal suppression in young animals deteriorated spatial memory in the retention phase, but the long term T treatment prevented this deficit by means of increasing the search for goal sector and reducing the number of errors in the test. Conversely, neither the orchidectomy nor T treatment modified the spatial memory of aged rats in the acquisition or retention phases. On the other hand, the ambulatory activity was significantly reduced in aged animals, independently of their hormonal condition, however the increased travelled distance and the error numbers of aged rats in the maze suggested that their poor performance is associated with a cognitive damage. In conclusion, declination in T levels could partially explain the age-related deficits in the learning and spatial memory of males rats

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant T32 AG050061

Title: Aging impairs the flexible use of environment-specific representations in humans

Authors: *M. R. FORLOINES[1], L. HEJTMÁNEK[1,2], D. L. OCHOA[1], B. A. OBER[1], A. D. EKSTROM[3]
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Abstract: Remembering a spatial environment entails encoding its details and discriminating it from other spatial environments. Recent work from our lab suggests that participants show a small behavioral cost when pointing to landmarks in a new environment after learning a first environment, an index of "remapping" (Kyle et al. 2015). Participants' multivariate hippocampal codes, measured with fMRI, show less correlation in different environments than same environments, providing a potential neural measure of remapping. Older adults often show difficulty differentiating similar experiences during memory recall, or memory rigidity. The extent to which rigidity applies to navigation in humans is unknown. In rodents, older rats showed consistency in their neural representations of learned environments within session, but when placed in a new space, their representation corresponded equally with the original and to the subsequent space. This result suggests that older rats are similar to young rats initially, but their neural representations vary in a second environment, whereas neural codes in young rats showed differentiation between environments (Barnes et al. 1997). Determining the nature of remapping deficits in elderly humans is important due to increased difficulty navigating in aging. To address this, participants (young: 18-25, elderly: 65-90) encoded layouts of virtual cities, and subsequently recalled store locations within each city. Participants learned multiple cities with slight variations; stores varied in their placement or their identity, which allowed for an analysis of interference effects across similar cities, and the ability to create new representations through remapping, in other words, using a different representation for a new city versus reverting to an old one. Initial results showed that older adults took longer and made more errors than their younger counterparts overall. We found evidence that older adults showed impairments in remapping. Specifically, the small sample tested so far perseverated when switching to a different environment compared to younger adults, demonstrating remapping impairments. These findings thus suggest that studying remapping may be a means of better understanding navigation-related impairments that accompany aging.

Disclosures: M.R. Forloines: None. **L. Hejtmánek:** None. **D.L. Ochoa:** None. **B.A. Ober:** None. **A.D. Ekstrom:** None.

Poster

512. Age-Related Cognitive Deficits and Treatments

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 512.11/GGG14

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant AG054180
NIH Grant AG038070
AFAR New Investigator Award
Glenn Award for Research in Biological Mechanisms of Aging

Title: Comparative analysis of mouse resources for systems genetics of normal cognitive aging

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Abstract: Classical inbred mouse strains, such as the C57BL/6J, have played an important role in defining physiological changes associated with normal cognitive aging. However, given the limited genetic variation in inbred models, results from these studies may not generalize to other mouse strains - let alone human populations. Using the BXD genetic reference panel, we have shown that that increasing genetic variation in aging models significantly enhances translatability of mouse data at the genome, transcriptome, and phenome level of analyses [1,2]. Since the BXDs vary to a lesser degree in genetic complexity than the highly admixed Collaborative Cross (CC) population [3,4], we tested the hypothesis that using the Collaborative Cross (CC) population would enhance the phenotypic variation of cognitive traits. To do this, we analyzed the performance of CC lines on the Y-maze working memory task (% Spontaneous Alternation, %SA), acquisition of contextual fear (CFA), and contextual fear memory (CFM), and compared the results to those previously collected on age-matched BXD strains. Although we predicted the CC panel would exhibit wider variation in cognitive performance than the BXDs, comparative analysis of working memory (range; BXD= 30%-75%, CC=38%-70%), CFA (range; BXD= -2.43-19.43, CC= 1.12-10.16), and CFM (range; BXD=1-82%, CC=9-48%) did not support this hypothesis, as BXD strains showed a wider variation for CFA and CFM. Heritability (h^2) for %SA was comparable in the CCs (BXD h^2=0.27, CC h^2=0.24), whereas h^2 for CFA and CFM was higher in the BXDs (CFA; BXD h^2= 0.65, CC h^2= 0.20, CFM; BXD h^2=0.75, CC h^2=0.32). As heritability reflects the within-strain (technical/environmental) variance compared to the between-strain (genetic) variance, these results may suggest that cognitive performance across the CC panel is more sensitive to these external factors than the BXD panel, and thus, there may be a greater impact of genetic variants on phenotypic variance within the BXD panel. It is possible that observed differences in phenotypic range and heritability may have resulted from differences in housing conditions, diet, microbiome and other unknown factors. Lastly, it is also important to note that we analyzed fewer CC strains (n = 9) on CFM than BXD strains (n = 21), which may affect both h^2 calculations and the phenotypic range. Ongoing work aims to evaluate cognitive performance on a larger number of CC strains to facilitate more robust comparisons, so that future experiments can select the population most appropriate for studies of cognitive aging.
[1] Neuner et. al, Neurobiol Aging, 2016, [2] Neuner et. al., BioRxiv, 2017, [3] Srivastava, et al. 2017, [4] Taylor et al. 1973

Disclosures: A. Ouellette: None. **S. Neuner:** None. **G. Churchill:** None. **C.C. Kaczorowski:** None.

Poster

512. Age-Related Cognitive Deficits and Treatments

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 512.12/GGG15

Topic: H.01. Animal Cognition and Behavior

Support: NIH AG052050
NIH AG033649
NIH AG004542
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NIH ES007380

Title: Sexually dimorphic effects of dietary vitamin D supplementation on cognition in aging rats

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Abstract: Increasing evidence suggests that vitamin D plays a role in maintaining cognitive function and that vitamin D deficiency may accelerate age-related cognitive decline. In our previous study using aging male rats (Latimer et al., 2014), we attempted to model the range of human serum vitamin D levels, from deficient to sufficient, to test whether vitamin D could preserve or improve cognitive function with aging. For 5–6 months, mid-aged F344 rats were fed diets containing low, medium (standard amount), or high (100, 1,000, or 10,000 IU/kg diet, respectively) vitamin D3 (VitD3, cholecalciferol). The Morris water maze (MWM) was used to test hippocampal-dependent learning and memory. Rats on high VitD3 achieved the highest blood levels (in the optimal range for humans) and significantly outperformed low and medium groups on MWM reversal, a particularly challenging task that detects more subtle changes in memory.
Here, we attempted to replicate those findings and determine whether VitD3 effects were sex-dependent. Beginning at 12 months of age, 20 male and 20 female F344 rats were fed an AIN-93 diet containing either standard (1000 IU/kg diet) or higher VitD3 (10,000 IU/kg). Following 6 months of treatment, rats were trained in the MWM to assess effects on learning and memory. Rats were trained for 3 days and the probe trial performed on day 4 to assess memory for platform location. The probe test indicated that higher VitD3 significantly reduced path length and latency ($P = 0.01$) to the digital platform in females but not males. On day 5, we switched the location of the platform and performed one day of reversal training. No performance differences were detected according to sex or diet. On day 8 and three days after reversal training, we

conducted the reversal probe test. Results indicated that higher dietary VitD3 improved performance in males but not females by significantly reducing path length and latency to the digital platform ($P<0.05$). Upon completion of behavioral analyses, we examined the cecal contents of these animals to determine whether dietary VitD3 affects the gut microbiome - brain axis and possibly influence behavior. A Shannon Diversity Index of the gut microbiome indicated a significant treatment effect of higher dietary VitD3 in females ($P = 0.01$). Together, these MWM results not only replicate our previous study in aging male rats but also indicate that vitamin D may have sexually dimorphic effects on specific cognitive pathways involved in memory formation. Further, our studies provide further support that serum vitamin D levels considered in the optimal range for humans may improve the likelihood of successful brain aging.

Disclosures: L.D. Brewer: None. **J.R. Thibault:** None. **J.C. Gant:** None. **K.C. Chen:** None. **K.L. Anderson:** None. **H.N. Frazier:** None. **A.O. Ghoweri:** None. **J.B. Hoffman:** None. **S.D. Kraner:** None. **P.W. Landfield:** None. **O. Thibault:** None. **E.M. Blalock:** None. **N.M. Porter:** None.

Poster

512. Age-Related Cognitive Deficits and Treatments

Location: SDCC Halls B-H

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Program #/Poster #: 512.13/GGG16

Topic: H.01. Animal Cognition and Behavior

Support: NSF IOS 13-18490
NIA AG07648
NIDA DA038798
Syracuse University Center for Aging and Policy Studies (NIA P30 AG034464)

Title: A multiple memory systems approach to understanding cognitive aging: Not all aging is equal

Authors: *R. S. GARDNER[1], P. E. GOLD[2], D. L. KOROL[2]
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Abstract: Extensive evidence across species and contexts highlights an age-associated decline in hippocampus-sensitive learning and memory with relatively little consideration of effects of aging on other memory systems. These experiments compared the effects of aging in male rats on learning and memory in distinct tasks that require participation of hippocampal or striatal memory systems. Relative to young adult (3-mo-old) Fischer-344 rats, 2-yr-old rats were impaired on a set of hippocampus-sensitive tasks, including a place maze and a double object displacement recognition task. However, old rats showed no impairment and sometimes

enhancement on striatum-sensitive tasks, including a response maze and a double object replacement recognition task. Additionally, when trained on a dual-solution task that can be solved with either place (hippocampal) or response (striatal) strategies, young rats predominantly expressed a place solution and old rats a response solution. In young rodents, these memory systems sometimes competitively interact; for example, disruption of one structure can lead to enhancement of learning on a task dependent on the other. Thus, we examined whether interference across systems contributes to learning and memory in old rats and to age-related learning impairments. Using young and old rats, we inactivated either the hippocampus or striatum with central lidocaine (2%) infusions prior to response or place training, respectively. As seen in young animals, inactivation of the striatum prior to training enhanced hippocampus-dependent place learning in old rats. Thus, learning disabilities in some cognitive domains in old rats may result in part from exaggerated interference or competition across memory systems and not strictly from deterioration of the canonical neural system. These findings suggest that interventions to down-regulate striatal processing may effectively improve hippocampus-dependent learning across the life span and highlight the utility of a multiple memory systems approach for understanding cognitive aging.

Disclosures: R.S. Gardner: None. **P.E. Gold:** None. **D.L. Korol:** None.

Poster

512. Age-Related Cognitive Deficits and Treatments

Location: SDCC Halls B-H

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Program #/Poster #: 512.14/GGG17

Topic: H.01. Animal Cognition and Behavior

Support: George Mason University's Office of Student Scholarship, Creative Activities, and Research

Title: The effects of A. bisporus (white button mushrooms) on the circadian rhythms and spatial memory of human amyloid precursor protein (hAPP) transgenic mice

Authors: *T. DIMOPOULOS, S. L. P. LIPPI, C. L. C. NEELY, C. M. HERNANDEZ, E. N. DOHERTY, N. T. COSCHIGANO, M. T. DECOITO, Y. DHAKAL, K. R. MILLS, K. FLORES, A. B. BOOTH, J. M. FLINN
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Abstract: Alzheimer’s Disease (AD) is the most common form of dementia and the 5th leading cause of death in the United States. Antioxidant-rich diets have been shown in previous studies to reduce the toxicity of amyloid (Aβ). White button mushrooms (WBMs) are an antioxidant and are shown to mimic nerve growth factors (NGFs), which are neuroprotective and prevent cognitive decline. WBMs constitute 90% of the mushrooms eaten in the US. One of the

symptoms of AD is disrupted circadian rhythms. We are examining effect of WBMs on spatial memory, circadian rhythms, and nesting.
J20/hAPP transgenic mice and wildtype (C57BL/6J) mice from Jackson Laboratories were fed a 10% WBM feed triweekly to yield a 5% total diet of WBMs. Behavioral tests were conducted at 3.5 months and will be retested at 8 months of age. Tests include: Morris Water maze (MWM), circadian rhythm (CR), and nesting. Preliminary MWM data has shown that mice at 3.5 months on the WBM diet spent significantly more time in the target quadrant during probe trials on days 2 ($p=0.045$) and day 4 ($p=0.032$) of the test, indicating mice on WBMs have greater spatial ability. Testing at 8 months will determine whether long term consumption of WBMs has a positive effect on behavior and on amyloid levels in hAPP and wildtype mice.

Disclosures: T. Dimopoulos: None. **S.L.P. Lippi:** None. **C.L.C. Neely:** None. **C.M. Hernandez:** None. **E.N. Doherty:** None. **N.T. Coschigano:** None. **M.T. Decoito:** None. **Y. Dhakal:** None. **K.R. Mills:** None. **K. Flores:** None. **A.B. Booth:** None. **J.M. Flinn:** None.

Poster

512. Age-Related Cognitive Deficits and Treatments

Location: SDCC Halls B-H

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Program #/Poster #: 512.15/GGG18

Topic: H.01. Animal Cognition and Behavior

Support: CA893/6-1 and 8-1
DIGS-BB/TU-Dresden

Title: Increasing hippocampal neurogenesis rejuvenates learning strategies and memory throughout life

Authors: *G. BERDUGO-VEGA[1], A. LOPEZ-FERNANDEZ[1], B. ARTEGIANI[3], A. GARTHE[4], G. KEMPERMANN[1], F. CALEGARI[2]
[2]Calegari Lab., [1]Ctr. for Regenerative Therapies - TU Dresden, Dresden, Germany; [3]Hubrecht Institute, Developmental Biol. and Stem Cell Res., Utrecht, Netherlands; [4]German Ctr. for Neurodegenerative Dis. (DZNE), Dresden, Germany

Abstract: Age-related cognitive decline particularly affects hippocampal function, being contextual learning, allocentric navigation and episodic memory severely compromised in old people.
Adult hippocampal neurogenesis is a prime form of plasticity that allows the flexible contextualization of information and also decreases with age. In this work, we asked if rescuing the natural decline in neurogenesis in old age or throughout life would compensate the many effects of ageing on hippocampal function in rodents.
Thus, we further explored a method described by our group to genetically and cell-intrinsically

increase the proliferation of hippocampal neural stem cells (NSC; Artegiani et al., 2011). Acute NSC expansion in old mice (16 months old) successfully increased the number of integrated adult-born neurons in the hippocampus and rejuvenated its function by reverting the age-related switch from allocentric to egocentric navigational strategies. Furthermore, chronic expansion of NSC throughout life delayed the age-related decrease in neurogenesis and preserved contextual learning strategies and episodic memory by a change in hippocampal versus striatal neuronal activity.
In summary, our study demonstrates that critical aspects of hippocampal cognitive impairment can be reversed in old age or compensated throughout life by extrinsically exploiting endogenous brain reserves.

Disclosures: G. Berdugo-Vega: None. **A. Lopez-Fernandez:** None. **B. Artegiani:** None. **A. Garthe:** None. **G. Kempermann:** None. **F. Calegari:** None.

Poster

512. Age-Related Cognitive Deficits and Treatments

Location: SDCC Halls B-H

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Program #/Poster #: 512.16/GGG19

Topic: H.01. Animal Cognition and Behavior

Support: T32 AG020506
R37 AG008796

Title: The effects of learning and aging on functional characteristics of layer v pyramidal neurons of the lateral entorhinal cortex

Authors: *K. B. KELLY, C. LIN, M. M. OH, J. F. DISTERHOFT
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Abstract: Increased human longevity has caused a steady rise in the prevalence of aging-related health issues, most notably age-related cognitive decline, including forms of dementia, such as Alzheimer's disease (AD). While many aged individuals experience some level of cognitive impairment (age impaired, AI), there are other individuals, 'super-agers' (age unimpaired, AU), that maintain cognitive performance similar to that of younger adults (Y). The lateral entorhinal cortex (LEC) is known to be vitally important for temporal associative learning, and is among the first areas of the brain to exhibit AD pathologies prior to the observation of behavioral deficits. One of the prominent features of layer V LEC pyramidal neurons is their ability to exhibit a graded persistent firing activity, a cholinergic dependent property that is a potential mechanism underlying associative learning and memory. Cholinergic activity is reduced in aging and AD, which could reduce cellular excitability and negatively impact persistent firing throughout the LEC. The LEC is thus a rich potential target in which to study memory and age-

related changes in cognition.
This project utilizes whole-cell patch clamp electrophysiology to evaluate age-related changes in the intrinsic excitability of layer V pyramidal neurons of the LEC. All recordings were derived from young adult (3-6 month) or aged (28-31 month) hybrid Fisher 344 x Brown Norway rats. To incorporate behavioral changes in learning and memory, I used trace eye blink conditioning (tEBC) to separate aged individuals into AU or AI cohorts.
I analyzed postburst AHP to investigate changes in intrinsic excitability. Results from recordings taken 24 hours after the final training session indicate that the slow AHP (sAHP) is reduced in young and AU rats that underwent tEBC, when compared to young pseudoconditioned and AI rats. Data indicates there is no difference between sAHP of young and AU rats. However, one month after the final training session, AU rats exhibit a sAHP similar to that seen in AI rats, indicating that the decrease in sAHP seen at the 24hr time point is transient in nature.
While it is currently unknown how cholinergic tone within deep layers of LEC is affected with age, one component of AD pathology is the degradation of cholinergic neurons and receptors. By applying the muscarinic receptor agonist carbachol I can elicit persistent firing in layer V LEC pyramidal neurons. Results indicate that persistent firing is less robust in aged tissue, potentially stemming from a loss of cholinergic tone. Combined, the observations from this study are among the first to reveal how aging and learning affect the cellular physiology of the LEC.

Disclosures: K.B. Kelly: None. **C. Lin:** None. **M.M. Oh:** None. **J.F. Disterhoft:** None.

Poster

512. Age-Related Cognitive Deficits and Treatments

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Program #/Poster #: 512.17/GGG20

Topic: H.01. Animal Cognition and Behavior

Support: NIH 5R37AG008796
NIH 5RF1AG017139

Title: Carbachol-induced increase in calcium transients is occluded in CA1 pyramidal neurons from aged-unimpaired rats

Authors: *M. M. OH, J. F. DISTERHOFT
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Abstract: The enlarged postburst afterhyperpolarization (AHP) of CA1 pyramidal neurons is hypothesized to be a main source of the learning and memory (L&M) impairments observed in aging subjects (Disterhoft & Oh 2006). Since the AHP is comprised mainly of Ca^{2+}-dependent potassium conductances, the increased cytosolic Ca^{2+} levels ($[Ca^{2+}]$) during a train of action potentials (APs) observed in aged CA1 neurons (Oh et al. 2013) has also been hypothesized to be

a source of L&M deficits. Thus, many studies have focused on reducing the Ca^{2+} rise in aged CA1 neurons to rescue the aging-related deficits. Other pharmacological manipulations have also been proven to reduce the AHP and rescue aging-related deficits; such as increasing cholinergic levels with cholinesterase inhibitors in the brain (Disterhoft & Oh 2007). Our preliminary data strongly suggest that bath application of the cholinergic agonist, carbachol, reduces the AHP while increasing evoked [Ca^{2+}] in aged (~30%, n=16) and young (~20%, n=9) CA1 neurons from behaviorally naïve animals. However, it is unknown if learning alters the cholinergic-induced [Ca^{2+}] increase. Therefore, the present study was designed to determine if bath application of the cholinergic agonist, carbachol, causes a change in [Ca^{2+}] evoked with AP trains in young (3-4 mo) and/or aged (27-33 mo) CA1 neurons from male F344xBN rats trained on the hippocampus-dependent, trace eyeblink conditioning (TEBC) task.
Hippocampal slices were prepared 1 day after the last training session. Whole-cell current clamp and Ca^{2+}-imaging (OGB-6F and Alexa 594) data evoked with 100Hz AP trains were collected using a custom built 2-photon laser scanning microscope system before and 20 min after 10μM carbachol was added to the perfusate. Our preliminary data suggest that bath application of carbachol caused increases in evoked [Ca^{2+}] in CA1 neurons from young pseudoconditioned (~12%, n=5) and trained (~15%, n=11) rats. Bath application of carbachol increased the evoked [Ca^{2+}] by ~26% in CA1 neurons (n=3) from aged impaired rats. Surprisingly, carbachol-induced [Ca^{2+}] increase was considerably smaller in CA1 neurons from aged unimpaired (AU) rats: ~12% reduction in 4 neurons. These preliminary data suggest that cholinergic signaling pathway has been used for successful learning in the AU rats: i.e., occlusion. Alternatively, although highly unlikely, it is possible that the cholinergic signaling cascade (e.g., cholinergic receptors) is missing in CA1 neurons from the AU rats. Ongoing experiments are being conducted to address the latter possibility by conducting these experiments on CA1 neurons from hippocampal slices prepared 1 month after the last TEBC session.

Disclosures: M.M. Oh: None. **J.F. Disterhoft:** None.

Poster

512. Age-Related Cognitive Deficits and Treatments

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Topic: H.01. Animal Cognition and Behavior

Support: NS022061

Title: Entorhinal cortex cholinergic circuits in cognitive decline

Authors: *M. ANANTH[1], D. A. TALMAGE[2,3], L. W. ROLE[1,3]
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Abstract: In the central nervous system, cholinergic neurons of the basal forebrain (BFCNs) exert tight, context specific control over cortical processes. The enormous reach of their projections makes cholinergic axonal arbors difficult to maintain and vulnerable to loss. Numerous studies since the 1970s have demonstrated that decreases in cholinergic markers accompany decline in cognitive function. As such, we asked what role the cholinergic system plays in cognitive decline. The entorhinal cortex (EC), a cortical region that receives an extensive cholinergic projection from the BFCNs has been shown to be vulnerable early on in aging. Using the entorhinal cortex as a model region of early cortical dysfunction, we investigated the relationship between altered cholinergic integrity and cortical function. To assess EC-function in cognitive decline, we used a mouse model where aging pathology (amyloid beta plaques and hyperphosphorylated tau tangles) was present at an earlier physical age (5XFAD X NOS2-/-; aging model). We found that aging model mice had impaired performance on an EC-based memory task. We postulated that this impaired performance was related to changes in engagement of the EC, and asked whether this was driven by alterations to cholinergic inputs to the EC. We found significant reductions to cholinergic terminal field density in the EC of the aging model mice as compared to control mice, and that baseline EC activity was markedly higher in aging model mice as compared to controls. We postulated that loss of cholinergic tone results in an imbalanced ratio of excitation to inhibition, leading to increased EC firing. Using viral labeling strategies, we investigated whether there were reductions in cholinergic synapse density in EC in the aging model, and whether these changes were specific to cholinergic synapses apposed to excitatory or inhibitory neurons. In addition, we asked whether augmenting endogenous ACh (using optogenetics) in the aging model mice. In parallel studies in humans, we used Positron Emission Tomography (PET) with a marker that targets cholinergic synapses to examine the relationship between altered EC cortical function (cognitive testing) and altered EC cholinergic circuits. Future experiments in both humans and rodents systematically map out changes to cholinergic circuits in health and cognitive decline and will determine whether changes to cholinergic EC circuits can be regarded as a marker of early cognitive impairment.

Disclosures: M. Ananth: None. **D.A. Talmage:** None. **L.W. Role:** None.

Poster

512. Age-Related Cognitive Deficits and Treatments

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Program #/Poster #: 512.19/GGG22

Topic: H.01. Animal Cognition and Behavior

Support: NIH F31AG055331
NIH T32AG020506
NIH R37AG008796

NIH RF1AG017139

Title: Learning and aging affect functional characteristics of lateral entorhinal cortex layer iii pyramidal neurons

Authors: *C. LIN, K. B. KELLY, M. M. OH, J. F. DISTERHOFT
Dept. of Physiol., Northwestern Univ., Chicago, IL

Abstract: Normal aging is often associated with a decline in hippocampus-dependent learning and memory, and altered intrinsic excitability of hippocampal neurons has been shown as contributing to these changes. In the CA1 region, for example, the intrinsic excitability of pyramidal neurons decreases with aging, reducing the probability that the neuron is recruited into a neural network for learning, and resulting in aging-related cognitive deficits. Previous research from our laboratory also indicates that CA1 neurons from animals, young or aged, that have acquired a hippocampal-dependent task are more excitable relative to control animals. As the entorhinal cortex is a relay station to the hippocampus, it is another important region in which to study aging and learning-related changes in excitability, to better understand the mechanisms underlying aging-related cognitive decline. The lateral entorhinal cortex (LEC) is the focus of this study, as it has been suggested to support hippocampus-dependent associative learning and is also an initial site of manifestation for Alzheimer's disease. In particular, pyramidal neurons from layer III, which project directly to the CA1 region via the temporoammonic pathway, are being examined in this study. Current clamp recordings were made from neurons of young adult (3-6-month-old) and aged (29-32-month-old) F1 F344xBN hybrid rats. Our data indicate that neurons from aging animals accommodate more than neurons from the young population, meaning they fire fewer action potentials to depolarizing input. The reduced excitability may contribute to the aging neurons' decreased ability to demonstrate persistent firing after the termination of a depolarizing stimulus, an EC phenomenon that has been suggested to underlie associative learning. Not only are neurons from the aging population less likely to persistently fire, but they are also less able to maintain the frequency of their firing. Current clamp recordings taken 24 hours after trace eyeblink conditioning, a hippocampus-dependent temporal associative task, indicate that there do not seem to be learning-related intrinsic excitability changes in either the young or aged population. There do, however, seem to be synaptic excitability changes, as neurons from animals that have learned the trace eyeblink task are able to fire more synaptically-evoked action potentials relative to neurons from control animals. In addition, synaptic stimulation that evokes one single spike in control or behaviorally naïve animals can elicit burst firing in neurons from trained animals, which may be an indicator of changes in persistent firing activity following learning.

Disclosures: C. Lin: None. **K.B. Kelly:** None. **M.M. Oh:** None. **J.F. Disterhoft:** None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.01/GGG23

Topic: H.02. Human Cognition and Behavior

Support: DFG Grant TH866-8/1

Title: Dopamine dependent nicotine effects on cognitive control in non-smokers

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Abstract: Cognitive control compromises the functions cognitive stability and flexibility, which have often been tested by assessing distractor suppression and task switching respectively. Cognitive stability and flexibility are related to prefrontal cortex (PFC) and basal ganglia (BG) dopaminergic activity. While increased dopamine levels in PFC promote cognitive stability, enhanced dopamine in the BG support flexibility[1]. In addition, there is evidence for the cholinergic agonist nicotine to modulate distractor processing and flexible reorienting. However, nicotine effects show interindividual variability and baseline dependency presumably related to the dopaminergic system[2,3].
We addressed the question, whether the effects of nicotine on cognitive control depend on baseline dopamine levels. 29 young, healthy non-smokers (20 female / 9 male, age: 18-35) were tested twice on a cognitive control task with distractor and switch trials[4]. To manipulate dopamine levels, we administered 2 g L-Tyrosine or placebo in a between subject design 2 hours prior to task. 1 hour later, both groups received in a within subject design on one day a 7 mg nicotine patch and on another day an inactive placebo. Response time costs for distractor and switch trials were entered to a repeated measures ANOVA with between-subject factor dopamine level (placebo/L-Tyrosine) and the within-subject factors nicotine (placebo/nicotine) and cost (distractor/switch).
Switch-costs were higher than distractor-costs (main effect cost $p<0.05$). Subjects with L-Tyrosine had significantly higher costs than subjects with placebo (main effect dopamine level $p<0.05$), mainly driven by a stronger increase in switch-costs as compared to distractor-costs (trend for an interaction dopamine level*cost $p<0.1$). Nicotine reduced switch-costs but increased distractor-costs (interaction nicotine*cost $p<0.05$). Separate analyses in both groups (Placebo / L-Tyrosine), revealed stronger nicotine effects under L-Tyrosine, i.e. with higher baseline dopamine levels. The interaction of nicotine with costs was solely significant in those subjects ($p<0.05$).
Our data suggest that increased dopamine availability in young healthy subjects increases the

costs of task switching, hence reducing flexibility. Subjects with higher dopamine levels are further more prone to the behavioural effects of nicotine showing improvements in task switching, however at the costs of increased distractor interference.
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Disclosures: S. Ahrens: None. **J. Laux:** None. **C. Mueller:** None. **C.M. Thiel:** None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.02/GGG24

Topic: H.02. Human Cognition and Behavior

Support: NIDA Grant Contract Number : HHSN271201100009C, Reference Number : N44DA-12-1206

Title: Neurophysiological indices of cannabis and impairment

Authors: *S. J. SMITH[1], B. STONE[1], A. MEGHDADI[1], A. SPURGIN[2], T. BROWN[2], C. BERKA[1]
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Abstract: Cannabis and its chemical constituent that is responsible for the majority of its psychoactive effects, Tetrahydrocannabinol (THC), is the most commonly used illicit substance in the United States. With state laws and regulations undergoing changes in terms of the legality of sales, distribution, and use of THC products, the prevalence of cannabis use and abuse is projected to increase. However, quantitative assessments of performance alterations, as well as, the underlying neurological mechanisms of cannabis intoxication have not undergone the same level of systematic investigation as other substances, such as alcohol. The objective of this study was to provide quantitative assessments to supplement subjective measures related to cannabis through the use of neurophysiology in conjunction with cognitive tasks. Participants were recruited through a database registry and through distributed flyers at smoke shops (selling legal drug paraphernalia) in the counties of Johnson and Lynn within the state of Iowa. The final dataset (n = 21) was comprised of 20.2% females with 92.36% of the participants identifying as Caucasian. This dataset had a mean age 24.5 yr (range: 18-42 yr). We assessed the psychoneurophysiological differences of drugged versus placebo subjects using a double-blind study design with four neurocognitive tasks: 3-Choice Vigilance Task (3CVT), Auditory Psycho-Vigilance Task (APVT), Visual Psycho-Vigilance Task (VPVT), and a Standard Image

Recognition task (SIR). Repeated measures ANOVAs revealed an increase in Heart Rate during the 3CVT and SIR tasks while under the influence of cannabis: $F(1,37) = 6.49$, $p < 0.05$, and $F(1,38) = 4.60$, $p < 0.05$, respectively; an increase in Central EEG alpha(8-10Hz) hemispheric asymmetries during the 3CVT:$F(1,37) = 3.56$, $p < 0.05$, an increase in Central EEG beta(13-30Hz) hemispheric asymmetries($F(1,39) = 5.77$, $p < 0.05$) and bilateral differences in alpha(8-10Hz; $F(1,39) = 4.53$, $p < 0.05$), and a decrease in Central EEG delta (1-3Hz) hemispheric asymmetries ($F(1,39) = 3.93$, $p < 0.05$)during the APVT due to cannabis. We observed a decrease in variability in correct response to the interference stimuli ($F(1,37) = 3.97$,$p < 0.05$) during the 3CVT, but an increase inaccuracy during the SIR ($F(1,38) = 3.97$, $p < 0.05$) while under the influence of cannabis. No significant differences were found within the VPVT. These results show promise for providing easily applied objective methods to assess quantitative indices of impairment resulting from marijuana use and offering further insight on behavior and physiological responses to determine an individual's impairment resulting from cannabis consumption.

Disclosures: S.J. Smith: A. Employment/Salary (full or part-time):; Advanced Brain Monitoring. **B. Stone:** A. Employment/Salary (full or part-time):; ADVANCED BRAIN MONITORING. **A. Meghdadi:** A. Employment/Salary (full or part-time):; ADVANCED BRAIN MONITORING. **A. Spurgin:** A. Employment/Salary (full or part-time):; University of Iowa. **T. Brown:** A. Employment/Salary (full or part-time):; University of Iowa. **C. Berka:** A. Employment/Salary (full or part-time):; ADVANCED BRAIN MONITORING.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.03/GGG25

Topic: H.02. Human Cognition and Behavior

Title: Attention and memory are predictors of worse performance on cognitive tasks in caffeine addiction

Authors: *C. R. SANTANA, P. E. MARINHO, N. L. ALMEIDA, T. M. P. FERNANDES, N. A. SANTOS
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Abstract: Although caffeine increases alertness, wakefulness and prevent memory losses, the complete benefits of caffeine on cognitive functions remain unclear. There is evidence that caffeine effects are dose-related. The effects of caffeine addiction are under investigation; however, addictive use of caffeine can be classified as the use of more than 400 mg/day. Based on the known mechanisms of action, the main purpose of this research was to investigate the relationship between caffeine addiction, caffeine abstinence and cognitive functions such as

working memory, sustained and divided attention and cognitive flexibility. In the present study, 12 controls (CG), 12 caffeine- addicted (CAG) users, and 12 abstinence caffeine-addicted (ACG) users were recruited from the Federal University of Paraiba, Brazil. All caffeine users were classified by means of DSM-5 criteria for dependence. Participants who used caffeine were randomized into the groups. An abstinence period of six hours was used as a criterion for abstinence. Craving and anxiety levels were measured before and after the experiments. On the first study, cognitive functions were investigated using the Trail-Making Test (A and B), Stroop and Flanker Task. On the second study, we investigated if these tests would be predictive of a facial detection task. The results indicated that the participants of ACG had a worse performance than CG and CAG on all cognitive tasks. There were no significant differences between CG and CAG. It was also verified that cognitive measurements were predictors for facial detection. Our findings highlight the need to evaluate cognitive functioning in high caffeine users (with and without abstinence). The results here targeted contribute to psychological and neuroscience research.

Disclosures: C.R. Santana: None. **P.E. Marinho:** None. **N.L. Almeida:** None. **T.M.P. Fernandes:** None. **N.A. Santos:** None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.04/GGG26

Topic: H.02. Human Cognition and Behavior

Support: Indiana University of Pennsylvania, Faculty Senate Grant

Title: Impulsivity and self-perceived emotional feedback predict alcohol-related problems

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Abstract: Previous research has implicated the prefrontal cortex and associated executive functions in the development alcohol use and alcoholism. However, executive functions represent a diverse set of abilities that may differentially predict alcohol use and alcohol-related problems. This study examined the relationship between self-report and performance-based measures of executive function (impulsivity and emotion perception) and varying degrees of alcohol use and alcohol- related problems among 326 undergraduate college students. After controlling for participant sex, age, ethnicity, and frequency of nicotine and marijuana use, a hierarchical multiple regression was used to assess the effect of impulsivity as measured by The Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency

Impulsive Behavior Scale (UPPS-P) and emotion recognition of self (Facial Manipulation Expressions Task) and others (The Adult Eyes Test and The Reading the Mind in Films Task). Frequency of participants alcohol use was assessed as was the amount of alcohol consumed and time spent drinking using the Daily Drinking Questionnaire (DDQ). The Alcohol Use Disorders Identification Test (AUDIT) and The Rutgers Alcohol Problem Index (RAPI) were used to measure harmful drinking behavior. Impulsivity and emotion perception failed to predict drinking frequency and the number of drinks consumed in a typical week. However, impulsivity (UPPS-P subscales for Lack of Premeditation and Positive Urgency) predicted the number of hours spent drinking in a typical week and hazardous drinking on the AUDIT. Emotion Self-Perception was also a significant predictor on these drinking measures, though it did not add to the predictability of problematic drinking beyond impulsivity measures. The Positive Urgency subscale of the UPPS-P also predicted alcohol-related problems on the RAPI. These results are noteworthy as they illustrate specific domains of impulsivity differentially predict alcohol consumption and more problematic use and suggest self-perception of emotions via manipulation of facial expressions is also predictive of alcohol-related problems.

Disclosures: I. Comnick: None. **W.M. Meil:** None. **M. Berman:** None. **E. Morgan:** None. **R. Frazier:** None. **W. Farrell:** None. **J. Mills:** None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.05/GGG27

Topic: H.02. Human Cognition and Behavior

Support: AA016624

Title: Behavioral and neural correlates of response inhibition and error processing in binge drinkers: An fMRi study during the go/nogo task

Authors: *A. B. ALDERSONMYERS[1], S. M. MOLNAR[3], L. A. HOLCOMB[2], K. MARINKOVIC[1]
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Abstract: Inhibiting behaviors considered unsuitable for achieving goal-oriented outcomes and the ability to flexibly adapt following errors is an integral feature of executive functioning. Impaired response inhibition is associated with increased risk of problem drinking and has been considered an important dimension in the development of alcohol dependence. This is particularly relevant to binge drinking (BD), a mode of alcohol consumption especially common amongst college age youth and a public health concern of increasing importance. Neuroimaging studies in young binge drinkers have reported inconsistent results with some observing increased

and others decreased activation in prefrontal and parietal cortical areas during response inhibition tasks mainly in the absence of behavioral impairments.
The present study used functional magnetic resonance imaging (fMRI) to examine response inhibition in young adults performing an event-related Go/NoGo inhibitory task that induced a prepotency to respond. Participants assigned to the BD group reported consuming 5+/6+ drinks (females/males) within two hours five or more times within the previous six months. Light drinking (LD) individuals formed the comparison group, reporting two or fewer binge episodes in the past six months. These groups were otherwise matched for age, gender, IQ, race/ethnicity, and family history of alcoholism. Voxel-wise and region-of-interest analyses were carried out with AFNI (Analysis of Functional Neuroimages) on correct response inhibition (NoGo) trials and on those inducing commission errors. No significant group differences were found regarding task accuracy and reaction times. However, in comparison to light drinkers, BDs exhibited increased activity in the anterior cingulate, bilateral inferior prefrontal, and posterior cortices during correctly inhibited trials. This finding is consistent with studies in AUD cohorts suggesting compensatory recruitment of extended neural resources to maintain accurate task performance. Conversely, BDs had lower activation to errors in the anterior cingulate, rostral frontal, and temporo-occipital cortices implying deficient cognitive control ability to carry out post-error adjustments. Regional activity to correct rejections and commission errors correlated with various self-reported measures of alcohol intake, impulsivity, and risk-seeking behaviors. This study provides further evidence that binge drinking is associated with a deterioration of cognitive control that may precede the development of alcohol use disorders.

Disclosures: A.B. Aldersonmyers: None. **S.M. Molnar:** None. **L.A. Holcomb:** None. **K. Marinkovic:** A. Employment/Salary (full or part-time):; San Diego State University.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.06/HHH1

Topic: H.02. Human Cognition and Behavior

Support: AA016624

Title: Reward and top-down control network alterations in binge drinkers

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Abstract: Effective cognitive processing requires efficient communication within and among different neurofunctional systems in the brain. Resting State Functional Connectivity (RSFC) analysis measures connections between brain regions based on temporal correlations of the

spontaneous fluctuations of the blood-oxygen-level-depend (BOLD) signal during wakeful rest. Studies of alcohol use disorders (AUD) have shown altered connectivity patterns especially in the reward-motivational and top-down control networks. Even though binge drinking has been on the rise among young adults and is a public health issue of increasing importance, there is a paucity of studies investigating neural changes associated with heavy episodic drinking. This study examined the functional connectivity as a function of binge drinking. Given extant evidence in AUD, we focused particularly on the reward-motivational and inhibitory control networks. fMRI BOLD images were acquired with a 3T scanner (GE) and analyzed with the CONN-fMRI Functional Connectivity toolbox. Young, healthy adult participants who reported consuming 5+/6+ drinks in two hours five or more times in the past six months were assigned to a binge drinking (BD) group. They were compared to light drinkers (LD) who reported two or fewer binge episodes but were matched on demographics, family history of alcoholism, and IQ. Seed-to-voxel connectivity maps were created using as seeds the brain regions that have been implicated in the reward function and top-down regulation in studies on AUD. False Discovery Rate at ≤ 0.05 was applied to correct for multiple comparisons. BD showed increased connectivity between the striatum (dorsal: caudate nucleus; ventral: nucleus accumbens) and the orbitofrontal cortex (OFC) which was positively correlated with binge episodes and the Alcohol Use Disorder Identification Test (AUDIT) scores. Conversely, BD showed decreased connectivity between the right inferior frontal cortex and the inferior temporal cortex which was negatively correlated with binge episodes, AUDIT scores, and harmful drinking consequences. These results suggest enhanced salience of alcohol-related reward mediated by ventral striatum and increased tendencies toward habitual and compulsive behavior mediated by dorsal striatum. This is accompanied by weakened top-down control associated with alcohol intake. In sum, these findings confirm that the initiation of alcohol addiction may depend on a combination of dysregulated reward circuitry and deficient top-down influence. Support:AA016624

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Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.07/HHH2

Topic: H.02. Human Cognition and Behavior

Support: NIH/NIDA R01DA043676

Title: Subcortical and cortical brain anatomy link opioid use to risk tolerance in addiction

Authors: *N. V. BANAVAR[1], A. B. KONOVA[1], S. LOPEZ-GUZMAN[1,3], K. LOUIE[1], J. ROTROSEN[2], P. GLIMCHER[1]

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Abstract: With deaths from opioid-related overdoses continuing to surge, the need for a deeper understanding of the neurobiological mechanisms behind the risky decision-making that can lead to overdose has never been more pressing. Recent work has begun to elucidate how individual differences in brain anatomy constrain individual preferences, particularly decision making in the face of known risk. While differences between substance users and healthy controls in brain structure, and separately risk-taking, have long been observed, it is not known whether the same anatomical correlates as those identified in health subserve risk taking behavior in addiction. We collected structural MRI scans in 17 individuals with opioid use disorder (OUD) (age = 39, 15 males) and 20 matched community controls (age = 42, 16 males). All participants also completed a decision making task for real monetary incentives that could be received with different known probability levels. We applied voxel-based morphometry to quantify regional grey matter volume (GMV) and standard economic models to quantify risk tolerance. Preliminary analyses focused on the relationship between opioid use and GMV in the brain's valuation system, the amygdala and the right posterior parietal cortex (rPPC). We further examined the relationship between GMV in these regions and risk tolerance in OUD. All analyses controlled for age, sex and total grey and white matter volume. OUD chronicity (years of opioid use, average = 11, range: 2 - 28) was associated with increased GMV in the ventral (vSTR) and dorsal striatum, ventromedial prefrontal cortex and amygdala (all $p < 0.04$). Of these, only increased GMV in the vSTR differed between patients and controls and increased GMV in this same region also correlated with greater risk tolerance. While we found no significant relationship between opioid use (chronicity or diagnosis of OUD) and GMV in the rPPC, higher GMV in the rPPC for controls correlated with greater risk tolerance - a finding we have previously reported. Interestingly, we found an interaction ($p < 0.003$) between rPPC GMV and recent heroin use in patients, such that, for patients who used more recently, greater rPPC GMV actually indicated lower risk tolerance. GMV in the vSTR and rPPC was uncorrelated, suggesting at least partially independent contributions. Our preliminary findings highlight the role of brain anatomy in both subcortical and cortical GMV in OUD, specifically, as related to chronic opioid use (vSTR) and risk tolerance (vSTR and rPPC). Implications of these findings suggest multiple neural mechanisms and, as such, therapies targeting both cortical and subcortical regions may be more effective.

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Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

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Program #/Poster #: 513.08/HHH3

Topic: H.02. Human Cognition and Behavior

Support: Centers for Medicare and Medicaid Services Grant 1B1CMS330880

Title: Relationship between cognition and nicotine dependence in smokers with mental illness

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Abstract: Introduction Rates of cigarette smoking are significantly higher among people with a mental illness compared to the general population. This is particularly true for schizophrenia, with lifetime smoking rates up to 81%. The self-medication hypothesis posits that people with schizophrenia smoke to ameliorate negative symptoms and cognitive deficits. The high concentration of nicotinic acetylcholine receptors in the prefrontal cortex, an area essential for cognitive functioning, makes this hypothesis plausible. Furthermore, subjective perception of cognitive benefit may lead to more smoking even in the absence of a biological explanation. Approximately 90% of individuals with schizophrenia have impairments in cognitive functioning. Cognitive deficits are also prevalent in individuals with bipolar disorder, major depressive disorder, and PTSD. In a secondary analysis of baseline data from a large cessation study, we explored the relationships among cognitive functioning, perception of cognitive benefits from smoking, and severity of nicotine dependency. **Methods** Daily smoking Medicaid beneficiaries (n = 661) were assessed at baseline with a structured interview for smoking characteristics and attitudes, record review for diagnosis (schizophrenia spectrum (n = 148), bipolar (n = 150), major depression (n = 158), and other disorders (n = 205), and cognitive battery for cognition. A cognitive composite score was computed based on selected subscales from the Delis-Kaplan Executive Function System (Trails Conditions 2 and 4, Color-Word Interference Condition 4, FAS). Participants' level of agreement with the statement, "After a cigarette, I am able to concentrate better," served as the measure of perception of cognitive benefit from smoking. Linear regressions were conducted to examine whether baseline cognition and perceptions of cognitive benefit predicted baseline level of nicotine dependence accounting for diagnosis, level of education, IQ equivalency (using the WRAT-3 Reading score), and approximate time since last cigarette smoked. **Results** The final model including all variables, accounted for 8.8% of the total variance in nicotine dependence (F (8, 627) = 7.48, p <.001). Cognitive functioning (β = -.13, p = .002) and perceived cognitive benefits from smoking (β = .08, p = .033) significantly predicted level of nicotine dependence. **Conclusions** Greater cognitive impairment and higher levels of perceived cognitive benefits from smoking were associated with greater nicotine dependence among smokers with mental illness. Augmenting smoking cessation treatment with cognitive training tasks may prove beneficial for these individuals.

Disclosures: C. Bianco: None. **S.I. Pratt:** None. **M.F. Brunette:** None. **J.C. Ferron:** None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.09/HHH4

Topic: H.02. Human Cognition and Behavior

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Title: Disadvantageous decision-making in methamphetamine users: Loss aversion and dopamine D2/D3 receptor availability

Authors: *Z. R. GUTTMAN[1], D. G. GHAHREMANI[2], C. L. ROBERTSON[3], K. OKITA[4], K. ISHIBASHI[5], M. A. MANDELKERN[6], E. D. LONDON[2]
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Abstract: Most people tend to display an aversion to loss. This phenomenon has been demonstrated using economic choice tasks in which choices are made involving potential losses and gains. Theories of decision-making assume that individuals compute the value of each option by transforming components of the choice (e.g., magnitude and probability of potential gain or loss) into subjectively equivalent quantities that can then be integrated and compared. When an option involves a cost, such as the potential to lose money, the value of the reward is discounted as a function of the loss. The degree to which loss contributes to the discounting of subjective value shows individual variation, which can be measured by modeling individual choice parameters that can then be related to markers of neural function. The context of reward-based choices that present potential losses is particularly relevant to individuals with addictive disorders, for whom maladaptive decision-making contributes to the vulnerability to and persistence of their disorders. Despite behavioral and neural studies of loss sensitivity in addictions, analysis of individual choice parameters to distinguish the nature of differences between healthy and more biased decision-making has not been assessed in individuals with substance use disorder. Moreover, loss aversion is modulated by brain regions associated with

dopamine function, which is dysregulated in addiction, yet the relationship between measures of dopamine function and loss aversion has not been directly assessed. Therefore, we aimed to determine whether dopamine function is related to individual differences in loss aversion. Individuals with Methamphetamine Use Disorder (MUD; n=19) and healthy controls (n=24), matched for age and sex, completed a standardized Loss Aversion Task where they were shown gambles offering a 50% chance of winning or losing different amounts of money, or the option to opt out and accept $5 for sure (e.g., 50% chance of winning $10, 50% chance of losing $8; accept $5 for sure). Participants also underwent positron emission tomography (PET) with [^{18}F]fallypride to assess dopamine D2/D3 receptor ($DRD_{2/3}$) binding potential (BPND). MUD participants were significantly more loss averse than healthy controls ($p=0.01$), in contrast to the prevailing view that loss aversion is lower in individuals with addictions. Loss aversion was also negatively correlated with $DRD_{2/3}$ BPND in the nucleus accumbens of healthy controls ($p<0.05$), but not in MUD participants, suggesting a role for dopamine function in sensitivity to loss that may be dysregulated in MUD.

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Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.10/HHH5

Topic: H.02. Human Cognition and Behavior

Support: K23NS080988

Title: Inhibitory control deficits in patients with essential tremor

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Abstract: Objective: Essential Tremor (ET) is a movement disorder characterized by action tremor which impacts motor execution. Disruptions incerebellar-thalamo-cortical networks in ET could also interfere with cognitive control mechanisms involved in regulating motor performance, for example the ability to inhibit or stop actions . The current study investigated the speed of action initiation and two forms of action control, response stopping and proactive slowing in ET. **Method:** Thirty-three ET patients and 25 healthy controls (HCs) performed a simple choice reaction task and a stop signal task to assess going speed, proactive slowing and stop latencies. **Results:** Going speed was significantly slower in ET patients (649 ms) compared

to HCs (526 ms, $F(1, 56) = 42.37$, $p<.001$), but proactive slowing did not differ between groups. Stop signal reaction times were significantly slower in ET patients (320 ms) compared to HCs (258 ms, $F (1, 56)=15.3$, $p<.001$). Additionally, more severe motor symptoms of ET were associated with longer stopping latencies (*Spearman rho* = .48, $p<.05$). **Conclusions:** ET patients showed slower action initiation, similar to previous studies measuring reaction times. However, inhibitory control was impaired whereas proactive slowing remained intact in comparison to HCs. The more severe ET motor symptoms were associated with slower stopping speed which may reflect more progressive changes to the cerebellar-thalamo-cortical network. Imaging studies investigating structural and functional changes in ET could help explain changes in inhibitory action control.

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Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

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Program #/Poster #: 513.11/HHH6

Topic: H.02. Human Cognition and Behavior

Support: DGA SMO-2-0411

Title: Impact of acute stress on decision-making

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Abstract: Prefrontal cortex seems to be particularly sensitive to stress which could generate an impairment of its functions including decision-making. To test this assumption and to evaluate the impact of an acute stress on decision-making, we submitted healthy subjects to an acute stress while they performed a response selection task that may be considered as the simplest form of decision-making
To induce an acute stress, we used a fear conditioned protocol Indeed, fear is a stressful emotional state. Fear conditioned was obtained by associating a sound (CS+ positive conditioned stimulus) to an unpleasant electric stimulation on the left leg whereas another sound (CS- negative conditioned stimulus) was not associate to any stimulations. After a certain time, CS+ was enough to generate a stress without any unpleasant stimulation.
Decision-making was explored thank to a choice reaction time task with spatial conflict. Stimulus were digits which were presented on the right or the left side of a fixation cross and we asked subjects to associate the parity of digits to a side of response. The position of the stimulus on the screen aimed to interfere with the stimulus-response association required. When the

stimulus was presented on the same side as the required response, the trial was congruent. When the stimulus was presented on the opposite side of the required response, the trial was incongruent. During the task, a sound (CS+ or CS-) was presented before each visual stimulus. Trials following CS+ represented the stress condition instead trials following CS- represented the control condition. The impact of stress on decision-making was evaluated with an electrophysiological marker : the N-40. It is a fronto-central event related potential which is a physiological index of response selection processes.
A expected, N-40 slopes were sensitive to congruity effect on control condition (CS-), slope was steeper on incongruent condition than on congruent condition. On the other hand, on stress condition (CS+), the congruity effect on N-40 slopes was not found. The difference between slopes on congruent and incongruent conditions has been interpreted in term of demand of the choice. Indeed, on incongruent condition, choice is more demanding than on congruent condition. It seems that on stress condition, the facilitation on congruent choices and the dysfacilitation on incongruent choices are modified.
This study shows that an acute stress affects selection processes as revealed by the different sensitivity of the N-40 to congruity effect on control and on stress condition.

Disclosures: C. Ramdani: None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.12/HHH7

Topic: H.02. Human Cognition and Behavior

Support: Cleveland Clinic Imaging Institute

Title: Structural imaging findings in individuals with PTEN Hamartoma tumor syndrome (PHTS) and cognitive dysfunction

Authors: *R. M. BUSCH, L. MOURANY, L. FERGUSON, S. DURGERIAN, K. A. KOENIG, M. J. LOWE, S. S. JONES, S. M. RAO, K. KRISHNAN, C. ENG
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Abstract: *PTEN* Hamartoma Tumor Syndrome (PHTS) is the umbrella term for disorders associated with mutations in phosphatase and tensin homolog (*PTEN*), a major tumor suppressor gene located on chromosome band 10q23.3 with a documented role in heritable and sporadic malignancies. PHTS often presents with macrocephaly and cognitive dysfunction primarily involving frontal lobe systems (Busch, 2013). The objective of this pilot study was to determine if there are associated structural brain anomalies using MRI (Siemens Prisma 3T). Neuropsychological testing and structural MRI characteristics (i.e., cortical/subcortical volumes

and cortical thickness obtained with FreeSurfer 6.0) were compared between a subsample of patients with PHTS (n=4) and demographically matched healthy controls (HC; n=4). Given small sample size, Cohen's d was used to measure effect size (d≥0.80 represents large effect), and no correction was made for multiple comparisons. Individuals with PHTS demonstrated poorer performance on measures of executive functioning, learning, and fine manual dexterity (Cohen's d range 0.86 to 3.33). PHTS patients had significantly larger intracranial volumes than HC (1942 vs. 1351 cm^3, Cohen's d=2.32), consistent with the macrocephaly often associated with this disorder. After normalization for intracranial volume, volumetric differences in the hippocampus, putamen, and cerebellar cortex remained (d range 1.84 to 3.18). Cortical thickness was *higher* in PHTS compared to HC overall as well as for many brain regions. In contrast, PHTS patients showed *reduced* cortical thickness in regions of the right frontal lobe (d=0.97 to 1.34) as well as bilateral anterior cingulate (d=0.84 to 1.25) and parahippocampal (d=1.42 to 3.21) regions. These pilot data are the first to demonstrate structural brain changes in adults with PHTS as compared to HC in brain regions that are consistent with the cognitive deficits observed on neuropsychological testing. Connectivity and functional imaging studies are currently underway to provide further insight into the neuroanatomical abnormalities that may underlie cognitive dysfunction in PHTS.

Disclosures: R.M. Busch: None. **L. Mourany:** None. **L. Ferguson:** None. **S. Durgerian:** None. **K.A. Koenig:** None. **M.J. Lowe:** None. **S.S. Jones:** None. **S.M. Rao:** None. **K. Krishnan:** None. **C. Eng:** None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.13/HHH8

Topic: H.02. Human Cognition and Behavior

Support: the Research and Innovation Foundation of Academic Degree Graduate of Jiangsu Province(No. KYZZ16_0010)
the Humanity and Social Science Foundation of Education Committee of Anhui province (Key Program; No. SK2017A0084)

Title: Test anxiety: A situation-specific trait

Authors: *W. ZHANG, Q. HUANG[1], R. ZHOU, SR[2,3]
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Abstract: Introduction
Test anxiety is a situation-specific trait, high test-anxious (HTA) individuals experience more anxiety and react negatively to the examinations and tests (Keogh & French,2001). Previous studies found that HTA individuals are more susceptible to distraction and fail to inhibit attention to distraction (Alting& Markham, 1993; Mogg at el., 2008). However, it is still not clear that: (a) whether test anxiety is a stable trait or will change according to the test situation, and (b) the specificity of test anxiety. In this study we try to examine these two characteristics of test anxiety.
Method
According to the degree of test anxiety (by Test Anxiety Scale score; Sarason, 1978) and situations (be allocated in stress-free or test stress condition randomly) participants (agd from 18-26 years; all right handed) were divided into four groups: HTA stress-free (n=23; 11 males), HTA test stress (n=23; 10 males), LTA stress-free (n=20; 8 males), LTA test stress (n=22; 10 males) groups. Emotional-Stroop task (ES) was employed with ERP technology to observe the specificity of test anxiety by comparing the emotional interference of test-related threat and of general threat.
Results
In stress-free condition, HTA individuals show emotional interference both of test-related threat (on N2, P3 ERP components) and general threat (on P1, N1, N2, P3, LPP ERP components), and the emotional interference of general threat is stronger than of test-related threat (on N1, N2, LPP ERP components). While in test stress condition, HTA individuals just show emotional interference of test-related threat (on P1, N1, N2, P3, LPP ERP components), and show greater than in stress-free condition (on P1, N1, N2, LPP (450-600ms) ERP components).
Conclusion
The results show that HTA individuals have both of these two characteristics: trait and state-specificity. Specifically, in the stress-free condition, HTA individuals have problems of ability of attentional inhibition (both for test-related threat and general threat), which shows the anxious trait in HTA individuals. While in the test stress condition, this kind of problems just exists for test-related threat and be enhanced especially on perceptual stages of cognition and emotion, which shows the situation specificity of test anxiety in HTA individuals. Additionally, P3 may be a specific indicator of test anxiety because whether HTA felt test stress or not, the emotional interference of test-related threat words on P3 component exists persistently.

Disclosures: Q. Huang: None. **R. Zhou:** None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.14/HHH9

Topic: H.02. Human Cognition and Behavior

Title: Neural underpinnings of prolonged exposure (PE) treatment effect on inhibitory control in post-traumatic stress disorder (PTSD)

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Abstract: Prolonged Exposure (PE), a type of cognitive behavioral therapy, has been identified as a promising behavioral treatment for Post-traumatic Stress Disorder (PTSD). However the mechanisms by which this empirically based treatment helps to alleviate PTSD symptoms remain poorly understood. One hypothesis is inhibitory learning, that is PE may help individuals strengthen inhibitory control function. The purpose of this study was to isolate neuro-cognitive markers of change in inhibitory control associated with PE.
A total of 20 trauma-exposed Veterans diagnosed with PTSD were recruited and completed a course of PE treatment (each participant completed a range of 6 to 12 PE one-hour sessions). They completed a stop-signal task (SST), a standard inhibitory control task, while undergoing functional magnetic resonance imaging (fMRI) at two time points, i.e., both prior to starting treatment and post-treatment (immediately after completing treatment).
Preliminary analyses identified one area in the right lateral prefrontal cortex/supplemental motor area (SMA; Brodmann Area 6) in which activation on stop success trials with a longer stop signal delay (i.e., more difficult to inhibit) increased from baseline to post-treatment ($p<.001$; Cohen $d=1.65$). This result is consistent with the notion that PE treatment may help strengthen neural responses supporting successful inhibitory function among individuals with PTSD.

Disclosures: K.M. Harle: None. **A.D. Spadoni:** None. **S. Norman:** None. **A. Simmons:** None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

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Topic: H.02. Human Cognition and Behavior

Support: NIH Grant 1K23NS091344
NIH Grant UH3 NS100543-01

Title: Response inhibition in advanced Parkinson's disease patients on and off dopaminergic medication

Authors: *D. P. FLODEN[1], H.-J. PARK[1], J. BIARS[2], A. G. MACHADO[1]
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Abstract: Response inhibition in advanced Parkinson's disease patients on and off dopaminergic medication.
Executive function deficits are common in Parkinson’s disease. However, dopaminergic medications can improve performance on some executive function tasks. The goal of this study was to examine whether dopaminergic medication would improve choice reaction time and response inhibition. We recruited 30 patients with moderate to severe Parkinson’s disease to complete a choice reaction time test and the stop signal paradigm both on and off their regular Parkinson’s medications as part of a larger experiment. Performance on the choice reaction time test was significantly slower while off medication ($t=2.3$, $p < .05$), whereas there was no difference in reaction times under conditions of uncertainty in the stop signal task ($t < 1$). Incorrect responses to the stop signal were significantly faster than average “go” signal responses ($t = 2.4$, $p < .05$), consistent with the independent race model of stop signal performance. Nonetheless, estimated stop signal reaction time did not differ between medications states ($t < 1$). This finding stands in contrast to evidence that Parkinson’s patients at earlier stages of the disease do demonstrate faster response inhibition while on medication. Together with other demonstrations of performance changes with high frequency stimulation in advanced Parkinson’s patients, this work may help to inform the pathophysiology of response inhibition deficits in this population.

Disclosures: D.P. Floden: None. **H. Park:** None. **J. Biars:** None. **A.G. Machado:** None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.16/HHH11

Topic: H.02. Human Cognition and Behavior

Title: A time study of prefrontal activation during executive tasks in people with Parkinson's disease: A NIRS study

Authors: *J. K. LANGE KOCH, A. SMILEY-OYEN
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Abstract: We examined change in activation of the dorsolateral prefrontal cortex (DLPFC) during a working memory task using near-infrared spectroscopy (NIRS) to determine how people with Parkinson’s disease (PD) modulate prefrontal brain activation over time and the effect it has on accuracy and reaction time. We tested off and on medication while performing the N-back task, predicting greater accuracy, longer reaction times and less activation in the off-medication state. Greater activation was predicted in the more difficult conditions and to be right lateralized across n-back conditions. Time studies have not been previously reported, but theories of automatization suggest we can expect activation changes over time due to increasing

familiarity with non-executive aspects of the task (Milham et al., 2005). The right DLPFC is expected to maintain activation while the left decreases throughout task duration. **Methods.** Changes in concentration in the DLPFC were assessed while 23 PDs completed the 0-, 1- and 2-back working memory tasks. Zero-back was performed only once, but 1-back and 2-back were performed twice in both off and on-medication states in randomized order collecting 120 seconds of 0-back NIRS data and 240 seconds of 1- and 2-back NIRS data. Accuracy and reaction time were averaged for off and on medication states. Time was blocked into 10-second averages. Time blocks 1,3,5,7, and 9 were then analyzed in a repeated measures ANOVA to assess differences associated with medication status. **Results.** Accuracy was greater when off medication, but reaction time was faster when on medications across conditions. There was less change in oxygenation when PDs were on medication across conditions. Change in activation increased from 0-back to 1-back to 2-back and was lateralized to the right in both medication states. Interactions showed the right increasing and the left decreasing over time, with change increasing from 0-back to 1-back to 2-back in both medication states. **Discussion.** This is the first study to examine activation changes over time in DLPFC during a working memory task in people with PD. Overall, activation was lower while on medication and PDs demonstrated the ability to modulate activation over time across conditions regardless of medication status, suggesting that despite less dopaminergic activation in the striatum, a stable pattern of activation is exhibited. Condition-related differences in activation appear to be the result of the cognitive effort necessary to perform executive tasks that require inhibition or working memory.

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Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

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Program #/Poster #: 513.17/HHH12

Topic: H.02. Human Cognition and Behavior

Support: U.S. Department of Veterans Affairs (CX000146; CX00813)

Title: Functional reorganization of the inhibition network precedes cognitive impairment in Parkinson's disease

Authors: *D. L. HARRINGTON[1,4], Q. SHEN[5], R. J. THEILMANN[4], G. N. CASTILLO[4], I. LITVAN[6], J. V. FILOTEO[2], M. HUANG[7], R. R. LEE[4], C. S. TAKAHASHI[3]
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Abstract: Introduction: Deficient inhibitory control in Parkinson's disease (PD) is often observed in situations requiring inhibition of impulsive or prepotent behaviors. Although activation of a right-hemisphere frontal-basal ganglia response inhibition network is partly altered in PD, disturbances in interactions of these regions are poorly understood, especially in patients without cognitive impairment. Methods: The present study investigated context-dependent functional connectivity of the response inhibition network in cognitively unimpaired PD patients and controls while performing a stop single task during fMRI. Patients were tested off antiparkinsonian medication. To determine if functional disturbances depended on underlying brain structure, aberrant connectivity was correlated with brain volume and tissue diffusivity. Results: No group differences were found in response inhibition proficiency. Yet the PD group showed functional reorganization in the long-range connectivity of inhibition network regions, despite preserved within-network connectivity. Successful inhibition in PD differed from the control group by strengthened connectivity of the right dorsolateral prefrontal cortex, pre-supplementary motor area and right inferior frontal gyrus with the ventral and dorsal attention networks, the default mode network, and the substantia nigra. In contrast, successful inhibition in healthy controls was distinguished by strengthened long-range connectivity of the right rostral inferior frontal gyrus and subcortical inhibition network nodes (right caudate, substantia nigra, and subthalamic nucleus). In both groups, the strength of regional connectivity correlated with inhibition proficiency, but only for regions that distinguished successful inhibition in the control group. The absence of a relationship between inhibition proficiency and abnormal connectivity in PD may suggest that functional reorganization helps maintain performance at normal levels, but does not correlate with individual variations in inhibitory control. Aberrant functional connectivity for some regions was linked to individual differences in underlying brain structure only in PD participants, despite no group differences in the structural variables. Conclusions: Altogether, the findings demonstrate that functional reorganization of the inhibition network in PD predates the development of inhibition deficits and clinically significant cognitive impairment. Altered inhibition network interactions with attention-related networks and the dopaminergic system may presage future decline in inhibitory control in PD.

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Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

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Program #/Poster #: 513.18/HHH13

Topic: H.02. Human Cognition and Behavior

Support: BBSRC AFL Fellowship to MA BB/M013596/1

Wellcome Trust Fellowship to MH 098282

Title: Dopaminergic tone and apathy modulate foraging decisions in health and Parkinson's disease

Authors: M. A. APPS, C. LE HERON, N. KOLLING, O. PLANT, A. KIENAST, S. FALLON, M. HUSAIN
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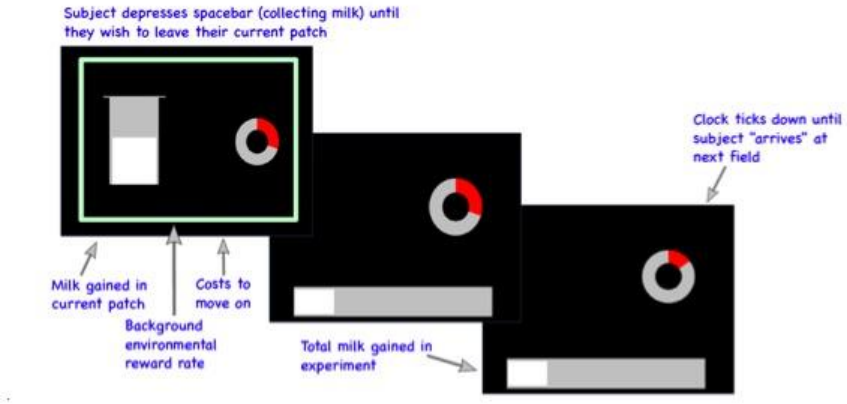
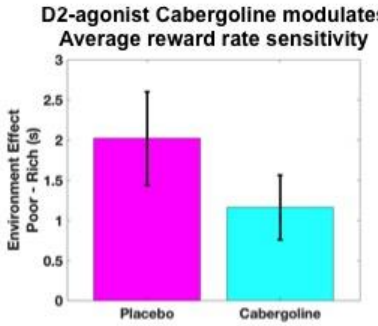
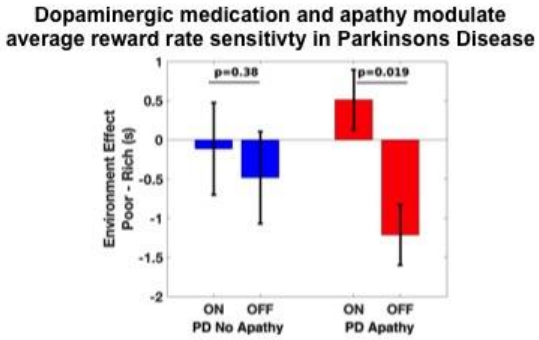
Abstract: Theories of mesolimbic dopamine have long highlighted the role of tonic firing for signalling the 'average' background reward rate in an environment, which in turn serves to invigorate movements. When the average reward rate is high, tonic firing is high, leading to faster movements. Yet, mesolimbic dopamine is also implicated in motivation and decision-making, with degeneration in Parkinson's Disease (PD) linked to apathy - a reduction in goal-directed behaviour. However, little is known about how - or whether - dopaminergic tone signals the average reward rate for more abstract behaviours, nor whether disrupted tonic dopamine can provide a framework for apathy in PD.

Here, to precisely manipulate both the average background and foreground (instantaneous) reward rates we used an abstract 'patch-leaving' foraging task in which participants have to decide "when to leave". Participants received rewards continuously within 'patches', with accrual exponentially depleting at one of three rates (high/medium/low yield). These patches were situated in either rich (more high yield patches on average) or poor environments (more low yield patches on average). By measuring time spent in a patch we could precisely quantify people's sensitivity to changes in foreground and background reward rates. We examined the effects of (i) dopamine D2-agonist Cabergoline compared to placebo in healthy people (n = 29) and (ii) dopaminergic medications (on vs off) in apathetic vs non-apathetic PD patients (n = 35). Strikingly, manipulating tonic dopamine in both healthy people and PD patients selectively modulated patch leaving times in response to changes in the background - and not foreground - reward rates. In addition, only apathetic PD patients, rather than non-apathetic, show an effect of dopamine on their sensitivity to the background rate.

These findings suggest that tonic dopamine may selectively modulate people's processing of the background average reward rates in an environment which impacts on abstract foraging decisions, and that disruptions to dopaminergic tone may underlie apathy in PD.







Disclosures: M.A. Apps: None. **C. Le Heron:** None. **N. Kolling:** None. **O. Plant:** None. **A. Kienast:** None. **S. Fallon:** None. **M. Husain:** None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

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Program #/Poster #: 513.19/HHH14

Topic: H.02. Human Cognition and Behavior

Support: BBSRC AFL Fellowship to MA (BB/M013596/1)
Wellcome Trust Fellowship to MH (098282)

Title: Tired of working: Neurocomputational mechanisms of the effects of fatigue on effort-based decisions

Authors: *T. MÜLLER[1,2], C. LE HERON[3,2], M. HUSAIN[1,3,2], M. A. J. APPS[1,2]
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Abstract: Prominent theories suggest that fatigue - a feeling of exhaustion arising from effortful exertion - has a significant impact on motivation, reducing the willingness to exert effort over time. A considerable body of research has identified the role of sensorimotor brain systems in effortful behaviour and implicated fronto-striatal systems in ascribing value to - and motivating - the exertion of effort. However, the majority of studies assume that motivation is static. As a result, how these systems change in response to fatigue, and how this modulates effort-based choices, is poorly understood. Using an effort-based decision-making paradigm in combination with computational modelling and fMRI, we were able to quantify the neural mechanisms underlying moment-to-moment fluctuations in fatigue and their effects on effort-based decisions. Young healthy participants (N = 32) made a series of choices between two alternatives: a rest option for a low reward (1 credit) or a work option, requiring the exertion of one of three levels of grip force (30-48% of their maximal grip strength), for one of three higher amounts of reward (6-10 credits). Computational modelling revealed that the willingness to exert effort, in particular high effort, declines over trials as a function of (i) the effort previously accumulated over the course of the whole task and (ii) a recoverable component that increases after effortful trials and is restored by rest trials. fMRI analysis suggests that the effects of fatigue on subsequent motivation are mediated by sensorimotor systems as well as by fronto-striatal systems previously implicated in effort-based decision-making.

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Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

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Program #/Poster #: 513.20/HHH15

Topic: H.02. Human Cognition and Behavior

Title: Effect of Neuroinflammation o the glymphatic clearance of macromolecules in an LPS model

Authors: *S. SUESH, K. JENROW
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Abstract: Introduction: Recent evidence suggests that the clearance of macromolecular waste from the brain occurs primarily via the glymphatic system during slow wave sleep and also under anesthesia. Movement of subarachnoid CSF into and out of the brain occurs within perivascular space and the flux of CSF-ISF through interstitial space is facilitated by specialized water channels called aquaporins (AQP) localized on astrocytic endfeet processes. We hypothesized that chronic neuroinflammation, induced by lipopolysaccharide (LPS), might be sufficient to impair glymphatic clearance by disrupting the distribution of AQP and/or by restricting the movement CSF-ISF through intersititial space. Methods: Chronic

neuroinflammation was induced in male Sprague Dawley rats via single i.p. injections of LPS (5 mg/kg) or saline (Control). Four weeks later, florescently-tagged dextran tracers (3 KD Texas red, 10 KD FITC) were injected into the cisterna magna. Cohorts were sacrificed 15, 30 and 45 minutes post-injection, with 1 ml blood samples drawn from the heart prior to perfusion. Brains were removed and postfixed for 48 hours before being vibratome sectioned at 100 µm for ex vivo imaging. Separate groups of LPS and Control animals were assayed for cognitive deficits (open field, novel object recognition, and contextual fear conditioning) with brain tissue subsequently processed for immunohistochemistry and western blots for Aquaporin-4, amyloid beta, and GFAP. Results: Relative to Controls, serum dextran concentrations were significantly reduced in the LPS group. Ex vivo imaging analysis also revealed qualitative and quantitative reductions in tracer distribution. Contextual fear conditioning was also impaired in the LPS in group, however open field and novel object recognition were not impaired. Observable differences in amyloid beta and aquaporin distribution were seen in the LPS brains compared to control, whereas the distribution of GFAP was unchanged. Conclusions: Our results suggest that chronic neuroinflammation alone is sufficient to impair glymphatic clearance from the brain, resulting in selective functional impairment, and is likely a major contributor to age-related cognitive decline and associated neurodegenerative disease processes

Disclosures: S. Suesh: None. **K. Jenrow:** None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

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Program #/Poster #: 513.21/HHH16

Topic: H.02. Human Cognition and Behavior

Support: CIHR Grant MOP-FDN-148418

Title: Oculomotor behavior as a measure of cognitive control in psychiatric illness

Authors: *R. YEP[1], B. COE[1], D. BRIEN[1], C.-A. WANG[1], J. HUANG[1], A. MARIN[2,1], D. MUNOZ[1,3]
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Abstract: Diagnosing psychiatric illness is often complicated by the heterogeneity of clinical populations and the overlap in diagnostic criteria between disorders. This is evident in disorders such as attention-deficit hyperactivity disorder (ADHD), bipolar disorder (BD), and borderline personality disorder (BPD), which, despite differences in age of onset and course of illness, share symptomology and behavioural deficits which can be difficult to differentiate. Our understanding of the pathophysiology underlying these disorders is currently limited by a lack of behavioral

biomarkers to support clinical assessment and diagnosis. Deficits in cognitive control present as an ideal domain to assess to establish such biomarkers, however few studies have directly compared ADHD, BD, and BPD individuals using paradigms which reliably probe the fronto-striatal circuitry underlying these behaviors. The goal of this exploratory study was to characterize adults with ADHD, BD, and BPD on a saccade paradigm shown to be a robust measure of cognitive control. Given the extensive overlap of oculomotor circuitry with the regions of the brain involved in cognitive control, we hypothesize that performance on this task may identify subtle differences between clinical groups which traditional clinical assessments are not sensitive enough to capture. ADHD, BD, BPD, and sex- and age-matched healthy control participants performed an interleaved pro/antisaccade task (look towards vs. look away from a visual target, respectively). Oculomotor behavior, including saccadic reaction time, direction error percentage, microsaccade rate, and pupil response was compared between pro/antisaccade trials and participant groups. Consistent with previous findings, oculomotor measures differentiated prosaccade from antisaccade trials across all participant groups. Clinical groups performed poorly on this task as compared to healthy controls, indicating deficits in cognitive control. Differences between clinical groups in saccade, microsaccade, and pupil response behavior further indicated differences in the recruitment of fronto-striatal circuitry while performing the task. These findings support the notion for cognitive control as a candidate domain to assess in ADHD, BD, and BPD to establish valid behavioral biomarkers, and that oculomotor measures such as saccades, microsacccades, and pupil response can provide a sensitive means of assessing the circuitry underlying these deficits. Further characterization of these deficits will be an important step forward in developing behavioral biomarkers to aid in the understanding, diagnosis, and treatment of these disorders.

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Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

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Program #/Poster #: 513.22/HHH17

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH103366-01A1

Title: Cognitive control in psychosis: An fMRI and saccadic eye movement study

Authors: *B. S. JACKSON[1], C. R. BURTON[2], E. R. AUGER[1], A. L. RODRIGUE[4], M. S. KESHAVAN[5], G. D. PEARLSON[6], E. S. GERSHON[7], C. A. TAMMINGA[8], B. A. CLEMENTZ[3], J. E. MCDOWELL[3]
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Abstract: Saccadic eye movements have been implemented to examine behavioral and neural processes involved in cognitive control. Samples with psychosis show impairments to various aspects of cognitive control, including attention, inhibition and working memory, but it is still unclear what underlying neural functioning is implicated in these problems. The current study utilized a series of saccadic eye movement tasks and functional magnetic resonance imaging to examine behavior and brain function in samples with psychosis. Subjects were recruited from a sample of the Bipolar and Schizophrenia Network for Intermediate Phenotypes consortium and had a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder with psychosis. Healthy control subjects were compared to the groups with psychosis in order to examine neural correlates of cognitively complex saccadic tasks. Participants performed prosaccades (a reflexive, more autonomic task) and antisaccades (a cognitively complex task) in the MRI scanner. Behavioral and brain responses were compared between the prosaccade task and the antisaccade task as well as between healthy control subjects and the differing psychosis groups. Individuals with psychosis made significantly more errors on the antisaccade task compared to healthy control subjects. Between the psychosis groups, individuals with schizophrenia made the highest percentage of errors, followed by the individuals with schizoaffective disorder, and those with bipolar disorder made the fewest. In terms of brain function, groups with psychosis had significantly less overall activation in the brain during these tasks compared to healthy control subjects. Additionally, groups with psychosis displayed distinct patterns of neural activation; in the right cuneus individuals with schizoaffective disorder had more overall activation than those with schizophrenia. However in frontal, parietal, and striatal regions individuals with schizophrenia had more overall activation than those with schizoaffective disorder. These differing patterns of neural activation may provide critical information for understanding similar and distinct networks contributing to clinical disorders characterized by psychosis.

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Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

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Program #/Poster #: 513.23/HHH18

Topic: H.02. Human Cognition and Behavior

Support: UCSD ORA Grant

Title: Creativity in autism: An integrative interaction-based approach to studying creativity in interaction

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Abstract: Using methods from cognitive and computational neuroscience as well as the social sciences, we present a novel approach to studying creativity in children diagnosed with autism spectrum disorder (ASD). Previous research in this area tends to be divided between biological and social science approaches, with little integration. While laboratory research on the biological markers of autism tends to study children in isolation, performing decontextualized tasks, social science research focuses on the child in situated, daily interaction with family members, educators and clinicians. An influential study (Abell, Happé & Frith, 2000) asked ASD and typically-developing (TD) participants to watch stop-motion animations of moving triangles made to evoke descriptions of random interactions, goal-directed interactions, or mentalising. The study's findings—that while ASD populations used mentalising language, they identified *inappropriate* mental states, and were thus impaired in this domain—seem less robust in light of a subsequent finding that lower performance on *appropriateness* aligned neither with parent-reported behavior, nor with the child's interaction with an observer (Salter et al. 2008). In the present preliminary study, we took a different approach and instead attempted to capture *alternate styles of creativity*—including in regards to mentalizing as an interpretive or expressive strategy—in ASD-diagnosed and TD children (10-17 yrs, n=8), who were given the opportunity to create their own DIY stop motion animations in open-ended collaboration with a researcher. Their interaction was video recorded, and data from gaze tracking, body motion and EEG were collected from both the participant and researcher. Using qualitative social science methods, specifically an ethnomethodological approach that tracks locally emergent meaning in naturally occurring interaction, the video was analyzed to identify meaningful events characterized by shifts in communication strategies and the emergence of shared objects of attention. These events

of interest (EOIs) guided statistical analyses of the neuroscience data to identify patterns of correlated activity at the level of gaze and bodily movement, and were further correlated with neural activity during such EOIs. While in this pilot study each participant worked collaboratively with a researcher, a future study will examine peer-dyads (ASD-TD, TD-TD, ASD-ASD). We expect this work to contribute to supporting inclusion and expression for growing numbers of ASD children in educational contexts, as well as to broader methodological questions in creativity research.

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Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.24/HHH19

Topic: H.02. Human Cognition and Behavior

Title: Predictive processing in changing environments in autism: Electrophysiological, pupillometric and behavioral assays

Authors: *S. TIKIR, S. MOLHOLM
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Abstract: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by deficits in social communication, as well as restricted and repetitive patterns of behavior. Several groups consider ASD a disorder of prediction, proposing a link between predictive impairments and insistence on rituals (Sinha et al., 2014; Van de Cruys et al., 2014). Given evidence that environmental unpredictability is strongly correlated with anxiety and ritualistic behaviors, repetitive behaviors and insistence on sameness may be a way to alleviate anxiety arising out of unpredictability. In a volatile environment where contingencies fluctuate often and predictions are violated recurrently, neurotypical individuals opt for a low level of confidence (precision), and thus prediction errors are less surprising; whereas in a low volatility environment, one tends to be highly confident in their predictions, and get surprised when they are violated. Individuals with ASD are often bothered by seemingly trivial changes in everyday life, leading us to hypothesize that they are lacking a specific ability that is crucial in predictive processing: flexibly adjusting the confidence level of predictions according to volatility in the environment. To test this, we first trained adults with and without ASD to perform a sequential pattern recognition task, where shapes are presented in specific orders. We then presented conditions with varying levels of pattern violation and environmental volatility, while high-density electroencephalography (EEG), behavioral responses and pupillometry were recorded.

To understand whether the environmental volatility was accurately estimated in ASD, we measured changes in pupil dilation, which served as a proxy for surprise (Lawson et al., 2017). An abnormal absence of surprise upon a prediction error is evaluated as volatility overestimation, while an abnormal increase in surprise levels upon prediction error is evaluated as volatility underestimation. Evoked response potentials (ERPs: CNV, P300, and error related responses) and reaction times were analyzed to infer predictive processing mechanisms (Thillay et al., 2016). Preliminary analysis of the data indicate that our manipulation of volatility is effective. Ongoing analysis is directed at determining whether the data support the thesis that volatility estimation is impaired in ASD.

Disclosures: S. Tikir: None. **S. Molholm:** None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

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Topic: H.02. Human Cognition and Behavior

Support: Peter Bossaerts received financial support from the University of Melbourne through the R@MAP program.
Carsten Murawski received financial support from the University of Melbourne in the form of a Faculty of Business and Economics Strategic Research Initiatives Grant.

Title: Use of pharmaceutical cognitive enhancers in the Australian financial services industry

Authors: *E. A. BOWMAN, B. FENG, C. MURAWSKI, P. BOSSAERTS
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Abstract: There is growing interest in the non-medical use of so-called “smart drugs” (such as methylphenidate, amphetamine and modafinil) to enhance cognitive performance. This has been explored in college students, medical students and surgeons in the US and Europe. Here we present the an anonymous online survey of “smart drug” use among professionals working in the Australian financial services industry. Our primary hypothesis was that different industry sectors would report use of different drugs in response to different workplace task demands. The survey was advertised at presentations to industry groups, in online media articles, and social media outlets between September 2016 and October 2017. 372 responses were received, of which 140 were valid and complete, and 69 were variously incomplete but usable. 182 responses answered the major question of interest: “Do you believe your colleagues take any drugs that enhance their performance?”. 68 responded “Yes” and 114 responded “No” (37.4%). Different sectors of the financial services industry reported significantly different rates of use among colleagues (Pearson’s chi-squared test, $\chi^2(4)=19.39$, $p = 0.0006$). Respondents from capital markets and

trading, and from asset management, most frequently reported cocaine use in the workplace. However, respondents from commercial banking more frequently reported modafinil, amphetamine and methlyphenidate use. Participants were asked about their workplace, industry sector, hours worked per week, and other demographic and personal health factors. There was a significant difference in reported hours slept per night between those who reported workplace use and those who didn't ($\chi^2(6)= 19.54$, $p = 0.003$). A number of side effects were also reported, including headaches and mood swings. Significant variation in the total rates of reported use of pharmacological cognitive enhancement was found between different sectors of the Australian financial services industry. However, differences between rates of use of different substances nominated by respondents from different sectors did not reach significance. This is an important first step in exploring the use of attempted cognitive enhancement in professional competitive workplaces with diverse task demands.

Reported use by by sector, by substance.

	Capital markets and trading	Asset management	Commercial banking	Retail banking	Other	Totals
Cocaine	7	6	5	1	11	30
Amphetamines	3	4	7	0	9	23
Modafinil	4	4	8	0	6	22
Benzodiazepine	5	4	3	0	7	19
Methylphenidate	3	2	7	0	4	16
SSRIs	2	3	2	0	7	14
Betablockers	2	2	2	0	2	8
Piracetam	2	1	3	0	1	7
Ketamine	1	3	0	0	3	7
Donepezil	1	0	1	0	1	3
Methedrone	1	0	1	0	1	3
Atomoxetine	0	0	0	0	1	1
Other	1	1	0	1	1	4
Totals	32	30	39	2	54	157

Disclosures: E.A. Bowman: None. **B. Feng:** None. **C. Murawski:** None. **P. Bossaerts:** None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.26/HHH21

Topic: H.02. Human Cognition and Behavior

Support: NIH grant R01 AA016624
NIH grant 32 AA013525
NIAAA, Laboratory of Neurogenetics

Title: Genetically determined cortical dopamine availability modulates alcohol-induced impairments in error-monitoring

Authors: J. HAPPER[1], C. A. HODGKINSON[2], D. GOLDMAN[2], *K. MARINKOVIC[1,3]
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Abstract: Moderate alcohol intoxication impairs inhibitory control and performance monitoring, resulting in the inability to flexibly respond to environmental demands and compensate for errors. Extensive evidence suggests the anterior cingulate cortex (ACC) is the central node subserving performance monitoring and post-error adjustments. It is a principal generator of theta oscillations during cognitive control tasks and is particularly sensitive to acute alcohol intoxication. It is also a major recipient of mesocortical dopaminergic projections. This study examined the role of dopamine (DA) availability in alcohol's disruptive effects on the oscillatory dynamics of performance monitoring during response inhibition. DA availability was estimated via *COMT* $Val^{158}Met$ (rs4680) genotype which has functional consequences for DA metabolism and has been shown to correlate with DA availability. Young, healthy social drinkers with no personal or familial alcohol-related problems homozygous for the Val^{158} (low DA) or Met^{158} (high DA) alleles participated in both alcohol (0.6 g/kg ethanol for men, 0.55 g/kg women) and placebo sessions in a counterbalanced design. The Go/NoGo task required response inhibition on 20% of the trials (NoGo). Whole-head magnetoencephalography signals during error and matched correct trials were decomposed with wavelets for the theta (4-7Hz) frequency band. Event-related spatiotemporal source power estimates were obtained with an anatomically-constrained minimum norm inverse method which combines MEG and structural MRI for each subject. Alcohol intoxication selectively decreased error reaction times overall, but no genotype differences were detected. Error-related processing was characterized by increased theta in the bilateral inferior frontal cortices, which was especially prominent for met/met homozygotes. With alcohol intoxication, met/met homozygotes showed greater theta power attenuation in the ACC and right prefrontal cortex compared to val/val homozygotes. This attenuation correlated with higher breath alcohol concentration and impulsivity scores for met/met homozygotes. Taken together, these data indicate that while greater frontal DA availability facilitates phasic responses to salient stimuli under placebo, alcohol-induced attenuation of neural activity to errors in met/met homozygotes is modulated by dopamine. These findings are consistent with other evidence suggesting that heritable variation in the *COMT* gene conferring greater frontal DA availability is associated with increased vulnerability to alcohol effects during performance monitoring.

Disclosures: J. Happer: None. **C.A. Hodgkinson:** None. **D. Goldman:** None. **K. Marinkovic:** None.

Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.27/HHH22

Topic: H.02. Human Cognition and Behavior

Support: Supported by a Wellcome Trust Senior Investigator award to TWR 104631/Z/14/Z

Title: Deterministic and probabilistic reversal learning in obsessive compulsive disorder

Authors: *A. M. APERGIS-SCHOUTE[1], F. F. VAN DER FLIER[3], J. W. KANEN[4], N. A. FINEBERG[5], B. J. SAHAKIAN[2], T. W. ROBBINS[6]
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Abstract: Obsessive-compulsive disorder (OCD), which affects approximately 2.5% of people worldwide and is characterized by intrusive thoughts and repetitive behaviour, also has cognitive flexibility as an endophenotype. Reversal learning, modulated by punishment and reward, has provided a powerful translational tool for investigating cognitive flexibility in humans, monkeys and rats. We used a probabilistic single reversal and a deterministic reversal learning paradigm with three reversals to determine how OCD patients were influenced in reversal learning, as well as by positive and negative feedback. We tested 49 OCD patients (28 medicated (predominantly with selective serotonin reuptake inhibitors (SSRI)) and 21 unmedicated) matched with 48 healthy controls. Our probabilistic paradigm (80% true feedback and 20% spurious feedback) revealed profound deficits in OCD patients in all four domains, with reduced adaptive behaviour (win-stay to true feedback and lose-stay to spurious feedback) and increased maladaptive behaviour (lose-shift to spurious feedback and win-shift to true feedback). Spurious negative feedback during acquisition prior to probabilistic reversal caused deficits only in medicated OCD patients, whereas both medicated and unmedicated OCD patients were impaired during reversal. Our novel deterministic paradigm, however, revealed a true reversal deficit in OCD patients under punishment (monetary loss), with intact performance only on the initial learned rule, and impaired performance after the first and final reversal, in both medicated and unmedicated patients. The combination of these two reversal paradigms demonstrates that cognitive inflexibility in OCD is exacerbated by uncertainty (probabilistic feedback) and by punishment, as shown by our novel deterministic reversal paradigm. They also show that the effects may occur independently of serotonergic medication, but is unclear whether this benefits or further impairs performance. The data are relevant to previous data showing abnormalities in

orbitofronto-striatal systems in OCD and to work with experimental animals confirming a role for homologous structures in reversal learning, modulated by serotonin transmission.

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Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.28/HHH23

Topic: H.02. Human Cognition and Behavior

Support: NINDS R01NS092701
NIH 5KL2TR001421
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Virginia Tech
Wake Forest School of Medicine

Title: Simultaneous sub-second measurements of dopamine and serotonin in human striatum reveals that neuromodulatory signals are disconnected from behavior in patients taking SSRIs

Authors: *K. T. KISHIDA[1,2], R. J. MORAN[3], J. P. WHITE[5], T. M. LOHRENZ[6], I. SAEZ[7], A. W. LAXTON[2], M. R. WITCHER[2], S. B. TATTER[2], E. LAWRENCE[5], P. E. PHILLIPS[8], P. DAYAN[9], P. R. MONTAGUE[5,10,4]
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Abstract: The impact that selective serotonin reuptake inhibitors (SSRIs) have on adaptive learning signals delivered by serotonin, and also dopamine, in the human brain is unknown. Concentrations of these neuromodulators fluctuate on timescales of tens-to-hundreds of milliseconds. Until recently, technological barriers have prevented direct sub-second measurement of dopamine and serotonin in the human brain during conscious behavior. Here, we report and compare simultaneous and colocalized sub-second (10Hz) measurements of dopamine and serotonin release in the striatum of patients with Parkinson's disease (PD) who were (N=9) or were not (N=10) taking selective serotonin reuptake inhibitors (SSRIs). These measurements

were performed while volunteers performed a monetarily incentivized sequential investment game that has previously been shown to elicit positive and negative reinforcement learning signals that guide value-based choices (Lohrenz et al., 2007; Kishida et a., 2016; Moran et al., 2018). PD patients not taking SSRIs (N=10) perform this task in a manner similar to healthy participants. PD patients taking SSRI's (N=9) show significant differences in behavior (lower average investments and more impulsive changes in investment size), along with significant differences in dopamine and serotonin fluctuations on sub-second time scales. Whether the differences in behavior and neurochemical signals are caused by SSRIs or are the cause of the symptoms for which the SSRIs are prescribed is unknown; however, these data are consistent with SSRI driven enhancement of dopamine and serotonin co-release from the same terminals (Zhou et al., 2005). Further our results support the soft cross-wiring hypothesis (Montague et al, 2016), which proposes an efficiency framework for understanding how dopamine and serotonin co-release could enhance how value-predicting information is integrated into an adaptive decision-making process.

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Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.29/HHH24

Topic: H.02. Human Cognition and Behavior

Title: A multimodal neuroimaging investigation of the neural correlates of doubt in obsessive-compulsive disorder

Authors: *A. I. GOLD[1,2], L. Y. CHEN[2], K. H. ALM[2], K. E. TOBIN[2], C. L. SPECK[2], J. KRASNOW[2], J. SAMUELS[2], V. KAMATH[2], G. NESTADT[2], A. BAKKER[3]
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Abstract: Doubt can be defined as a lack of certainty or confidence in one's memory, attention, intuition, and perceptions, making it difficult to trust one's internal experiences and hindering satisfactory responses to information. In extreme cases, as is the case in patients with obsessive-compulsive disorder (OCD), this may present as a clinically-relevant trait, e.g. repetitive checking behaviors or contamination concerns, causing functional impairment. While a number of studies have observed alterations in brain regions implicated in decision-making, confidence, or uncertainty in patients with OCD, the neural correlates of doubt, in the context of anxiety disorders and OCD, remain poorly understood.

The current study aimed to identify neural correlates of doubt using high-resolution functional and diffusion-weighted neuroimaging methods in a sample of age- and education-matched female participants, stratified into high doubt and low doubt groups using the Doubt Questionnaire (DQ). In the scanner, participants were asked to make a perceptual decision in a random-dot matrix task, which was designed to induce doubt and explore brain regions involved in decision formation and subjective uncertainty.
Participants with high doubt showed elevated task-related activation when compared to those with low doubt. Specifically, the left insula and left fusiform gyrus showed significantly increased activation in the high doubt group compared to the low doubt group. Activation in the insula was positively correlated with scores on the DQ, the Decision-Making Questionnaire (DMQ), the State- and Trait-Anxiety Inventory, and the Beck Depression Inventory (BDI), but not with scores on the Obsessive-Compulsive Inventory (OCI-R). Fusiform activation did not correlate with any behavioral measures, including the DQ. Additionally, analyses of the diffusion-weighted images revealed significantly decreased fractional anisotropy (FA) values in the white matter surrounding the left insula, suggesting altered white matter integrity in participants with high doubt compared to those with low doubt. Across the total sample, mean FA was negatively correlated with the DQ, as well as state- and trait-anxiety levels, but was not significantly correlated with the DMQ, OCI-R, or the BDI.
These results suggest that the insula may play a critical role in the experience of subjective doubt and anxiety levels. Moreover, these findings are consistent with the idea that doubt may constitute a trait dimension common to cognitive function and perception that finds its pathological expression in psychopathologies like anxiety disorder and OCD.

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Poster

513. Human Cognition and Behavior: Effects of Disorders and Addictive Drugs

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 513.30/HHH25

Topic: H.02. Human Cognition and Behavior

Support: DFG Grant BR1766/4-1

Title: Deciding without consequences: Revisiting indecisiveness in individuals with obsessive-compulsive disorder

Authors: *B. ZUROWSKI[1], A. RUBART[2], T. VAN EIMEREN[3], A. WAHL-KORDON[2], H. R. SIEBNER[4], F. HOHAGEN[2]

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Abstract: INTRODUCTION: The observation of every-day problems in decision making in patients with obsessive-compulsive disorder (OCD) is reflected by their inclusion in psychometric scales for OCD and even the existence of OCD-specific indecisiveness scales along with concepts formulating OCD as a disorder of decision-making (DM). Nevertheless, experimental studies in OCD patients did not consistently find deficits in DM. Most importantly, typically employed experimental paradigms like the Iowa Gambling Task often cannot disentangle DM deficits from possible deficits in working memory capacity, reward/punishment processing, planning and strategy switching or even symptom provocation by obsession-related experimental material. METHODS: We conducted an event-related 3T-fMRI study in 12 unmedicated OCD patients and 10 healthy controls. We used a forced-choice reaction time (RT) paradigm with parametrically increasing number of choice alternatives (0-4). Choices were based on abstract stimuli and rules, with no feedback provided. RESULTS: As expected both groups showed nearly errorless task performance and increasing RTs with increasing number of choice alternatives (0-4). This effect was paralleled by a parametrically increasing recruitment of a bilateral parieto-premotor-prefrontal cortical network and the cerebellum in all subjects. However, we did not observe any group differences applying a p=0.05 (FDR) threshold with correction for multiple comparisons in SPM8. Analoguously, patients with OCD did not differ from controls regarding error rate or RT. DISCUSSION: Using a "purified" DM task we suggest that forming and executing simple decisions without switching contingencies and without delivering reward or punishment is unimpaired in OCD, both in behavioural and neural terms. Further studies will need to determine which additional task requirements associated with DM may be responsible for observable deficits.

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Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

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Program #/Poster #: 514.01/HHH26

Topic: H.02. Human Cognition and Behavior

Support: DARPA TNT N66001-17-2-4008
NIH R01-DC015504
NIH R01-DC012379

Title: Learning novel speech sounds reorganizes acoustic representations in the human superior temporal gyrus

Authors: *H. G. YI[1], M. K. LEONARD[1], B. CHANDRASEKARAN[2], K. V. NOURSKI[3], M. A. HOWARD, III[4], E. F. CHANG[1]
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Abstract: Speech perception requires listeners to be sensitive to a wide range of acoustic cues for phonetic category, speaker identity, and pitch. Although these cues exist in all languages, they are often used differently, which presents challenges when listening to an unfamiliar language. For example, whereas English uses pitch primarily to signal a variety of prosodic cues, Mandarin Chinese also uses four distinct pitch patterns, called lexical tones, to change word-level meaning. Here, we ask whether learning to identify lexical tones is associated with the emergence of new neural representations, or whether existing pitch representations used for prosody are reorganized to accommodate lexical tone. To answer this question, we directly recorded cortical activity using electrocorticography in humans while they performed a multi-day training task to learn to identify tones from words produced by male and female native Mandarin Chinese speakers. We found neural populations in bilateral mid-anterior superior temporal gyrus (STG) that were highly selective for particular tones, independent of phonetic or speaker information. Crucially, behavioral performance was associated with neural clustering of tones in these populations, such that increased identification accuracy was associated with more distinct neural representations. Finally, we demonstrate that neural representation of Mandarin Chinese tones in STG reflected the same representation of relative pitch that encoded lexical stress in English sentences. Together, these results demonstrate that learning to identify unfamiliar speech sounds enhances pre-existing representations of the relevant acoustic cues, rather than generating novel encoding patterns.

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Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

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Program #/Poster #: 514.02/HHH27

Topic: H.02. Human Cognition and Behavior

Support: NYUAD Institute G1001
European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie Grant Agreement No. 660086
5R01DC005660

Title: Parsing continuous speech into linguistic representations

Authors: *L. GWILLIAMS[1], J.-R. KING[2], D. POEPPEL[1]
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Abstract: Language comprises multiple levels of representation, from phonemes (e.g. /b/ /p/) to lexical items (e.g. bear, pear) to syntactic structures (e.g. bears [SUBJECT] eat [VERB] pears [OBJECT]). Here we address two research questions that arise in online processing of naturalistic speech: 1) which representational *states* are encoded in neural activity; 2) what overarching *algorithm* orchestrates these representations to ultimately derive meaning? Eighteen participants listened to four narratives that were fully annotated - from speech sounds to syntactic structures - such that each level could be correlated with brain activity. Two ~1 hour sessions were recorded from each participant. This naturalistic but controlled setup allowed us to decode, localise and track phonological, lexical and syntactic operations from magnetoencephalography recordings (MEG) using machine learning approaches. First, acoustic-phonetic features (e.g. voicing, manner, place of articulation) could be successfully discriminated from a sequence of neural responses unfolding between ~100 ms to ~400 ms after phoneme onset. Second, part of speech (e.g. verb, noun, adjective), indicative of lexical processing, was decodable between ~150 ms and ~800 ms after word onset. Third, we could decode and track proxies of both syntactic operations (e.g. number of closing nodes) and syntactic states (e.g. depth of tree). Interestingly, some of these syntactic representations were clearly present several hundreds of ms before word onset, whereas others maximally peaked ~300 ms later. These sustained and evoked MEG responses suggest that the human brain encodes each level of representation as proposed by linguistic theories. Importantly, the corresponding neural assemblies overlap in space and time, likely facilitating concurrent access across these low-to-high-level representations, in line with a cascade architecture. Finally, our study demonstrates how the combination of machine learning and traditional statistics can bridge the gap between spatiotemporally-resolved neuroimaging data and rich but tractable naturalistic stimuli.

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Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

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Program #/Poster #: 514.03/HHH28

Topic: H.02. Human Cognition and Behavior

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MEXT KAKENHI Grant Number 18H04950 (Nonlinear Neuro-oscillology)
JSPS KAKENHI Grant Number 18H02709
JSPS KAKENHI Grant Number 16K19510

Title: An electrocorticogram analysis based on the theoretical coupling between subpopulation network structure and cross-spectral power

Authors: *N. SATO[1], R. MATSUMOTO[2], A. SHIMOTAKE[3], M. MATSUHASHI[4], T. KIKUCHI[5], T. KUNIEDA[6,5], H. MIZUHARA[7], R. TAKAHASHI[2], A. IKEDA[3]
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Abstract: Our recent computational simulation using biologically plausible network demonstrated the coupling between subpopulation network structure and local field potential (LFP) coherence. This finding has importance in developing an analytical method for evaluating subpopulation network structure based on signals generated in larger spatial scales, such as in electroencephalogram (EEG) and electrocorticogram (ECoG). This method can be used for various types of networks associated with distributed representation, and it is compatible with recent machine learning techniques for visual and auditory signals, or natural languages. The present study aimed to develop a theoretical formulation of the method for estimating the subpopulation network, and to test it using experimental data. First, the theoretical coupling between subpopulation network structure and LFP coherence was successfully transformed into the coupling of cross-spectral power in the EEG-level signals. Individual weights of distributed features at each electrode were calculated by applying multiple regression analysis with a constraint on the theoretical coupling. The estimated weights were used in predicting EEG cross-spectral power in response to novel stimuli. Second, the predictability of cross-spectral power based on the proposed method was tested using ECoG data obtained during a picture naming task from one subject. In the analysis, words were represented by 100-dimensional semantic vectors, which were calculated using the Word2Vec algorithm and a large text database. The predictability was tested with a 20-fold cross-validation procedure; the weights were calculated from training dataset and the predicted cross-spectral power to test set words was calculated by using the estimated weights and compared with true cross-spectral power. Results showed significant predictions in a frequency range of 4-20 Hz as well as 60-100 Hz, and the time period of 0.2-0.8s after the onset time of picture presentation. Pictures with 8 or 16 semantic features had higher predictability than those with 2 or 4 semantic features. This suggests that higher dimensional features contributed to the prediction. Standard regression analysis of cross-or auto-spectral power resulted in significantly lower predictability than that of the proposed method. This study demonstrates that the theoretical coupling between subpopulation network structure and cross-spectral power can be used in ECoG data analysis. However, the stability of the proposed method needs to be assessed further using larger experimental data.

Disclosures: N. Sato: None. **R. Matsumoto:** None. **A. Shimotake:** None. **M. Matsuhashi:** None. **T. Kikuchi:** None. **T. Kunieda:** None. **H. Mizuhara:** None. **R. Takahashi:** None. **A. Ikeda:** None.

Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 514.04/HHH29

Topic: H.02. Human Cognition and Behavior

Support: JST PRESTO

Title: Predictor of programming language learning success: The development of the right inferior frontal cortex and the bilateral supramarginal cortex

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Abstract: About 60 % people could not acquire the ability of programming language(Dehnadi S. et al, 2006). However, an issue remains unsettled if programming language ability relies exclusively on the innately privileged brain structure or function, or is more flexibly shaped through neuroplasticity involving interactions among potentially relevant neural nodes. We investigated whether programming language ability relies on the brain structure or function of individuals, or is shaped through learning. 45 university male students with a mean age of 22.5 years (SD ±1.3, range 19-26) were enrolled. All participants who were new to the programming language underwent 12-week JAVA programming language intervention in everyday. Before and after intervention, we obtained structural magnetic resonance imaging (MRI), multi-angular diffusion-weighted magnetic resonance images (DWI), resting state MRI (rsMRI) and the Test for JAVA programming (Oracle certified Java programmer, Bronze). The average learning time per day was 70.4(±3.1)minutes. However, 25 out of 45 subjects could not acquire the programming ability (poor group). The total learning time was tend to be longer in poor group than in the subjects who could acquire the programming ability (good group, n=20) (p=0.06) but the score of JAVA programming test was higher in the good group than that in the poor group(p=0.02). Furthermore, the volume of greater GM before the intervention, the diffusion-based connectivity, and the resting state in the following regions predict whether the subjects could acquire the programming ablirity after intervention; the right inferior frontal cortex(IFG), and the functional and structural connectivity between and supramarginal gyrus(SMG)- inferior frontal pathway. In addition, after the invention, SMG volume and SMG-cerebellum connection changes were positively correlated with improvement of JAVA programming language comprehension. Therefore, the people in good group had greater increase in SMG volume and SMG-cerebellum functional and structural connection compared with others. The present findings provide the first evidence that the development of right IFG and the connectivity between and SMG-IFG pathway are essential factor of acquisition of programming language

ability. Moreover, the acquisition of programming language ability facilitates the plastic change of SMG structure and SMG-cerebellum connection.

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Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

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Program #/Poster #: 514.05/HHH30

Topic: H.02. Human Cognition and Behavior

Title: Resolving discrepancies between incoming auditory information and linguistic expectations

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Abstract: Speech perception in noise is dependent on stimulus-driven and knowledge-driven processes. Here we investigate the neural correlates and time course of discrepancies between incoming auditory information (i.e. stimulus-driven processing) and linguistic expectations (knowledge-driven processing) by including 20 normal hearing adults in a MEG study. Participants read 48 rhyming sentence pairs beforehand. In the scanner, they listened to sentences that corresponded exactly to the read sentences except that the last word (presented after 1600 millisecond delay and with 50% intelligibility) was only correct in half of the cases. Otherwise, it was 1) phonologically but not semantically related, 2) semantically but not phonologically related, or 3) neither phonologically nor semantically related to the sentence. Participants indicated by button press whether the last word matched the sentence they had read outside the scanner. Behavioural results showed more errors in condition 1 than in conditions 2 or 3, suggesting that phonological compatibility overrides semantic discrepancy when intelligibility is poor. Event-related field analysis demonstrated larger activity on frontal sites for correct than unrelated words, suggesting that the former were more accurately expected than the latter. An early M170 component was also observed, possibly reflecting expectation violation in the auditory modality. Dipole analysis will reveal whether M170 could be modulated by type of linguistic discrepancy. Distributed-network analysis will further our understanding of the time course and neural correlates of discrepancies between incoming auditory information and linguistic expectations.

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Poster

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Program #/Poster #: 514.06/HHH31

Topic: H.02. Human Cognition and Behavior

Support: SEV-2015-490
PSI2014-53277

Title: L2 word recognition in noise: Modulatory effects of semantic and crosslinguistic overlap on brain activity

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Abstract: Spoken language comprehension in a second language (L2) depends on the ability to map an acoustic signal onto one of two co-existing acoustic-perceptual systems. This mapping process commonly occurs in noisy listening conditions. The neural systems that support the mapping of sound-to-meaning in L2 and how they are affected by the presence of a native language (L1) are not well understood. Different models of bilingual spoken word recognition predict different types of interactions between L2 and L1. The aim of the current fMRI study is to probe the neuro-functional organization of L2 spoken word recognition. A recent study, conducted in a group of early balanced Spanish-Basque bilinguals, found improved L2 spoken word recognition accuracy in noise when it was preceded by a semantically related L2 prime (semantic priming effect). The semantic priming effect was modulated by the degree to which L2 words shared phonological-lexical overlap with their L1 translation equivalents (Guediche, Baart, Samuel, 2018); greater effects were found for L2 words that share a high degree of overlap (cognate words). Impaired performance was found for cognates in the unrelated context, potentially due to increased competition from L1; the semantic prime may facilitate L2 lexical-semantic integration and inhibit lexical competition effects from L1 over-riding the negative effects of recognition accuracy. We investigate how changes in brain activity are affected by 1) the degree to which L2 words share overlap with L1 translations, 2) semantic priming, and 3) their interaction. Listeners perform a lexical decision task on noisy L2 targets that are preceded by either a semantically related or unrelated L2 prime. Increased lexical competition from L2-L1 phonological lexical overlap should increase activity in brain regions that have been associated with phonological and lexical processing including the superior and middle temporal gyrus (STG) and (MTG). Semantic priming should modulate activity in areas similar to those found for

bilinguals in their L1 including areas such as the angular gyrus (AG) and MTG. Of most interest to the current study is the interaction between semantic priming and crosslinguistic overlap. If semantic priming improves inhibition of L1 competition, interaction effects should recruit brain regions involved in inhibitory control processes such as the inferior frontal gyrus (IFG), potentially affecting MTG activity. Preliminary analyses based of a limited dataset (data collection is ongoing) show semantic priming effects in ATG and MTG, crosslinguistic overlap in MTG and posterior STG, and interactions in middle ATG and left middle frontal gyrus.

Disclosures: A. de Bruin: None. **M. Baart:** None. **A.G. Samuel:** None.

Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

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Program #/Poster #: 514.07/HHH32

Topic: H.02. Human Cognition and Behavior

Support: NINDS R01-NS091139

Title: Spatial-temporal dynamics of neural activity in Broca's area during lexical selection: An intracranial EEG study

Authors: *Y. WANG[1], A. KORZENIEWSKA[2], K. USAMI[3], A. VALENZUELA[2], N. E. CRONE[4]
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Abstract: While it is widely accepted that Broca's area plays an important role in spoken word production, its exact role remains controversial. Previous studies have suggested that Broca's area and adjacent cortex serve as a key network hub for integration of syntactic, phonological, and lexical-semantic representations during comprehension and production of sentences. Using direct intracranial cortical recordings, we investigated the spatial-temporal dynamics of neural activity (indexed by 70-150Hz high gamma frequency band activation) in six patients undergoing invasive monitoring for seizure localization. All patients performed a sentence completion task in which the difficulty of lexical selection (indexed by sentence cloze probability) was systematically varied. Across all six patients, neural activity in Broca's area appeared to accumulate throughout stimulus presentation, and decreased before the onset of response articulation. More importantly, neural activity in Broca's area was significantly higher during completion of sentences with greater demands on lexical selection in the interval between onset of the cue to respond and the response itself, corresponding to lexical selection. Further, analyses of effective connectivity found that more demanding sentences elicited larger neural interactions within Broca's area, as well as between Broca's area and areas in posterior temporal

lobe that have been shown in other studies to store lexical representations. Our findings provide a detailed picture of the fine temporal dynamics by which Broca's area coordinates lexical selection during speech.

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Poster

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Program #/Poster #: 514.08/HHH33

Topic: H.02. Human Cognition and Behavior

Support: National Science Foundation of China (NSFC) 61621136008 and 61473169 (B.H.)

Title: The frequency-band specific information flows in speech network

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Abstract: Characterizing the functional organization of speech network has been a focus of investigating the neural basis of language. Evidences have shown that there exists two cortical areas, roughly over superior temporal gyrus (STG) and inferior frontal gyrus (IFG), which are intensively involved during the speech related tasks, with STG more related to speech perception, and IFG to speech production (Hickok & Poeppel, 2007). Recent studies also found these two speech-related regions could be both activated in the perception and the production process (Cogan, 2014). However, the nature of interactions among this large-scale speech network, has not yet been elucidated. In this study, we recorded the intracranial EEG activities from 121 electrodes in brain-wide speech-related areas in three subjects, covering STG, IFG, anterior temporal lobe (AT), posterior temporal lobe (PT), parieto-temporal boundary (Spt) and motor areas. With high temporal resolution of the intracranial EEG, we characterized the dynamic activities in the speech networks, and quantified causal influences among these major network nodes during resting and speech-evoked states. In the intrinsic speech networks during resting, main information flows sourced from STG and IFG, and targeted to the other speech-related areas including AT, PT, Spt and motor areas. During speech perception and production tasks, strong information flow was found to modulate the high-gamma (60-140Hz) activities of STG & IFG ($p<0.01$, compared to resting state), exhibiting a recurrent pattern of the functional connectivity between STG/IFG and other major nodes of the speech network. We also found that the causal connections in speech network showed a frequency-band specific feature: the causal connections in alpha - beta range (8-32Hz) were insensitive to task involvements, while the high-

gamma band (60-140Hz) was strongly activated during the speech tasks ($p<0.01$). In short, our data revealed distinct pattern of causal connectivity of speech networks during resting and speech task states, with separated frequency bands for networking.

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Poster

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Topic: H.02. Human Cognition and Behavior

Support: Grant U01NS098976
James S McDonnell Foundation

Title: Visual cues contribution to audio-visual speech intelligibility in natural speech

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Abstract: Natural speech perception is multisensory; when conversing with someone that we can see, our brains combine visual information from face, postural and hand gestures with auditory information from the voice. The underlying speech processing is extremely rapid, with incoming audio-visual units arriving every few hundred milliseconds that must be encoded and passed on before the next syllable arrives. It has been suggested that low frequency neuronal oscillations play a key role in the integration of auditory-visual (AV) speech information and that phase reset of auditory oscillations by visual input is a critical step in the integration of auditory and visual speech cues. AV speech is usually studied by (1) using clear speech stimuli that create a ceiling effect for intelligibility, (2) comparing noisy and clear speech that differ in their acoustic properties or (3) presenting purely visual stimuli (lipreading) which is difficult for untrained participants and thus requires several repetitions of the same stimulus. To overcome these limitations, we designed a paradigm in which speech intelligibility is manipulated by presenting short gaps (at a rate of 3-7Hz) within the natural speech stimuli. Our aim was to test whether neuronal oscillations play a key role in the integration of auditory and visual speech information and the specific hypothesis that phase resetting in the low frequency range is the neural mechanism underlying increased intelligibility of AV relative to purely auditory (A) speech. Using ECoG we compared neuronal responses to AV segmented speech vs. auditory

segmented speech. We report that speech intelligibility increases when visual cues are present. Several brain regions showed significant high gamma power (HGP) speech tracking. Interestingly, speech tracking differences between the AV and A conditions were most prominent at electrodes that track the speech to a lesser degree. In addition, we found an increase in low frequency inter-trial coherence (ITC) for AV stimuli. These results suggest that visual speech cues influence auditory cortical processing of speech by phase-resetting its ongoing oscillations.

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Poster

514. Human Cognition and Behavior: Language Networks

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Topic: H.02. Human Cognition and Behavior

Support: Woodcock Institute Research Grant Program
NYUAD Institute Grant 1001
5R01DC05660

Title: The impoverished comprehension of non-native speech in noise

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Abstract: Introduction. There is strong evidence that under unfavorable listening conditions (e.g. noise) bilinguals have a deficit in the comprehension of their second language (L2) compared to their first language, despite performing similarly in quiet listening conditions. Although the prevalence of this phenomenon has been previously established, the causes and neurobiological bases of this dissociation have not been elucidated. In this study we used neural entrainment to different linguistic levels of representation to investigate the bases of the impoverished comprehension of L2 speech in noise.
Methods. We collected MEG data from 40 Chinese-English bilinguals. Participants listened to four-syllable isochronous sentences in English and in Chinese at 4 different levels of noise, ranging from completely clear speech (15 dB) to unintelligible speech in a noisy background (-15 dB), in 7.5 dB intervals. The sentences consisted of 4 monosyllabic words that were combined to form a two-word noun phrase (adjective/adverb + noun) and a two-word verb phrase (verb + noun). The combination of these two phrases resulted in a four-word sentence (e.g., “big rocks block roads”). In order to meaningfully characterize the effect of noise across

varied L2 proficiency levels, we tested bilinguals who were native speakers of Chinese with low level of English (16), with high level of English (12), and native speakers of Chinese who were currently English dominant (born to Chinese parents in the US; 12).
Results. Behavioral results show distinct psychometric curves for the comprehension of L1 and L2 speech, which vary by the language profile of the tested group. MEG results reveal two distinct phenomena: i) the tracking of syllabic rhythm decreases linearly as noise increases; and ii) the tracking of higher level phrasal structure is categorically disrupted by noise, as shown by a) the complete lack of entrainment to phrases at the highest level of noise (-15 dB) regardless of language profile and b) only native speakers (but not L2 speakers) tracking phrasal structures at -7.5 dB.
Conclusion. This study quantifies the influence of noise in the cortical tracking of linguistic structures in connected speech, and provides evidence to suggest that -7.5 dB may be the threshold level of noise at which L2 comprehension is disrupted. Previous research has posited that greater availability of higher-level top-down linguistic information may account for this difference in L1 vs. L2 comprehension. The present study shows that a more automatic lower-level phenomenon, oscillatory tracking of speech, may also underlie the prevalent effect of impoverished comprehension of L2 speech in noise.

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Poster

514. Human Cognition and Behavior: Language Networks

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Program #/Poster #: 514.11/HHH36

Topic: H.02. Human Cognition and Behavior

Support: NIH R01-DC04290

Title: Auditory language localizer: An fMRI/ECoG study with epilepsy patients

Authors: *B. F. SNOAD[1], P. E. GANDER[1], C. K. KOVACH[1], K. V. NOURSKI[1], H. KAWASAKI[1], E. FEDORENKO[2], M. A. HOWARD, III[1]
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Abstract: Language processing is supported by an extensive network including temporal, frontal and parietal regions. Recent electrocorticographic (ECoG) investigations during language-based tasks have provided new insights in functional localization of mechanisms that support language processing. We set out to expand this work using a novel passive auditory language 'localizer' task (Scott et al., Cogn. Neurosci. 2017, 8:167-76) to identify key language cortical regions in surgical epilepsy patients. The 16 pairs of clear and degraded speech monologues presented

across two runs. We collected non-simultaneous functional magnetic resonance imaging (fMRI) and ECoG data in each subject.
The speech vs. silence contrast in fMRI data showed distinct activations in bilateral auditory cortex and planum temporale ($p<0.05$, uncorrected). In each subject, the clear vs. degraded speech contrast showed bilateral superior temporal gyrus activation ($p<0.001$, uncorrected). Less consistent was activation of inferior frontal and premotor cortex. In contrast, degraded stimuli preferentially activated insula, anterior cingulate, orbitofrontal cortex, and prefrontal cortex ($p<0.001$, uncorrected). Strength of activation in these brain regions varied across the subjects in each contrast. Ongoing ECoG analyses will determine the oscillatory correlates of regions activated in the fMRI scan for the same subject. To the extent the ECoG coverage overlaps we hope to uncover the pattern of connectivity among the language network.
These results identify a network of high-level language processing regions at the individual subject level in pre-surgical epilepsy patients and support findings from previous studies. In addition to guiding neuroscientific investigations of language processing, we will be able to compare network level activation between fMRI and ECoG. As language localization is critically important for surgical planning in epilepsy patients, we plan to compare the results we obtain from the localizer task to the gold-standard epilepsy surgical planning data from the Wada test and electrical stimulation mapping results.

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Poster

514. Human Cognition and Behavior: Language Networks

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Program #/Poster #: 514.12/HHH37

Topic: H.02. Human Cognition and Behavior

Support: NIH 1U01NS098968-01

Title: Neural correlates of cognitive state during volitional communication

Authors: *A. E. HADJINICOLAOU[1], G. BELOK[1], J. W. LEE[2], B. S. CHANG[3], S. S. CASH[1]
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Abstract: Over the course of a conversation we make multiple shifts in our overall cognitive state. An understanding of the neural activity underlying these state changes would provide crucial insight into the systems that govern communication, how they are disrupted by neuropsychiatric disease, and how such disruptions might be restored by therapeutic intervention. Although most research on communication and volition thus far has been based on

the results of structured, highly controlled experimental tasks, brain activity is fluid and continuous, with much cognitive activity of interest being internally generated. To examine such processes under more natural conditions, we developed a platform in which the analysis of intracranial recordings from epileptic patients, who are implanted with cortical and subcortical electrode arrays for clinical purposes, can be augmented by information collected from synchronized video and audio recordings. In the present work we analyzed data from N=3 patients, collected using a 128-256 channel neural signal processor recording system (Cerebus, Blackrock Microsystems). The activity of interest was either (i) a loosely-structured conversation (45-120 min) with the experimenter, or (ii) spontaneous conversations with visitors. The majority of spoken dialog during these activities, captured by an audio recorder (H4n, Zoom), was transcribed and processed (CoreNLP, Stanford; in-house software) to yield word lexical categories and their timing within the iEEG recordings. Videos cameras (FireflyMV, Point Grey) captured non-verbal communication and informed the classification of different cognitive states. Intracranial recordings were analyzed in MATLAB (MathWorks) with the NPMK (Blackrock Microsystems) and FieldTrip (Donders Institute) toolboxes. Preliminary analyses suggested that varying speech complexity invoked markedly different spectral content in recordings of patient responses to questions. Specifically, we observed that greater question complexity resulted in greater theta band power, expressed 1-2 s after question onset. In this work we explore the extent to which speech complexity and other factors (e.g. syntactic branching) can modulate or delineate cognitive state changes, and employ coherence analysis to describe these state changes.

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Poster

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Program #/Poster #: 514.13/HHH38

Topic: H.02. Human Cognition and Behavior

Support: NIH 2R01DC05660

Title: The role of pMTG in word learning

Authors: *P. RIPOLLES, D. POEPPEL
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Abstract: The posterior middle temporal gyrus (pMTG) has been suggested as a candidate region to support the sound-to-meaning interface: semantic information—highly distributed throughout cortex—might be accessed (when lexicalized) through the pMTG, the main function of which would be to map phonological representations in superior temporal regions to

extensively distributed semantic representations (Hickok and Poeppel, 2007; Gow, 2012). Here we examine the emergence of new entries in the mental lexicon. Participants learned the name of real but unfamiliar objects (object drawings and descriptions of ancient artifacts previously used in Finnish households) in a gradual manner, over a two week period. In a first fMRI session, participants were aurally presented with 30 new words without meaning. Next, participants were presented with the drawings of 30 new objects with their descriptions (without their name). As control conditions, participants were also presented with 30 well-known objects and their names. In a first week of training, participants were repeatedly presented with the same stimuli once a day using an online training platform. After one week, subjects participated in a second fMRI session in which the first four fMRI runs were as those from the first fMRI session: 30 new (trained during the week) and 30 well-known aurally presented words and 30 new (trained during the week) and 30 well-known objects and their description. Then, on a fifth run we presented, for the first time and together, the new words with the objects that they represent. During the second week of training and once a day, participants were presented with the new words and the objects that they depicted: during the first week, participants had to learn and store phonological and semantic representations of each word separately; during the second, they had to create word-to-meaning mappings. Next, participants came to a final fMRI session in which the new words and their semantic representations were be presented once again. During these 3 fMRI sessions and 2 weeks of training, participants built, step by step, new entries in their mental lexicon: they created a new phonological entry, a new semantic entry and a new link between the two. Importantly to the hypothesis, fMRI activity within the pMTG was modulated by training, increasing from the first to the second MRI session and achieving activity levels similar to those elicited by well-known names of objects by the third MRI. These results further directly support the role of the pMTG as a lexical interface.

Disclosures: P. Ripolles: None. **D. Poeppel:** None.

Poster

514. Human Cognition and Behavior: Language Networks

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Program #/Poster #: 514.14/HHH39

Topic: H.02. Human Cognition and Behavior

Title: Surgical resections reveal functional regions of the temporal lobe for learning and memory

Authors: *K. TOMBRIDGE[1], C. DONOS[1], J. BREIER[2], P. ROLLO[1], J. JOHNSON[1], N. TANDON[1,3]
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Abstract: INTRODUCTION: Brain activation studies using functional MRI and electrocorticography have frequently been used to map language and memory in stroke and epilepsy patients. Voxel-wise lesion-based symptom mapping (VLSM) techniques, typically conducted in stroke patient populations, are vital in delineating the organization of language. This technique ignores both important pre-morbid individual differences and reorganization that might occur after damage while maximizing the predictive power connectivity has on behavioral outcome. By applying this technique in a controlled-lesioned epileptic patient population, we can disambiguate the components of the temporal lobe.
METHODS: We studied the brain-behavior relationships in a sample (n = 60) of individuals who underwent surgery to treat medically intractable epilepsy. These patients underwent one of three surgeries targeted at components of the left anterio-mesial temporal lobe: anterior temporal lobectomy (ATL, n = 10), ATL + Amygdalo-Hippocampectomy (ATL+AH, n = 20), or selective Laser interstitial thermal therapy-based amygdalo-hippocampectomy (LITT, n = 30). Pre- and post-operative behavioral and neuroimaging measures were conducted to measure pre-surgical differences and post-surgery reorganization of functional networks. The neuropsychological test battery included measures of verbal fluency, naming, and memory (semantic, verbal, and spatial). For each patient, we used FreeSurfer software to derive cortical and sub-cortical segmentation of the brain using the pre-operative MRI. Lesion volumes were outlined using a post-operative T1 contrasted MRI in MRIcron software. Seizure outcomes were measured using Engel classification.
RESULTS: Our between-subject analysis of voxel-based lesion symptom mapping yielded a more detailed measure of an individual's pattern of cortical reorganization. Power analyses provided a distinct relationship between percent damage to anterior temporal lobe sub-regions and neuropsychological task performance. Change in error type pre- to post-surgery provided a leveled representation of language.
CONCLUSIONS: This study leverages a unique patient population for lesion-symptom mapping that is unconstrained by limitations inherent to studies of post-stroke patients. Consequently, we can better quantify the functional organization of left language-dominant peri-Sylvian cortex. This will inform future refinement of psycholinguistic models of language and the instantiation of these models in specific neuroanatomic substrates.

Disclosures: K. Tombridge: None. **C. Donos:** None. **J. Breier:** None. **P. Rollo:** None. **J. Johnson:** None. **N. Tandon:** None.

Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

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Program #/Poster #: 514.15/HHH40

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant DC014279
NSF GRFP DGE 1644869
NSF IGERT DGE 1144854

Title: Characterizing the spatiotemporal pattern of neural activity during visual word recognition

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Abstract: Visual word recognition (VWR) is the process of mapping the written form of a word to its underlying linguistic item and is crucial for successful written communication. Characterization of healthy VWR neural mechanisms holds promise for individuals with reading deficits. While noninvasive neuroimaging studies have identified putative brain regions (fMRI, PET) and event-related potentials (EEG, MEG) involved in VWR, the spatiotemporal flow of information through the brain remains unclear. In this study, we analyzed high gamma neural activity from more than 90 intracranial neurophysiology patients as they read visually-presented words. We find that 9.5% of electrodes show a task-sensitive response, including 34% of electrodes in occipital lobe, 7% in frontal lobe, 4.9% in parietal lobe, and 4.8% in temporal lobe. By clustering the responses of all task-sensitive electrodes, we identified a variety of response types, including excitatory and inhibitory responses, onset and offset responses, and responses sustained for the duration of the word presentation. We observe a difference in the excitatory/inhibitory balance between lobes: 90% of responses in occipital lobe are excitatory, while temporal lobe is 76% excitatory, frontal lobe is 55% excitatory, and parietal lobe is 53% excitatory. Latency analyses reveal that on average, occipital lobe responds most quickly, followed by temporal lobe, with the slowest responses from frontal and parietal lobes. Middle occipital gyrus, cuneus, and fusiform gyrus (which contains the visual word form area) are among the fastest areas on average. Together, these results provide a high-resolution look at the spatiotemporal pattern of neural activity during visual word recognition in the human brain.

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Poster

514. Human Cognition and Behavior: Language Networks

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Topic: H.02. Human Cognition and Behavior

Support: NINDS R01 NS050915
NIA P01 AG019724
NIDCD K24 DC015544
NIH R01NS100440
NIA P50 AG023501
NIA U01 AG052943

Title: Taking the sub-lexical route: The spatiotemporal dynamics of reading in semantic variant of primary progressive aphasia

Authors: *V. BORGHESANI[1], L. HINKLEY[2], K. RANASINGHE[1], M. THOMPSON[2], W. SHWE[1], D. MIZUIRI[2], S. HONMA[2], J. HOUDE[3], Z. MILLER[1], S. NAGARAJAN[2], M. GORNO-TEMPINI[1]
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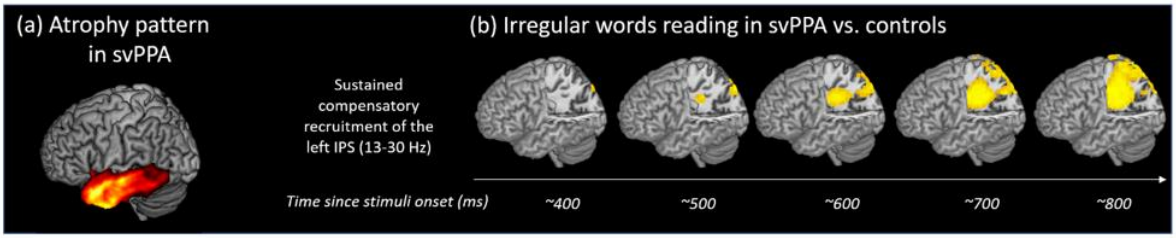
Abstract: According to the dual route model of word reading, words never encountered before can be read only mapping their orthographic representations to plausible phonological forms (i.e., sub-lexical route). Conversely, words with irregular spelling can be read only mapping their orthographic representations to their meaning (e.g., lexical route). This route appears affected by neurodegeneration in patients with semantic variant of Primary Progressive Aphasia (svPPA), who present with surface dyslexia (i.e., an impairment in reading words with atypical spelling-to-sound mapping).We recruited 9 svPPA patients and 12 healthy age-matched controls. All participants underwent comprehensive neuropsychological testing, were right-handed English native speakers and had no history of developmental dyslexia. Participants read regular words (e.g., *fact*), irregular words (e.g., *choir*), and pseudowords (e.g., *pook*), while we recorded brain activity using a 306-channel whole-head MEG system (CTF). We reconstructed and analyzed whole brain oscillatory activity with Nutmeg (nutmeg.berkeley.edu). In controls, the key contrast between pseudowords vs. irregular words revealed differential activity in beta bad (13-20 Hz) over the left IPS (L-IPS, ramping up after stimulus onset and peaking at ~700ms), supporting the involvement of this region in sub-lexical processes. This effect was absent in svPPA patients, and, crucially, direct comparison of svPPA patients and controls during irregular words reading isolated the same spatio-temporal cluster. These findings suggest that patients recruit L-IPS to read not only pseudowords (as controls do), but also irregular words. Taken together, our results

indicate sustained activity over the L-IPS as the neural correlate of svPPA patients' over-reliance on the sub-lexical route, arguably an active compensation for their impairment on the lexical one.



(a) VBM results in svPPA patients illustrating the neurodegeneration affecting the anterior temporal lobe, which leads to the profound semantic knowledge loss manifested by these patients. (b) Results of the direct comparison between svPPA patients and controls during irregular words reading. It indicates heightened recruitment of left IPS in the patient cohort [beta band (13-30Hz), FDR cluster corrected].

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Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

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Program #/Poster #: 514.17/HHH42

Topic: H.02. Human Cognition and Behavior

Support: Erasmus Mundus Postdoc Fellowship in Auditory Cognitive Neuroscience

Title: Causal role of specialized visual cortices in auditory foreign language vocabulary translation

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Abstract: Previous research suggests that multisensory training of foreign languages (L2) yields improved learning outcomes compared to unisensory training. One theory of multisensory learning (von Kriegstein & Giraud, 2006) proposes that improvements in learning outcomes following multisensory training are supported by visual brain responses to previously-learned auditory stimuli. We used the neurodisruptive effects of inhibitory transcranial magnetic

stimulation (TMS) to investigate whether visual cortical responses causally contribute to auditory L2 translation following multisensory L2 training. We targeted with TMS the biological motion superior temporal sulcus (bmSTS). bmSTS responses were previously found to associate with behavioral benefits of performing gestures during learning on L2 translation. According to the multisensory learning theory, inhibitory stimulation of the bmSTS should disrupt the translation of auditorily-presented L2 words if those words have become associated with visual biological motion during learning. Twenty-two adult learners were trained on L2 words and their native language translations over 4 consecutive days. Words were learned in two conditions: In one condition, participants viewed and performed gestures as L2 words were auditorily-presented, and in another condition, participants viewed pictures as L2 words were auditorily-presented. Gestures and pictures were congruent with word meanings. Following training, effective and sham TMS was applied to the bilateral bmSTS while participants listened to the L2 words that they had learned and translated the words into their native language. As expected, TMS of the bmSTS slowed translation response times for L2 words that had been learned while performing gestures compared to sham stimulation. TMS of the bmSTS did not affect translation response times for words learned while viewing pictures compared to sham stimulation. This result suggests that training with gestures led to changes in L2 representations within the bmSTS, which in turn facilitated the translation of L2 words. This effect was observed on the day following the learning period, as well as during a second TMS session that occurred 5 months post-learning, suggesting that cross-modal L2 vocabulary representations develop rapidly and decay slowly following learning. The current findings favor a framework in which improvements in learning outcomes following multisensory training originate in specialized sensory cortices.

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Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 514.18/HHH43

Topic: H.02. Human Cognition and Behavior

Title: Dissociating language and logic using TMS

Authors: *J. P. COETZEE[1], M. M. MONTI[2], M. IACOBONI[3], A. D. WU[4], M. JOHNSON[1]
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Abstract: The relationship between language and abstract thought has long been a topic of intense interest. One theory about this relationship is that the hierarchical and combinatorial operations that subserve natural language also serve as the basis for similar operations in a diverse range of abstract human though, such as mathematics, music cognition, and action

sequencing. With regard to deductive reasoning, there are two extant views about the relationship between this form of abstract thought and language. According to the first, deductive reasoning is parasitic on language, in the sense that the structure dependent operations which underlie deduction make use of the same neural machinery that underlies the structure dependent operations of language, with that common machinery being primarily found in the areas of the inferior frontal gyrus that have been traditionally referred to as Broca's area. According to the second, the structure dependent operations that underlie deductive reasoning, and the neural machinery that make them possible, are independent of and dissociable from the structure dependent operations of language. In this second view, the operations that support language occur primarily in Broca's area, while the operations that support deduction occur primarily in frontomedial (Brodmann area 8) and frontopolar (Brodmann area 10) cortices. We tested these two views using continuous theta burst stimulation (cTBS), a form of patterned transcranial magnetic stimulation (TMS) which has been shown to demonstrate relatively long lived inhibition of neural activity in a localized area. Using this approach, we were able to demonstrate that inhibition of Broca's area impairs accuracy on a linguistic task but not on a matched logic task. Additionally, we found that inhibition of frontomedial cortex (medial BA 8) produced a pattern opposite to that found in Broca's area. These results support the view the structure dependent operations which underlie deductive reasoning are not parasitic on those that support language, but are in fact ontologically distinct from them.

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Poster

514. Human Cognition and Behavior: Language Networks

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Program #/Poster #: 514.19/HHH44

Topic: H.02. Human Cognition and Behavior

Support: GPSA ASU Graduate research support program
ASHFoundation New Century Scholars Doctoral Scholarship

Title: Shared neural substrates for speech production and second-language word recognition in human motor cortex

Authors: *B. BARRAGAN[1], K. UEHARA[2], Y. JIAO[1], V. BERISHA[1], M. SANTELLO[3], J. LISS[1]
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Abstract: The primary motor cortex (M1) plays a role in speech perception tasks under difficult circumstances (Devlin, Aydelott, 2009; Adank, 2012; Nuttall et al., 2016), suggesting that recruitment of M1 facilitates speech perception (Du et al., 2016). Listening to sounds produced in a second language (L2) may be an instance of listening under difficult conditions, because it involves additional processing and cognitive-perceptual resources to distinguish among the new language sounds. The purpose of this study was to investigate the role of M1 representation of the lip orbicularis oris (OO) muscle in processing acoustic inputs in the native language (L1) and L2, using repetitive transcranial magnetic stimulation (rTMS)
A low-frequency rTMS protocol, which typically induces inhibitory changes in the stimulated brain area, was employed with a double-blinded, sham-controlled and crossover design, to alter neural activity in M1 in 13 healthy English/Spanish bilingual participants. The participants' voice was recorded reading a passage in L2 before and after 5 and 15 minutes of rTMS. Performance on a bilingual listening word-to-picture matching task was measured before and after the rTMS and sham conditions. rTMS was applied over the left representation of the OO muscle for 15 minutes at 0.6 Hz, and 100% of active motor threshold intensity, whereas sham was applied without magnetic pulses as a control condition. Single-pulse TMS-induced motor evoked potential (MEP) from the OO muscle, and an automated assessment of the vowel space area (VSA; Berisha et al., 2017; Sandoval et al., 2013), were used to assess the effect of rTMS on M1.
MEP area decreased after rTMS, indicating a successful inhibition of M1 activity. Similarly, VSA was compressed after rTMS, revealing functional speech production consequences of OO-associated M1 inhibition. Importantly, we also found evidence for a role of M1 for word recognition in L2: participants were significantly slower and less accurate in L2 word recognition after rTMS compared to the sham condition. The VSA and behavioral results suggest that rTMS-induced disruption of M1 associated with speech articulators interfered with L2 speech production and recognition, indicating that inhibition in the speech motor system during speech perception is functionally related to L2 word recognition ability. No effect of rTMS was found on L1. Our results provide support for the role of M1 on L2 word recognition, and highlights the notion that speech perception and production systems are intricately intertwined when listening to speech under difficult circumstances.

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Poster

514. Human Cognition and Behavior: Language Networks

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Topic: H.02. Human Cognition and Behavior

Support: Open Fund of State Key Lab of Cognitive Neuroscience and Learning (CNLYB1309)

Title: The effect of semantic relatedness on learning ambiguous words in a second language: An event-related potential study

Authors: *Y. LU, B. CHEN
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Abstract: Ambiguous words, or words with multiple meanings, is a prevalent phenomenon across languages. For learners of a second language (L2), as their proficiency improves, they are constantly learning new words or new meanings of already known words. Recent research has revealed that when learning a new meaning of already known L2 words, the new meaning is easier to acquire if it is semantically related to the prior meaning than when it is unrelated. However, the mechanism underlying the semantic similarity effect remains poorly understood. In the current study, we adopted event-related brain potential (ERP) technique to directly examine the neural correlates of semantic similarity effect in learning L2 ambiguous words. With semantic relatedness as the experimental variable, three type of words, i.e. unambiguous words (as the control condition), polysemous words (which had two semantically related meanings) and homonyms (which had two semantically unrelated meanings) were set as study items, yielding five conditions, i.e., unambiguous words, the first meaning of polysemous words, the second meaning of polysemous words, the first meaning of homonyms, and the second meaning of homonyms. During a three-day learning phase, Chinese-English bilinguals learned 105 novel English words, 35 for each word type, using bilingual flashcards. The learning of the first meaning started one-day earlier than the learning of the second meaning, and all types of words were studied six times. The electrical activities of the brain were recorded during the whole learning phase, and at the end of each day, the semantic representations established for the studied items were probed through a multiple choice test, in which the learned English words were presented with four candidate meanings and participants had to choose the correct meaning. Behavioral results showed the performance of the second meaning of polysemous words was better than any other conditions. ERP results revealed that for homonyms, the second meaning elicited a larger N400 than the first meaning; for polysemous words, the second meaning elicited a larger late positive component (LPC) than the first meaning. Moreover, the second meaning of homonyms elicited a larger N400 than the second meaning of polysemous words. Taken together, these results suggest that when the new meaning is semantically unrelated to the prior meaning, the establishment of the new meaning may be interfered with by the semantic representation of the prior meaning; and when the new meaning is semantically related to the prior meaning, the creating of the new meaning representation may be facilitated through semantic familiarization.

Disclosures: Y. Lu: None. **B. Chen:** None.

Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 514.21/HHH46

Topic: H.02. Human Cognition and Behavior

Title: Sleep and memory consolidation of higher-order language combinatorics: Insights from oscillatory brain activity

Authors: *Z. R. CROSS[1], L. ZOU-WILLIAMS[2], M. J. KOHLER[2], M. SCHLESEWSKY[2], I. BORNKESSEL-SCHLESEWSKY[2]
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Abstract: Language learning is a dynamic process involving the coordination of brain networks that extract, consolidate and generalise the meaning of linguistic units of varying complexity. Neocortical slow oscillations (SO) and thalamic spindles during sleep facilitate the reactivation of newly encoded memory traces, manifesting in distinct oscillatory activity during retrieval, particularly in the alpha-band (α, ~ 8 - 13Hz). However, it is currently unknown if the effect of sleep on memory extends to the mechanisms that subserve sentence comprehension. Here we report an exploratory EEG study that assessed the role of sleep in the consolidation of a modified miniature language containing various word orders.
24 monolingual English speakers (11 male, mean age=26.2, ± 1.65 years) participated in one of two conditions (Morning, Evening). Both conditions involved an implicit learning phase, baseline sentence comprehension task, followed by either an 8hr sleep opportunity (Evening, n=10) or an equivalent period of wake (Morning, n=14) and a delayed comprehension task. EEG was recorded during the tasks and sleep opportunity. Relative α power was computed during sentence presentation, while spindle-SO co-occurrence was quantified during non-rapid eye movement sleep.
Linear mixed-effects modelling revealed a significant Condition (Morning, Evening) by Session (Baseline, Delayed) interaction ($\chi^2(1)=45.86$, $p<.001$): α power during sentence comprehension decreased from baseline to delayed testing in the Morning condition, but increased in the Evening condition. There was also a significant increase in α power for sentences with incorrect word orders ($\chi^2(5)=67.78$, $p<.001$), the effect being larger for the Evening versus Morning condition at delayed testing ($\chi^2(5)=41.24$, $p<.001$). A linear regression revealed that spindle-SO co-occurrence positively predicted delayed comprehension performance ($\beta = 0.09$, $p = .003$, $R^2 = .69$).
Increased α synchronisation for incorrect word orders may reflect a gating mechanism, modulating the downstream flow of information and supporting internal (predictive) model updating. Further, we found that the beneficial effect of spindle-SO co-occurrence on memory

extends to sentence-level combinatorics and coincides with increased α synchronisation for incorrect word order identification, which may reflect the communication between neuronal ensembles responsible for the comprehension of a newly learned language.

Disclosures: Z.R. Cross: None. **L. Zou-Williams:** None. **M.J. Kohler:** None. **M. Schlesewsky:** None. **I. Bornkessel-Schlesewsky:** None.

Poster

514. Human Cognition and Behavior: Language Networks

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Program #/Poster #: 514.22/HHH47

Topic: H.02. Human Cognition and Behavior

Support: DFG Grant EXC 277

Title: Electrical stimulation while memorizing verbs and nouns: Comparison of tACS and tDCS in a single case study

Authors: *H. M. MUELLER, S. WEISS
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Abstract: Oscillatory brain activity typically up to the upper two-digit Hz-range can be measured during several cognitive tasks. Brain oscillations mostly associated with memory processes lay within the theta range (4-7 Hz) but higher frequencies are involved, too. In order to test the influence of frequency specific AC-stimulation on verbal memory processes, we compared transcranial alternating current stimulation (tACS) with the results obtained with transcranial direct current stimulation (tDCS).A right-handed female (27 y) had to memorize 300 different visually presented concrete words and freely recall them after each block. The stimuli consisted of 150 nouns and 150 verbs, each randomly presented in blocks á 25 words for two times. tDCS, tACS (18 Hz, beta band) as well as sham stimulation were applied on different days for 20 min via electrodes placed at left frontal and temporo-parietal sites in a double-blind design. Current intensity was 1000 µA (or below individual phosphene threshold).A significant difference between the stimulation and sham condition (Pearson $\chi 2 = 12.0$, $p = .03$, two-tailed) was found which differed for nouns and verbs. During tACS-stimulation the participant showed an 48% increase of recalled nouns (8% for verbs), during sham an 20% (36% for verbs) increase. Overall error rate was higher for verbs (Pearson $\chi 2 = 11.73$, $p = .008$, two-tailed). The tDCS-condition showed comparable results.Results support the notion that oscillatory activity within multiple rhythms plays an important role for verbal memory tasks. Rather, different rhythms are associated with different components of a cognitive operation and a direct relation between certain oscillatory frequencies and distinct language processes seems unrealistic. Presumably, participants will profit more, if the applied tACS frequency is adjusted to the participant's

individual beta frequency. This may be one of the reasons why tACS was not superior to tDCS results.

Disclosures: H.M. Mueller: None. **S. Weiss:** None.

Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

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Program #/Poster #: 514.23/HHH48

Topic: H.02. Human Cognition and Behavior

Support: Research Project Grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan 16K9709

Title: Eye voice coordination in Parkinson's disease

Authors: *Y. TERAO[1], S.-I. TOKUSHIGE[2], S. INOMATA-TERADA[3], Y. UGAWA[4]
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Abstract: Patients with Parkinson’s disease suffer from various reading abnormalities such as increased number of progressive saccades, smaller saccade amplitudes, increased number of regressive saccades, and longer fixation durations. This may partly be ascribed to the abnormal oculomotor control in relation to reading, although the exact nature of this disturbance is unknown. Methods: We compared eye-voice coordination while subjects read aloud Japanese texts presented on a monitor placed 50cm in front of their eyes. Subjects were 19 patients with Parkinson’s disease (11 males, 7 females, age: 70.3±4.0) and 19 age-matched normal subjects (7 males, 12 females, age: 68.8±9.6). The gaze position on the monitor was recorded using a video-based eye tracking system (Eyelink 1000). The voice was simultaneously recorded by a microphone. The texts were presented horizontally from left to right in 5-14 lines, and consisted of Chinese characters and hiraganas (Japanese phonograms), each subtending a visual angle of 0.6-1.3 degrees. The number of saccades per unit time, the mean amplitude of saccades, mean duration of fixation, and the amount of time by which gaze preceded the voice (eye-voice lead) were analyzed and compared between subject groups. Results: Reading speed was reduced in PD patients than in normal subjects for all texts. Reading speed was slower when the letter size was smaller, and as the readability of the text decreased, for PD patients and normal subjects alike. The fixation positions showed a more reduced distribution in PD patients than in normal subjects. On average, the number of saccades per unit time was reduced, the mean saccade amplitude was smaller (PD 3.4±1.3 deg, normal 3.9±1.6 deg), while the mean saccade fixation duration was longer in the PD group (PD 303.4±66.2ms, normal 236.7±70.4ms). The frequency of regressive gaze movements was comparable between the two groups (PD 26.4%, normal

24.1%), as was the eye-voice lead (PD 122.2±61.1ms, normal 131.6±23.8ms). Discussion: The longer fixation duration and the decreased number of saccades per unit time may contribute to slower reading in PD patients. Eye voice lead, presumed to reflect the phonological working memory buffer, was not impaired in PD. The results are discussed in comparison with eye voice coordination in spinocerebellar ataxia patients.

Disclosures: Y. Terao: None. **S. Tokushige:** None. **S. Inomata-Terada:** None. **Y. Ugawa:** None.

Poster

514. Human Cognition and Behavior: Language Networks

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Topic: H.02. Human Cognition and Behavior

Support: NSF Grant SBE1041707
NSF Graduate Research Fellowship

Title: Brains on books: Event-structure semantics predict cortical responses to naturalistic language

Authors: *A. A. HAFRI, M. F. BONNER, J. C. TRUESWELL, R. A. EPSTEIN
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Abstract: Events are not atomic; they have internal semantic structures that specify the relations among entities in the world. For example, despite differences in content, “the witch melted” and “the planet vaporized” have a common structure: an entity undergoing a state change. We attempted to identify representations of event structure in the human brain by using naturalistic linguistic stimuli and a voxelwise fMRI encoding model approach. We were inspired by the insight in linguistics that the syntactic frames in which verbs appear provide clues to the semantic structure of events (e.g. “Vader vaporized the planet” is grammatical while “Vader pounced the cat” is not, likely because the former indicates a State Change, the latter a Motion). Six participants listened to 3 hours of audiobook excerpts while undergoing fMRI. We constructed two models of the stimuli and tested how well each model captured the fMRI response in each voxel: (1) An event-structure semantic model (VerbNet). VerbNet is a database in which verbs are grouped into classes that share similar syntactic alternations. In our implementation, a verb token is assigned VerbNet features (e.g. ±Cause, ±State) based both on its class and its syntactic frame (e.g. intransitive). (2) A word distributional model (word2vec) in which vectors for each word are learned by a neural network based on co-occurrence statistics in a corpus. This model served as a comparison for our event-structure model, since similar distributional models have been found to predict fMRI responses to naturalistic speech (Huth et

al., 2016). In each voxel we used ridge regression to learn the feature beta weights in a 9 scan-run training set. We then used the learned weights to predict the fMRI timecourse of a held-out test set (5 scan-runs, new stimuli). Using the word2vec model, we predicted fMRI responses across cortex in individual subjects (i.e. we found a significant correlation between predicted and actual timecourses). This replicated previous work using word embeddings. Using the VerbNet model, on the other hand, we significantly predicted responses in temporal and inferior frontal regions and angular gyrus, areas previously implicated in language processing. Notably, 45% of verbs at test were novel (i.e. they did not appear in the training set), indicating that the success of the model reflects coding of event structure features rather than specific verbs. A control model in which features were randomly permuted between verb tokens showed no prediction accuracy. Altogether, our findings support the theory that an important aspect of how the brain represents event semantics is event structure, i.e. the nature of relations between entities.

Disclosures: A.A. Hafri: None. **M.F. Bonner:** None. **J.C. Trueswell:** None. **R.A. Epstein:** None.

Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 514.25/HHH50

Topic: H.02. Human Cognition and Behavior

Title: How selective is Broca's area for language syntax? A Bayesian neurostimulation meta-analysis

Authors: *M. JOHNSON[1], Y. BAEK[2], J. P. COETZEE[2], M. M. MONTI[2]
[2]Psychology, [1]UCLA, Los Angeles, CA

Abstract: Popular hypotheses propose that the classical language region known as "Broca's area" (left inferior frontal gyrus, LIFG, BA 44/45) may actually function as a shared neural resource for processing hierarchical, relational structures across multiple domains of cognition. To test this prediction, we conducted a novel neurostimulation meta-analysis, inspired by Poldrack's (2006) fMRI meta-analysis, to assess the selectivity of Broca's area for processing higher-order structures in six cognitive domains - action cognition, algebraic reasoning, artificial grammar, deductive reasoning, language syntax, and music syntax. A comprehensive literature search yielded a total of 41 neurostimulation studies on higher-order or syntactic processing across the six cognitive domains and involving stimulation of any brain region. Statistical contrasts reported in these studies were binary coded as showing either a presence or absence of a neurostimulation effect for cognitive syntax, yielding a total of 395 contrasts for language studies and 895 tests for nonlanguage studies. These contrasts were summarized into three different 2 x 2 factorial models for Bayesian probability inference, each involving a forward

inference (i.e., inferring an effect of cognitive change from a neurostimulation cause) and a reverse inference (i.e., inferring a neurostimulation cause from an effect of cognitive change). Model 1 compared stimulation of Broca's area versus any other region to a change in language syntax versus nonlanguage syntax. Model 2 compared stimulation of Broca's area versus any other region to the presence of absence of a change in only language syntax. Model 3 compared stimulation of any left hemisphere region versus any right hemisphere region to a change in language syntax versus nonlanguage syntax. The results for Model 3 indicated that the left hemisphere seems selective for language syntax, which is consistent with the known hemispheric laterality of language. For each model, the strengths of the inferences were assessed with Bayes factors as well as specificity and sensitivity metrics. The results for Models 1 and 2 indicated that, in general, Broca's area does not seem selective for language syntax, which supports proposed hypotheses of the domain-general role of Broca's area in higher-order cognition.

Disclosures: M. Johnson: None. **Y. Baek:** None. **J.P. Coetzee:** None. **M.M. Monti:** None.

Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 514.26/HHH51

Topic: H.02. Human Cognition and Behavior

Title: The neural computations underlying relational reasoning

Authors: *J. CHIANG[1], Y. PENG[2], K. J. HOLYOAK[2], H. LU[2], M. M. MONTI[2]
[1]Psychology, [2]UCLA, Los Angeles, CA

Abstract: Analogical reasoning, a powerful tool for human thinking and learning, involves complex computations applied to abstract semantic representations. Solving a verbal analogy problem requires retrieving or constructing a relation for each of two pairs of concepts, and then mapping the two relations to determine whether they are identical. Previous studies have identified neural correlates of analogical reasoning, specifically regions of the prefrontal cortex (BA10 in particular), but the neural basis for specific subprocesses have not been clearly established. In the present study, we combine behavioral fMRI with computational modeling to probe the neural computations underlying relational reasoning. In a rapid event-related fMRI design, 16 healthy volunteers were asked to determine the relationship between two pairs of semantic concepts. Each analogy was presented as two pairs of words, an AB pair (e.g., up:down) followed by a CD pair (e.g., high:low). On each trial, the two pairs were presented sequentially, and the participant was asked to judge whether the relationship matched between the two pairs. Each participant performed 288 trials distributed over 8 blocks. Data were analyzed using a univariate GLM approach (FSL) to identify regions engaged in forming semantic relations and mapping. This analysis was extended by a multivariate analysis to relate

BOLD activity with computational models of semantic and analogical processing.
The primary univariate contrast of interest was the C:D - A:B subtraction, which can be interpreted as the neural activity associated with mapping the two relations. This contrast revealed parietal areas in addition to the expected prefrontal areas, corroborating previous findings. Multivariate analyses on the A:B pairs also revealed prefrontal, parietal and temporal regions that were involved in representing semantic relations. Representational similarity analysis also reveals that, at least at the computational level, our explicit models of relational mapping are implemented by prefrontal regions, in particular BA10.

Disclosures: J. Chiang: None. **Y. Peng:** None. **K.J. Holyoak:** None. **H. Lu:** None. **M.M. Monti:** None.

Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 514.27/HHH52

Topic: H.02. Human Cognition and Behavior

Support: NIH R01DC014281

Title: Evaluating the reliability of fMRI for single subject language mapping

Authors: *A. BAJRACHARYA[1,2], C. S. ROGERS[2], M. S. JONES[2], S. M. MCCONKEY[2], J. E. PEELLE[2,1]
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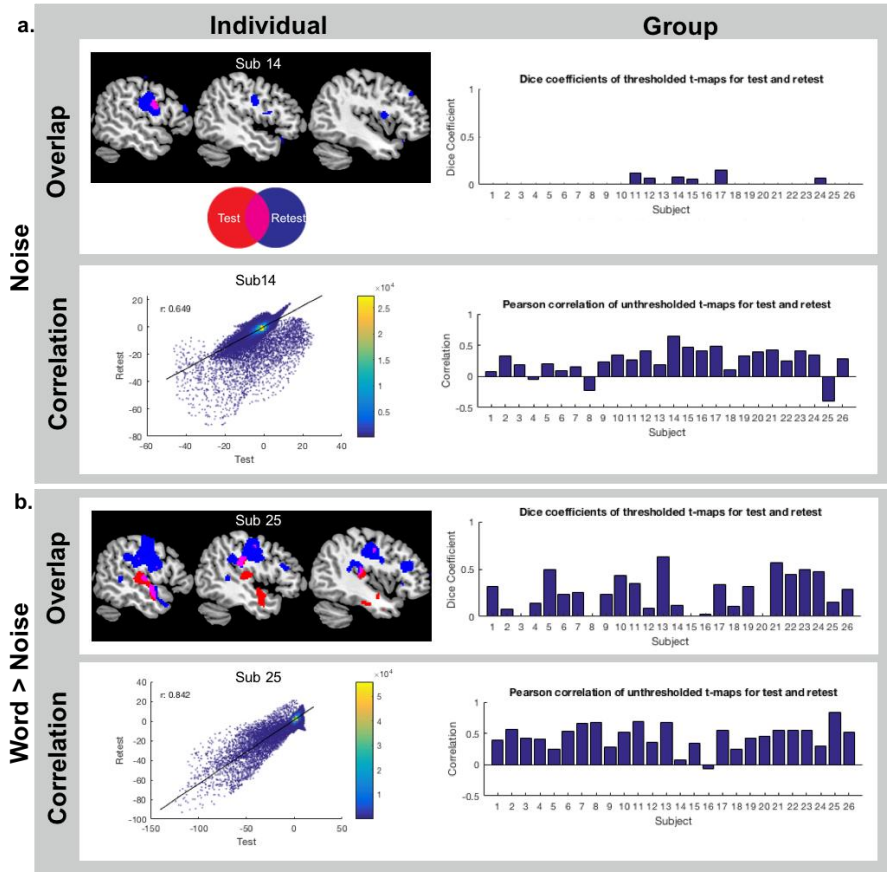
Abstract: Accurate mapping of language areas in the brain is integral to pre-surgical planning and research. However, a gold standard that obtains test-retest reliability in a single subject level has not been achieved. Functional magnetic resonance imaging (fMRI) is one of the most widely-used non-invasive methods for brain imaging. We conducted a systematic search of published literature through Oct 2017 that addressed language mapping using fMRI. The search resulted in 421 papers which were screened for the presence of single subject data. Out of the 62 papers that passed the screening, less than 5% discussed reliability measures.
To quantify the test-retest reliability of a straightforward speech perception task, we analyzed two sessions of an event-related study of spoken word perception. We scanned 26 young adults (18-35 yrs) for 8 mins per measure using sparse fMRI. Participants heard either a word or noise (1-channel noise vocoded speech) and were instructed to repeat only the words.
Test-retest comparisons for whole brain activity were made for noise and word>noise conditions using two complementary approaches. First, we used the Dice coefficient for each subject, calculated on binarized t-maps (voxelwise $p < .001$, uncorrected) as a measure of the extent of reproducibility of the activation. Second, we conducted correlations across the whole brain on

unthresholded t-maps. Figures a and b show the test-retest overlaps from thresholded t-maps for the subject with highest correlation, scatter plot for test vs retest activations for the same subject, and bar graphs for Dice coefficients (top) and Pearson correlation coefficient (bottom) for all subjects. We observed that, word>noise condition produced greater overlap (higher Dice coefficient) in language regions compared to the noise condition.
The result suggests that certain tasks might be better suited for generating reproducible activation maps. The lack of reliability in the test-retest comparisons highlights the need for stringent methods with considerations for scan duration, and motion parameters for assuring data quality.



Disclosures: A. Bajracharya: None. **C.S. Rogers:** None. **M.S. Jones:** None. **S.M. McConkey:** None. **J.E. Peelle:** None.

Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 514.28/HHH53

Topic: H.02. Human Cognition and Behavior

Title: Associations between music training and language learning on cognitive performance

Authors: *A. ZHU[1], J. A. BUGOS[2], J. BRYANT[2]
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Abstract: This research examines the associations between musical training and multilingualism on cognitive control in adults. Neurological evidence suggests that musicians have an enlarged corpus callosum as compared to non-musicians which may result in better cognitive performance on cognitive control and task switching measures (Habibi et al., 2017; Moradzadeh, Blumentahl, & Wiseheart, 2014; Moreno & Farzan, 2014). Similarly, research in bilinguals suggests neurological differences attributed to enhanced performance on executive functions as compared to monolinguals (Blanco-Elorrieta & Pylkkänen, 2017; Perani et al., 2017). Although music is considered a language, very little is known about the relationship between instrumental musical training and language learning. There is theoretical and practical significance in the OPERA hypothesis (Patel, 2011a) and the language and music hierarchy parallel (Patel, 2011b), which would explain why music training could lead to neuroplasticity in speech and language processing. Fifty-six adults (19 bilingual non-musicians, 18 bilingual musicians, and 19 multilinguals) completed a series of measures in cognitive control and processing speed. Cognitive control was measured through the auditory and visual modalities using a standardized Stroop paradigm. Results suggest that multilinguals process visual information slower than bilingual non-musicians and musicians. Data also suggests that bilingual non-musicians process auditory information slower than bilingual musicians and multilinguals. Additionally, increased processing speed was found for bilingual musicians compared to multilinguals. However, bilingual musicians and bilingual non-musicians were seen to have performed similarly on measures of processing speed. This research suggests differential benefits in music training and language learning.

Disclosures: A. Zhu: None. **J.A. Bugos:** None. **J. Bryant:** None.

Poster

514. Human Cognition and Behavior: Language Networks

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 514.29/HHH54

Topic: H.02. Human Cognition and Behavior

Support: NSF Award BCS1533691

Title: Frontal and temporal mobile EEG characterization of the preparation and generation phases of the creative writing process: A pilot study

Authors: *J. G. CRUZ-GARZA[1], A. S. RAVINDRAN[1], M. J. DELGADILLO[2], A. E. KOPTEVA[1], C. RIVERA GARZA, Ph.D.[2], J. L. CONTRERAS-VIDAL, Ph.D.[1]
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Abstract: The development of mobile brain-body imaging (MoBI) technology allows the study the human creative process outside of constrained laboratory settings. We conducted a pilot study to investigate the neural features associated with creative writing using EEG metrics to compare different phases of the process (i.e. Preparation, Generation) within a creative writing course.
We used portable dry EEG systems (four channels: TP09, AF07, AF08, TP10) and video cameras, to record the brain activity of seven Spanish heritage students as they developed their creative writing skills in an undergraduate course on creative writing in Spanish. The students recorded their own brain activity as they walked through and experienced areas in the city (Preparation phase), and while they worked on their creative texts (Generation phase). Differences in brain activity for the distinct stages of the creative writing process have been unexplored in the EEG domain.
The EEG data was pre-processed and cleaned by identifying time segments where the acceleration surpassed 1 ms^{-2}, there was an indication of poor contact quality, and by using artifact subspace reconstruction. The data was then segmented in 6s windows with 25% overlap. From the time windows, we measured Partial Directed Coherence, sample entropy, and band-power changes between the Preparation and Generation phases of the creative writing task.
We found *a)* higher average Partial Directed Coherence during the Preparation phase. High coherence was observed in connections originating in the temporal electrodes towards frontal and temporal electrodes. *b)* We found higher values of sample entropy and *c)* higher relative power in the alpha, beta and gamma bands (8-50 Hz), with lower theta and theta band-power (1-12 Hz) during the Generation phase.
These findings suggest that ideation, exploration, and observation during the Preparation phase of a creative writing task can be characterized by a state of long-range cortico-cortical communication between multisensory integration brain areas (temporal regions) and high-order execution and planning areas of the brain (prefrontal regions), perhaps leading to selective storage of ideas, concepts or observations candidate for creating writing during the generation phase. During creative writing, slower cortical rhythms underlying long-range cortico-cortical communication decreased and the brain activity could be better characterized by focal activity in alpha, beta and gamma range. We hypothesize this focal activity may be related to working memory, sequence production, and processing of filtered information from the Preparation Phase.
IUCRC BRAIN Center, NSF award #1650536.

Disclosures: A.S. Ravindran: None. **M.J. Delgadillo:** None. **A.E. Kopteva:** None. **C. Rivera Garza:** None. **J.L. Contreras-Vidal:** None.

Poster

514. Human Cognition and Behavior: Language Networks

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Program #/Poster #: 514.30/DP13/HHH55

Topic: H.02. Human Cognition and Behavior

Support: NIH 2R01DC05660
FP7 Ideas: European Research Council ERC-StG-313841

Title: Spontaneous speech synchronization predicts neurophysiology, brain anatomy and language learning

Authors: *M. F. ASSANEO[1], P. RIPOLLES[1], J. ORPELLA[2], R. DE DIEGO-BALAGUER[2], D. POEPPEL[3]
[1]New York Univ., New York, NY; [2]Univ. of Barcelona, Barcelona, Spain; [3]Neurosci., Max-Planck-Institute For Empirical Aesthetics, Frankfurt, Germany

Abstract: The ability to synchronize a motor output to an auditory input is a basic trait present in humans from birth with important cognitive implications. Infants' proficiency in following a beat, for example, is a predictor of language skills. From a phylogenetic perspective, spontaneous synchronization (i.e. without explicit training) to an external rhythm is argued to be a unique characteristic of vocal learning species, including humans. The study of this distinctive attribute has typically focused on how body movements are entrained by non-speech signals - e.g. music or a beat. Here, instead, we investigate how humans spontaneously align their speech motor output to auditory speech input.
To begin with, we introduce a simple behavioral task, where individuals simultaneously perceive and produce syllables, with a remarkable outcome. The general population shows two qualitatively different behaviors: while some individuals are compelled to temporally align their utterances to the external stimulus, others show no interaction between the perceived and produced rhythms. Subsequently, we investigate the neurophysiology and brain structure features underlying the segregation. First, with a magnetoencephalography protocol we show that, when passively listening to speech, synchronizers show increased brain-to- stimulus alignment over frontal areas as well as reduced rightward asymmetry in auditory cortex. Secondly, using diffusion weighted MRI technique, we find a distinct lateralization pattern in a white matter cluster -likely part of the arcuate fasciculus, pathway connecting frontal and auditory areas- that differentiated the groups, with synchronizers showing significantly greater left lateralization. Crucially, this structural difference relates to both the auditory and frontal neurophysiological results: increased leftward lateralization in the white matter was related to higher brain-to-stimulus synchrony in left frontal regions and to more symmetrical auditory entrainment. Finally, we demonstrate that the behavioral findings on audio-motor synchronization and its neural

substrate have ecologically relevant consequences: the synchronizers perform better on a word learning task.
In summary, the combined behavioral, neurophysiological, and neuroanatomic results reveal a fundamental phenomenon: whereas some individuals are compelled to spontaneously align their speech output to the speech input, others remained impervious to the external rhythm.

Disclosures: M.F. Assaneo: None. **P. Ripolles:** None. **J. Orpella:** None. **R. de Diego-Balaguer:** None. **D. Poeppel:** None.

Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.01/HHH56

Topic: H.02. Human Cognition and Behavior

Support: Helse Midt-Norge

Title: "Where is she and what did she say?": Web-testing differentiates spatial and verbal episodic memory

Authors: *J. PANI, D. SOKOLOWSKI, H. RØE EVENSMOEN, T. HANSEN, A. HABERG
Dept. of neuromedicine and movement science, NTNU, Trondheim, Norway

Abstract: Impairment in episodic memory is an early symptom of dementia. Using our self-administered web-based neuropsychological test platform Memoro, we are currently investigating the distribution of cognitive abilities in one of the world's largest prospective population studies, Helseundersøkelsen i Nord Trøndelag 4 (HUNT4). The aim of this study is to assess whether Memoro can separate spatial and verbal episodic memory function, as changes in these cognitive functions can be differently affected in normal aging and disease.
Participants are recruited through an invitation letter sent via regular mail. Participants log on to Memoro with a subject specific userID and pin code. Here results from two memory tasks were included: Verbal Memory Test (VMT) which is a 18 word list learning task using a similar structure as the CVLT-II where measures of learning, immediate recall, delayed recall were extracted; the Spatial Memory Test (SMT) which is a 10 stimuli object-location memory task where measures of object identity, immediate recall and delayed recall were extracted. Factor analysis was performed through Parallel Analysis using "minres" extraction and oblivion rotation in Rstudio (version 3.3.3).
Data from 1359 participants (13-90 years of age, 731 female) completing the test to date were used. The factor analysis gave a two factor model with RMSR=0.01, RMSEA=0.05; Tucker-Lewis=0.988. With intercorrelation between factors of -0.31. Loadings are presented in Table 1.

Table 1
Summary of exploratory factor analysis (n=1359)

Measure	Verbal factor (3.13)	Spatial factor (1.57)
Verbal memory learning	0.83	-0.04
Verbal memory delayed recall	0.93	0.01
Verbal memory immediate	0.95	0.02
Spatial immediate recall [a]	0.03	0.98
Spatial object identity [b]	0.06	-0.68
Spatial delayed recall [a]	-0.09	0.51

Note. Yellow denotes verbal and blue spatial memory factors.
[a] higher value indicates worst performance
[b] higher value indicates better performance

Our preliminary results in 1359 participants show that the Memoro platform separated between spatial and verbal episodic memory functions. A similar separation is not seen with traditional pen/paper testing. Separating these memory functions, known to be underpinned by partly distinct brain regions, can increase our understanding and help distinguish normal aging from pathological. Moreover, this distinction will help us design specific ways to preserve cognitive capacities and hopefully stimulate a positive effect on the affected abilities.

Disclosures: J. Pani: None. **D. Sokolowski:** None. **H. Røe Evensmoen:** None. **T. Hansen:** None. **A. Haberg:** None.

Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.02/HHH57

Topic: H.02. Human Cognition and Behavior

Support: Helse Midt-Norge

Title: How do older and younger people do it? Assessing web-based neuropsychological participation in a large-scale population study

Authors: *D. SOKOLOWSKI[1], T. HANSEN[2], J. PANI[2], A. K. HABERG[2]
[1]Dept. of Neuromedicine and Movement Sci., [2]NTNU, Trondheim, Norway

Abstract: Web-based neuropsychological test batteries provide a unique opportunity to assess cognitive abilities in large-scale population studies. Using Memoro, our web-based battery, we

are currently investigating the distribution of cognitive abilities in one of the world's largest prospective general population studies; Helseundersøkelsen i Nord-Trøndelag (HUNT4). The aim of this study was to assess who participates, and how they participate in a study involving a web-based neuropsychological test battery.
People taking part in the HUNT4 study above age 13 are invited by regular mail to participate in this study. Participants are asked to log on to the Memoro website with a participant specific userID and pin code and perform 13 tasks using their PC or any other device with internet connection. Data concerning demographics and hardware/software used is also collected.
Out of the 2656 people (age 13 – 90) who participated in the study to date, 56.2% (n=1492) were female, 43.7% (n=1161) were male and 0.1% (n=3) declared other gender.
Most participants used PCs (66.2%), followed by iPads (14.6%), Mac computers (10.1%) and Android devices (5.8%).
The most widely used browser was Google Chrome (41.6%), followed by Safari (21.4%), Internet Explorer (14.3%) and Microsoft Edge (13.4%).
People in the age groups 50-59 and 60-69 had highest participation rates, making up 45.4% of all participants.
The older participants were, the earlier they took the test during the day ($F(1,76) = 1.865$, $p<0.000$, with $R^2 = 0.052$), with 3:20 pm being the average time for people in the age group 13-19 and 1:11 pm for the 70+ group.
Completing a whole battery took 43 min on average. People between 20-29 years were fastest with a mean completion time of 40 min while 70+ were the slowest, mean of 46m.
The vast majority of participants who completed the battery did so in one session (91.7%). The rest took two (7.3%), three (0.8%) or four (0.2%) sessions.
Across all ages, participants reported that they were "rather comfortable" (4) or "very comfortable" (5) with using computers ($\mu=4.41$, $SD=0.79$) using a 5-point Likert scale.
Out of all participants, 65.4% completed every task and 82.5% completed 11 or more.
In summary, those who participate in web-based cognitive testing and invited via regular mail are likely to be older adults, and all age groups feel proficient using computers. Older people take the test earlier in the day and take longer to complete. Knowledge about these details can help with interpreting results and creating test batteries with high participation and completion rate.

Disclosures: D. Sokolowski: None. **T. Hansen:** None. **J. Pani:** None. **A.K. Haberg:** None.

Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.03/HHH58

Topic: H.02. Human Cognition and Behavior

Support: Canadian Cancer Society grant #310336
CIHR Operating Grant #FRN 130490
Cancerfonden
Wilfred and Joyce Posluns Chair in Women's Brain Health and Aging to GE
Alzheimer Society of Canada Posluns Postdoctoral Fellowship in Women's Brain Health and Aging to AA

Title: The effect of oophorectomy prior to spontaneous menopause on cortical thickness and measures of attention and working memory: Preliminary findings

Authors: *A. ALMEY[1], N. GERVAIS[1], A. DUCHESNE[2], R. REUBEN[1], L. GRAVELSINS[1], E. BAKER-SULLIVAN[1], S. T. WITT[3], Å. R. KERSLEY[4], E. CLASSON[4], N. LYKKE[4], M. SHILDRICK[5], C. ASBERG[4], E. THEODORSSON[4], J. ERNERUDH[4], E. Å. LUNDQVIST[4], P. KJØLHEDE[4], C. L. GRADY[6], G. EINSTEIN[1]
[1]Psychology, Univ. of Toronto, Toronto, ON, Canada; [2]Psychology, Univ. of Northern British Columbia, Prince George, BC, Canada; [3]CMIV, Linköping Univ., Linkoping, Sweden; [4]Linkoping Univ., Linkoping, Sweden; [5]Stockholm Univ., Stockholm, Sweden; [6]Baycrest Ctr. Geriatric Care, North York, ON, Canada

Abstract: Aim: Loss of ovarian hormones following spontaneous (natural) or surgical menopause is implicated in the elevated incidence of Alzheimer's Disease observed in women (Rocca et.al, 2007). It remains unclear how the loss of ovarian hormones contributes to cognitive decline; there is evidence that loss of estrogens leads to decreased hippocampal volume and function (Duchesne et al, 2017; Eberling et al, 2004), but research on the neocortex has been scarce with the exception of Witt et al., 2018. To continue investigating the effect of estrogen loss on the neocortex we compared structural scans of women with the BRCA mutation with preventative bilateral salpingo-oophorectomy (BSO) prior to spontaneous menopause to those of age matched controls (AMC). We asked whether early loss of ovarian hormones affects cortical thickness or performance on measures of attention and working memory. **Methods:** Participants in this study (n=34) were women recruited in Sweden and Canada who were divided into three groups: women with BSO not on hormone replacement therapy (HT; BSOnoHT), women with BSO on HT (BSOwHT), and AMC. All participants completed demographic and neurocognitive measures to assess attention and working memory. Scores on these tasks were compared between groups using a bootstrap approach with a General Linear Model (GLM). T1-weighted structural images were obtained using a Siemens or Phillips 3-T scanner and analyzed using the CIVET 2.1 pipeline. SurfStat software was used in the MATLAB environment to create a GLM that compared cortical thickness between BSO and AMC groups. **Results:** The BSOnoHT group performed significantly worse than the AMC and BSOwHT groups on the measure of attention and working memory, suggesting that HT protects against these cognitive declines following BSO. Correspondingly, the BSOnoHT group had significantly thinner right frontal cortices than AMCs, including the orbito, lateral, caudal, and dorsal frontal cortices. If the BSOwHT group is included in the analysis this effect disappears, suggesting that HT may also protect against the cortical thinning that can occur following BSO. **Conclusions:** These findings are preliminary and require further data collection to confirm the results. However, they suggest that early loss of

ovarian hormones following BSO is related to decreases in the thickness of the right frontal cortex (Witt et al., 2018) and poorer performance on working memory and attention tasks. Since attention and working memory depend, in part, on the prefrontal cortices (Kane & Engle, 2002), the thinning of the right frontal cortex may contribute to the poorer performance on tests of attention and working memory.

Disclosures: N. Gervais: None. **A. Duchesne:** None. **R. Reuben:** None. **L. Gravelsins:** None. **E. Baker-Sullivan:** None. **S.T. Witt:** None. **Å.R. Kersley:** None. **E. Classon:** None. **N. Lykke:** None. **M. Shildrick:** None. **C. Asberg:** None. **E. Theodorsson:** None. **J. Ernerudh:** None. **E.Å. Lundqvist:** None. **P. Kjølhede:** None. **C.L. Grady:** None. **G. Einstein:** None.

Poster

515. Human Cognition and Behavior: Cognitive Aging I

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Program #/Poster #: 515.04/HHH59

Topic: H.02. Human Cognition and Behavior

Support: CIHR Operating grant #FRN 130490
Wilfred and Joyce Posluns Chair in Women's Brain Health and Aging
Alzheimer's Association and Brain Canada Foundation Fellowship AARF-17-504715

Title: Bilateral salpingo-oophorectomy reduces CA1 volume and impairs hippocampal-dependent memory in middle-aged women: Preliminary findings

Authors: *N. GERVAIS[1], A. ALMEY[2,1], A. DUCHESNE[3], R. REUBEN[1], L. GRAVELSINS[1], E. BAKER-SULLIVAN[1], A. WONG[1], R. K. OLSEN[4], C. L. GRADY[5], G. EINSTEIN[1]
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Abstract: Considerable evidence demonstrates that estrogens have neuroprotective effects on the hippocampus (HPC). Estrogen loss via surgical menopause is associated with reduced verbal memory, and estrogen therapy (ET) prevents this reduction (Sherwin, 1988). Little is known about the impact of surgical menopause on the integrity of the HPC. Preliminary findings suggest that ET is protective in women that have had a BSO (Duchesne et al., 2017), yet no studies have examined the impact on HPC subfields. In addition to verbal memory, other abilities including associative memory are also sensitive to HPC function, yet limited studies have addressed the impact of estrogen deprivation on this ability. The aim of the present study is to determine whether BSO results in impaired associative memory and lower volume of HPC subfields. An additional aim is to determine whether ET is neuroprotective by preventing

negative changes resulting from BSO. Women with the BRCA mutation (BRCA 1/2) with a prophylactic BSO to reduce breast and ovarian cancer risk were recruited and comparisons were made between those taking estradiol-based ET (BSO-E2) and those not taking ET (BSO). Age-matched premenopausal women were also recruited and served as the comparison group (AMC) to both BSO groups. Demographic information was collected and a visual associative task was administered. This task involves an encoding phase, when face/name pairs are presented and participants are instructed to rate how well the name matches the face, and a test phase given 30 min later, when participants must identify the name previously paired with the presented face. Structural scans were obtained using a 3T Siemens scanner and volumes of HPC subfields were quantified manually using high-resolution T2-weighted scans. Preliminary group analyses (N = 21) were conducted on accuracy and response times obtained during the test phase of the memory task. While no group differences were observed on accuracy, the BSO group took longer to respond to correct trials, but not incorrect ones, indicating that they needed more time to recognize the correct association. The BSO group also had reduced CA1 volume. Performance and volume measures in BSO-E2 matched those in the AMC group. Taken together, these preliminary results suggest that BSO is associated with modest impairments in associative memory and a reduction in CA1 volume. E2-based ET appears to protect against these effects.

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Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.05/HHH60

Topic: H.02. Human Cognition and Behavior

Support: NIA AG025526
NIA AG019610
NIA AG049464
McKnight Brain Research Foundation
State of Arizona and Arizona DHS

Title: Relation of white matter lesion load to cortical gray matter thickness in healthy aging

Authors: *P. K. BHARADWAJ[1,2], L. A. NGUYEN[1,2], G. A. HISHAW[3], T. P. TROUARD[4], J. R. MOELLER[7], C. G. HABECK[8], G. E. ALEXANDER[1,2,5,6,9]
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Abstract: Cerebral white matter hyperintensities (WMH) measured by magnetic resonance imaging (MRI) are associated with vascular risk factors and are thought to reflect small vessel disease. Recently, Kern et al. (2017), used a multivariate technique, the Scaled Subprofile Model (SSM; Alexander & Moeller, 1994) to identify a WMH-related covariance network of regional gray matter volume related to differences in blood pressure control. Here, we sought to extend this multimodal multivariate approach, by deriving a covariance network of WMH-related cortical thickness (WMH-CTh), and to evaluate its relation to age and vascular risk in a cohort of community-dwelling, healthy older adults, 50 to 89 years of age. Volumetric T1 and T2-FLAIR MRI scans were acquired in 182 older adults (mean Age = 69.8 ± 10.4, 90F/92M, hypertension = 122N/60Y). Systolic blood pressure (SBP) was computed from average ambulatory blood pressure over 24 hours. T1 scans were processed using FreeSurfer v5.3 (Fischl et al., 2002) to extract cortical thickness values from 64 regions. Global WMH maps were generated from T1 and T2-FLAIR scans using a multispectral algorithm (Schmidt et al., 2012). The SSM was applied to regional cortical thickness measures to derive the covariance pattern related to total WMH load. The WMH-CTh pattern accounted for 15.1% of the variance in WMH load and was characterized by cortical thickness reductions bilaterally in superior temporal and right precentral regions, with bilateral relative increases in rostral and caudal anterior cingulate regions. Greater expression of the WMH-CTh pattern was associated with increasing age (r^2=0.36, p≤4.72E-19) and hypertension (r^2=0.03, p≤1.98E-2), but was not related to SBP (p = 0.15). After we controlled for gender, hypertension, diabetes, smoking history, and SBP, the relation between WMH-CTh and age remained significant (R^2 change=0.31, p≤2.49E-17). These results suggest that, in healthy older adults, aging is associated with an increasing relation between WMH lesion load and regional cortical thickness that is distinct from common vascular risk factors. Together, these findings support the use of multimodal network covariance methods to advance understanding of the relation between gray and white matter differences in the context of brain aging.

Disclosures: P.K. Bharadwaj: None. **L.A. Nguyen:** None. **G.A. Hishaw:** None. **T.P. Trouard:** None. **J.R. Moeller:** None. **C.G. Habeck:** None. **G.E. Alexander:** None.

Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.06/HHH61

Topic: H.02. Human Cognition and Behavior

Support: NIA AG025526

NIA AG019610
NIA AG049464
McKnight Brain Research Foundation
State of Arizona and Arizona DHS

Title: Hippocampal mediation of subjective memory complaints differs by hypertension status in healthy older adults

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Abstract: Subjective memory complaints may be an important early indicator of cognitive aging. We previously found that in healthy older adults with hypertension, having mild memory complaints was associated with poorer objective memory performance than in those without memory complaints, but this difference was not observed in those without hypertension (Nguyen et al., 2016). In the present study, we sought to investigate whether differences in hippocampal volume underlie subjective memory complaints, if this relationship differs by hypertension status, and how the association is related to objective memory performance in healthy older adults. A cohort of 208 older adults [104F/104M, mean±sd age = 69.9±10.4, mean±sd Mini-Mental State Exam = 29±1.2, hypertension (yes/no) = 69/139], 50 to 89 years of age, completed a scale of subjective memory complaints and a battery of neuropsychological tests. T1-weighted 3T volumetric MRIs were processed using Freesurfer (v5.3) software to obtain right and left hippocampal volumes. Total intracranial volume (TIV) was computed using T1 scans with SPM12 and white matter hyperintensities (WMH) were computed using T1 and T2 FLAIR scans and a lesion segmentation toolbox. Mediation analyses were performed using PROCESS macro software in SPSS (Hayes, 2012). Analyses revealed that the mediation of the relation between age and mild subjective memory complaints by right hippocampal volume was moderated by hypertension status (-.03 (SE= .01), 95% CI, [-.06, -.01]). These findings remained significant after including gender, education, hypertension duration, WMH volume, and total recall on word list learning test as covariates. There were no significant mediation effects of the relation between age and memory complaints for left hippocampal volume with or without covariates. Additionally, a sequential mediation model in individuals with hypertension revealed that age predicted right hippocampal volume, which then predicted subjective memory complaints, and in turn predicted objective memory performance (-.16 (SE= .08), 95% CI, [-.38, -.05]). There were no significant sequential mediation models for left hippocampal volume or in individuals without hypertension. These results indicate that, in healthy older adults, the combination of mild subjective memory complaints and hypertension has an anatomical substrate, reflected by reduced right hippocampal volume, which in turn leads to differences in objective memory performance. Together, these findings suggest that mild memory complaints may provide an

early marker of cognitive aging, when observed in the context of hypertension, a common age-related vascular risk factor.

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Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.07/III1

Topic: H.02. Human Cognition and Behavior

Support: NIA AG025526
NIA AG019610
NIA AG049464
McKnight Brain Research Foundation
State of Arizona and Arizona DHS

Title: Relation between physical sport activity and white matter hyperintensity volume in older adults

Authors: *M. FRANCHETTI[1,8,9], P. K. BHARADWAJ[1,8,9], L. A. NGUYEN[1,8,9], Y. C. KLIMENTIDIS[2], G. HISHAW[3], T. P. TROUARD[4], D. A. RAICHLEN[5], G. E. ALEXANDER[1,6,7,8,9]
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Abstract: Cerebral white matter lesion load, as measured by white matter hyperintensities (WMHs) on MRI, have been associated with cardiovascular risk factors like hypertension as well as increasing age and poorer cognitive performance. Physical activity (PA) may play an important role in maintaining cerebral white matter (WM) in the context of healthy aging. We sought to determine whether high levels of self-reported physical sport activity are associated with lower WMH volume. Self-report ratings of physical sport activity were obtained from 196 healthy older adults (mean ± SD age = 69.8 ± 10.6 years). Participants reporting high sport activity (n=36) were compared to those with low sport activity (n=160). MRI scans were acquired at 3T, including volumetric T1 and T2 FLAIR scans. Total WMH volume was computed with a multispectral, automated lesion segmentation method to produce probability maps using Statistical Parametric Mapping (SPM12) and the lesion segmentation toolbox (LST; Schmidt et al., 2012). ANCOVA tested age group (young-old (YO) = 50-69 years; old-old (OO)

= 70-89 years), PA group, and age by PA group interaction effects after controlling for gender and hypertension status. No main effect for PA group ($p > 0.05$) was observed. We found a main effect for age group ($p = 0.005$) and age by PA group interaction ($p = 0.005$). Simple effect analyses indicated that total WMH volume for the high PA group is comparable between the YO and OO. In addition, the OO with low PA had a significantly higher WMH volume than both the YO with low PA ($p = 2.72E-10$) and the OO with high PA ($p = 0.00038$). These findings remained significant after correcting for total intracranial volume (TIV). These results suggest that high levels of physical sport activity may be an important lifestyle factor that can help to diminish WMH lesion load in old age, potentially reducing the impact of brain aging.

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Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.08/III2

Topic: H.02. Human Cognition and Behavior

Title: Systemic inflammation is associated with longitudinal changes in cognitive performance among urban adults

Authors: *M. A. BEYDOUN[1], G. A. DORE[1], J. A. CANAS[4], H. LIANG[5], H. A. BEYDOUN[6], M. K. EVANS[2], A. B. ZONDERMAN[3]
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Abstract: BACKGROUND: Chronic systemic inflammation is a risk factor for neurodegeneration. In two waves of data, we examined the association of systemic inflammation with cognitive performance in 1,555-1,719 White and African-American adults aged 30-64y at baseline (2004-2013, mean±SD time(y) between visits: 4.64±0.93y). **METHODS**: Baseline cognitive performance and annual rate of cognitive change were assessed by eleven cognitive tests measuring mental status, attention, memory, executive function, visuo-spatial, psychomotor speed, and verbal abilities. Exposures were baseline serum C-reactive protein, Erythrocyte Sedimentation Rate (ESR), albumin, iron and an inflammation composite score combining all four markers (ICS). Linear mixed-effects regression models were conducted. **RESULTS**: Baseline serum CRP was associated with poorer baseline mental status among younger women (γ_{01}=-0.03±0.01, p=0.002) and poorer attention among older women(γ_{01}=-0.024±0.007, p<0.004)

and African-Americans(γ_{01}=-0.029±0.008, p<0.001). Baseline ESR was associated with a faster decline in verbal memory among older men (γ_{11}=-0.008±0.003, P=0.009); with poorer performance on tests of attention overall (γ_{01}=-0.010±0.003, P=0.003) and among African-Americans (γ_{01}=-0.013±0.004, P=0.002); on a test of verbal fluency among older women (γ_{01}=-0.037±0.013, P=0.004) and on a test of executive function, overall (γ_{01}=+0.62±0.21, P=0.004), among older men (γ_{01}=+1.69±0.53, P=0.001) and among African-Americans ((γ_{01}=+0.84±0.28, P=0.002). In contrast, serum albumin was linked to slower attention decline among older men (γ_{11}=+0.329±0.103, P=0.009), over-time improvement in executive function in the total population (γ_{11}=-6.00±2.26, P=0.008), and a better baseline performance in psychomotor speed among African-Americans (γ_{01}=+0.56±0.19, P=0.003). There were no significant associations between serum iron and cognitive outcomes. Finally, the ICS was associated with faster decline on a test of visual memory/visuo-constructive abilities, among older men only (γ_{11}=+0.17±0.06, p=0.003). **CONCLUSIONS**: There were strong associations between systemic inflammation and cognitive performance at baseline and over time for several domains of cognition, largely among older individuals and African-Americans. Future randomized trials should monitor systemic markers of inflammation and cognitive performance over time.

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Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.09/III3

Topic: H.02. Human Cognition and Behavior

Support: CIHR Grant MOP126105
Alzheimer's Society of Canada Grant# 1435

Title: Sex differences in brain-behaviour correlations in episodic memory: An adult lifespan study

Authors: *S. SUBRAMANIAPILLAI[1,3], S. RAJAGOPAL[3], S. PASVANIS[3], D. TITONE[1], M. RAJAH[2,3]
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Abstract: Healthy aging is associated with episodic memory decline (i.e., our ability to encode, store and retrieve personally experienced events in rich contextual detail). Prior studies have shown a tendency for women to outperform men on episodic memory tasks. For example, women perform better than men on object-location associative and face memory tasks (Herlitz

and Rehman, 2008). Many sociocultural and biological factors likely contribute to these sex differences in performance, which in turn may impact the functional neural networks supporting episodic memory in women, compared to men. This raises the possibility for the presence of sex differences in brain aging, particularly in episodic memory networks. In the current event-related fMRI study, we investigated sex differences in brain activity during face-location associative memory tasks across the adult lifespan (N = 86, mean age = 46.5 yrs, 50% females). Participants were scanned during encoding and retrieval. Our behavioural results indicate a robust effect of age on memory performance but no sex differences in face-location retrieval accuracy nor reaction time. However, our multivariate behaviour Partial Least Squares fMRI analysis revealed significant interaction between age and sex at encoding and retrieval. Specifically, in women, there was an age-related increase in parahippocampal activity at encoding. In contrast, in men, there was an age-related increase in parahippocampal activity at retrieval. In addition, only in men, there was a generalized pattern of inferior parietal activity across encoding and retrieval with advanced age. Overall, men and women engaged similar brain networks during memory encoding, but sex differences were observed in retrieval-related activity.

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Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.10/III4

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant EB006589
NIH Grant GM103526

Title: Frontal functional connectivity as a measure of cognitive reserve: An optical imaging study

Authors: *A. V. MEDVEDEV
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Abstract: Aims. Cognitive reserve (CR) is the ability to preserve cognitive functions in the presence of brain pathology. One commonly used proxy measure of CR is IQ. In the context of Alzheimer's disease (AD), patients with higher CR show better cognitive performance relative to brain damage therefore higher CR reduces the risk of dementia. There is a strong need to develop a reliable biomarker of CR given the growing interest in understanding protective brain mechanisms in AD. Recent fMRI studies indicate that frontoparietal network may play an important role in the maintenance of CR. The goal of this study was to demonstrate that near

infrared spectroscopy (NIRS) can be used to assess functional connectivity (FC) of the prefrontal cortex (PFC) in correlation with IQ, a proxy measure of cognitive reserve.
Methods. We analyzed resting state optical data from prefrontal cortex in 13 healthy individuals who were also assessed by Wechsler Abbreviated Scale of Intelligence (WASI) test and the Purdue Pegboard test (PPT). For each participant, activity of each prefrontal channel was correlated with all other channels and positive correlation coefficients were Fisher-transformed and averaged over all PFC channels giving the Global Functional Connectivity (GFC) of PFC. The resulting GFC number was then correlated with the individual IQ (WASI full score) and the PPT scores.
Results. Frontal connectivity was found to be significantly greater in the quartile subgroup of participants with higher IQ scores (the mean IQ = 131 ± 1.2; the mean GFC = 0.69 ± 0.18) compared to the quartile subgroup with lower IQ scores (the mean IQ = 113 ± 4.3; the mean GFC = 0.36 ± 0.16; the differences between subgroups in IQ and GFC are significant). Moreover, the individual GFC values were found to positively correlate with the individual IQ scores and negatively correlate with the PPT scores. These results demonstrate that optically measured PFC GFC can be used as a physiological measure of cognitive reserve.
Conclusions. Our data provide further confirmation that cognitive reserve depends on the functional integrity of the frontoparietal network, a major cognitive control hub. Also, our experimental approach demonstrates that functional connectivity can be assessed by optical imaging using the NIRS technology. As a cost-efficient and noninvasive technology, NIRS can be used in the development of new neurophysiological measures of cognitive reserve with numerous possible applications in the context of healthy aging and cognitive disorders.

Disclosures: A.V. Medvedev: None.

Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

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Program #/Poster #: 515.11/III5

Topic: H.02. Human Cognition and Behavior

Support: Pioneer Award DP1AG047744
Alzheimer's Association Research Fellowship AARF-18-533294
DA02399
EY00259

Title: Ultrastructural mapping of phosphodiesterase 4D (PDE4D) in rhesus macaque dorsolateral prefrontal cortex: Plausible role in the etiology of Alzheimer's disease

Authors: *D. DATTA[1], Y. M. MOROZOV[3], J. I. ARELLANO[2], P. RAKIC[5], A. F. ARNSTEN[4]
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Abstract: Tau pathology in Alzheimer's disease (AD) targets pyramidal cells in the aging association cortices, including the newly evolved dorsolateral prefrontal cortex (dlPFC). Our recent data revealed that aging rhesus macaques can be used to study late-onset AD pathology, as they recapitulate the qualitative pattern and sequence of tau and amyloid pathology seen in humans (Paspalas et al, Alzh&Dementia, epub Dec 11, 2017). Tau normally stabilizes microtubules, but phosphorylation by cAMP-PKA signaling at pS214Tau causes tau to detach from microtubules and fibrillate into classical paired helical filaments in tangles, and primes tau for hyperphosphorylation by GSK3β. These pathological alterations are associated with concurrent phosphorylation by cAMP-PKA signaling of type II ryanodine receptors (RyR2) at pS2808RyR2, suggesting calcium dysregulation. cAMP-PKA signaling becomes dysregulated in the aging dlPFC due to loss of phosphodiesterase (PDE4) activity, contributing to cognitive impairment and PKA-phosphorylation at pS214Tau (Carlyle et al, PNAS 111:5036-41, 2014). Previous research focused on the PDE4A isozyme, but PDE4D is of greater interest, as it is the predominate PDE4 in cortex, and PDE4D expression decreases with advancing age in the human dlPFC. However, the subcellular localization of PDE4D in dlPFC neurons is unknown. The current study used high-spatial resolution immunoelectron (immunoEM) microscopy to examine the subcellular distribution of PDE4D in layer III of the young adult primate dlPFC, the neurons that generate working memory. PDE4D was especially prominent in dendrites near microtubules and on the smooth endoplasmic reticulum (SER), in close proximity to mitochondria. There was also significant postsynaptic labeling in dendritic spines, in association with the SER spine apparatus near glutamate-like axospinous synapses. Importantly, these are the same sites where PKA pS214Tau accumulates in aged dlPFC. Our findings suggest that PDE4D is critically positioned in dlPFC glutamatergic microcircuits to modulate cAMP regulation of calcium signaling. Loss of PDE4D expression with advancing age may render association cortices particularly susceptible to cAMP dysregulation of internal calcium release, and cAMP-PKA phosphorylation of tau, factors which increase risk of AD. These events in the aging association cortex may provide an opportunity for therapeutic intervention at early stages of disease.

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Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.12/III6

Topic: H.02. Human Cognition and Behavior

Support: Alzheimers Association IIRG

Title: “How do you feel about your future?” Results of the study of knowledge and reactions to amyloid testing (SOKRATES), a qualitative study of cognitively normal older adults’ reactions to learning an “elevated” or “not elevated” PET scan result

Authors: *J. H. KARLAWISH, S. STITES, E. LARGENT, B. BEAR, K. HARKINS
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Abstract: The diagnostic criteria of late-life neurodegenerative diseases such as Alzheimer’s disease is transforming from using clinical to biomarker-based features. Measures of brain amyloid are, for example, used to define a pre-clinical stage of Alzheimer’s disease, and several clinical trials are testing anti-amyloid drugs in adults who are cognitively unimpaired but have PET scan measured evidence of “elevated” brain amyloid. One goal of the SOKRATES Study is to discover how knowledge of an amyloid result impacts on an adult’s perception of their future and the behaviors they adopt. Samples of persons with “elevated” amyloid (n=50, median age 72, range 65 to 85) who were enrolled in a five year long, multi-center, 1,800 subject, randomized and placebo controlled trial of an anti-amyloid drug and persons with “not elevated” amyloid (n=30, median age 70, range 65 to 80) who were ineligible for the trial participated in telephonic semi-structured interviews 1-3 months after learning their PET scan results and again 12 months later. Subjects were recruited from 10 research centers in the U.S. Answers to “*How do you feel about your future?*” and “*How did learning your result change how you feel about your future?*” were analyzed qualitatively. Persons with not elevated amyloid reported sustained feelings of relief and optimism. Initial reports of expansive remaining time had somewhat diminished. In contrast, persons with elevated amyloid provided nuanced responses, reporting that the future is unknown but hopeful, being present focused, not thinking about the future, or feeling that remaining time is limited. Some described optimism. Initial reports of pessimism and a bleak future diminished at 12 months. None reported feelings of relief, and few felt an expansive sense of remaining time. Answers to “*Are you changing or reassessing any plans in your life since learning your result?*” showed that about half of the persons with elevated amyloid were not at either time point. The other half were considering making plans related to a variety of life and health matters. Few with not elevated amyloid were considering any changes. These results suggest that knowledge of “elevated” brain amyloid causes a cognitively normal older to experience changes in how they feel about their future and these feelings may in turn lead to changes in behavior. In contrast, persons who learn a “not elevated” result generally report relief with little behavior change. The presentation will discuss how these results are explained by future time perspective, and their implications for how we define and understand cognitive aging and the decisions older adults make.

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Poster

515. Human Cognition and Behavior: Cognitive Aging I

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.13/III7

Topic: H.02. Human Cognition and Behavior

Support: R00 AG-036818-05
RO1 AG-56535-02
R00 AG-036848-05

Title: Genetic predisposition for inflammation exacerbates effects of striatal iron content on cognitive switching in healthy aging

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Abstract: Non-heme iron homeostasis interacts with inflammation bidirectionally, and both factors contribute to age-related decline in brain structure and function via oxidative stress. Thus, individuals with genetic predisposition toward inflammation may be at greater risk for brain iron accumulation during aging and more vulnerable to cognitive decline. We examine this hypothesis in a lifespan sample of healthy adults (N = 183, age 20-94 years) who underwent R2*-weighted magnetic resonance imaging (MRI) to estimate regional brain iron content. Interleukin 1β (IL-1β) is a pro-inflammatory cytokine and the T allelle of the single nucleotide polymorphism increases risk for chronic neuroinflammation; thus, heterozygote (n = 87) and homozygote (n = 23) T-carriers were considered to have greater inflammation risk than non-carriers (n = 73). Hypotheses were tested in a grouped latent modeling framework and all estimates were bootstrapped with bias-correction to produce 95% confidence intervals (BS 95% CI). Across individuals, older age was associated with greater striatal iron content ($b = 0.21$, $p < 0.001$; BS 95% CI: 0.16/0.29) that in turn accounted for poorer cognitive switching performance ($b = -0.26$, $p < 0.001$; BS 95% CI: -0.45/-0.17). However, heterozygote IL-1β T-carriers demonstrated worse switching performance in relation to striatal iron content ($b = -0.43$, $p < 0.001$; BS 95% CI: -0.80/-0.22) as compared to their no-risk counterparts (difference = 0.26, $p = 0.02$; BS 95% CI: 0.00/0.68), despite the two groups being of similar age. With increasing genetic inflammation risk, homozygote IL-1β T-carriers had lesser age-related variance in striatal iron content as compared to the other groups (difference = 0.19 and 0.15, p's = 0.002), but showed a similar association of greater striatal iron content predicting poorer cognitive switching (both p's > 0.80). Non-heme iron and inflammation, although necessary for normal neuronal function, both promote oxidative stress that when accumulated in excess, drives a complex

mechanism of neural and cognitive decline in aging. These findings highlight the importance and utility of investigating epigenetic effects in the study of individual differences in brain and cognitive aging.

Disclosures: A.M. Daugherty: None. **K.M. Kennedy:** None. **K.M. Rodrigue:** None.

Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.14/III8

Topic: H.02. Human Cognition and Behavior

Support: R00 AG-036818-05
R00 AG-036848-05
R01 AG-56535-02

Title: Age-related striatal iron accumulation is associated with decreased dynamic range of activation to working memory load and predicts executive function performance

Authors: K. M. RODRIGUE[1], A. M. DAUGHERTY[2], C. M. FOSTER[1], *K. M. KENNEDY[3]
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Abstract: Non-heme iron accumulation contributes to age-related decline in brain structure and function via a cascade of oxidative stress and inflammation. Although recent evidence illustrates the negative effects of increased iron content on human brain structure and cognition, its effect on brain function is largely unexplored. Thus, we examine, in vivo, using R2*-weighted magnetic resonance imaging (MRI), the impact of basal ganglia (BG) iron accumulation on the dynamic range of BOLD modulation to increasing cognitive challenge across the adult lifespan. Participants included 166 healthy adults (age 20-94 years) who underwent cognitive testing and an imaging session including n-back (0-, 2-, 3-, and 4-back fMRI collected across 3 blocks for 20min), R2*-weighted imaging, and pcASL to measure cerebral blood flow. A first-level linear contrast was computed that identified regions that either up- or down-modulated in response to task difficulty. At the second level, BOLD modulation was predicted by age, BG iron, age by BG iron, controlling for cerebral blood flow, sex, and task response time. We found a traditional set of working memory-related brain regions that up-modulated in response to task difficulty (bilateral dorsolateral prefrontal cortex, anterior cingulate, caudate, posterior parietal, cerebellum). Regions that down-modulated in response to difficulty included typical regions associated with the default mode network. Importantly, we found a significant interaction between age and BG iron burden on positive BOLD modulation in a cluster located primarily in

the putamen, caudate, and inferior frontal gyrus. The interaction indicated that greater iron content was associated with reduced modulation to difficulty, and this effect was strongest in younger adults with greater iron burden. Further, iron-related decreases in modulation were associated with poorer executive function performance outside the scanner in an age-dependent manner (BOLD modulation x iron x age interaction, p = .056). A simple slopes analysis of the interaction indicated that the slope of age on executive function is less steep in high-modulating, low iron individuals, and also less steep in low-modulating, high iron individuals. These findings suggest that striatal iron accumulation negatively alters dynamic range of modulation to difficulty locally and in prefrontal cortex. This iron-related alteration in BOLD response is also associated with poorer executive function performance, linking the iron cascade to brain function and cognitive outcome.

Disclosures: K.M. Rodrigue: None. **A.M. Daugherty:** None. **C.M. Foster:** None. **K.M. Kennedy:** None.

Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

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Program #/Poster #: 515.15/III9

Topic: H.02. Human Cognition and Behavior

Support: NSF Graduate research fellowship
RO1-AG034570

Title: Amyloid-beta spreads from multiple sources in healthy aging

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Abstract: The hallmark pathology of Alzheimer's disease, amyloid-β plaques (Aβ), typically exhibits advanced progression throughout cortex by the time cognitive symptoms manifest. Despite a characteristic spatiotemporal progression of Aβ pathology in the pre-symptomatic phase, there is no consensus on the earliest brain areas that accumulate Aβ. We developed a novel cross-sectional approach to examine regional accumulation relative to the total amount of Aβ pathology in the brain within different stages of Aβ progression in healthy aging - PIB-, Early PIB+, and Late PIB+ - by examining PIB-PET from 147 cognitively normal older adults (aged 65 to 91 years old) as well as from 16 young adults (aged 21 to 30 years old). We modeled the cross-sectional rates of accumulation to generate directed progression networks, which

measure progression from earlier to a later Aβ stages by drawing connections emanating from regions with accelerated accumulation in earlier Aβ stages and emanating to regions with accelerated accumulation in later Aβ stages. We identified potential sources of Aβ pathology in the PIB- stage, relays in the Early PIB+ stage, and targets in the Late PIB+ stage. The sources, relays, and targets of Aβ pathology were distributed across the brain, comprising multiple brain networks. The largest number of sources and relays were in the default mode network, however all regions of the memory network were impacted. Relays, and to a lesser extent sources, additionally impacted the other higher order brain networks whereas the targets primarily impacted sensory networks. This framework suggests that distributed brain areas across multiple networks may serve as sources of Aβ even before substantial Aβ pathology is detected in healthy aging. While specific brain networks such as the default mode and memory networks may be particularly impacted, especially as Aβ pathology progresses, accumulation of Aβ pathology is diffuse, multifocal, and does not appear to emanate from any single source or brain network.

Disclosures: K. Arnemann: None. **L. Digma:** None. **W.J. Jagust:** None.

Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.16/III10

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant NS082870
NIH Grant AG051846

Title: Cortical excitability as a marker of global cognitive function in pathological cognitive aging

Authors: *P. J. FRIED[1], S. S. BUSS[1], K. M. MCDONALD[1], D. Z. PRESS[1], A. PASCUAL-LEONE[1,2]
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Abstract: Background. Transcranial magnetic stimulation (TMS) provides a noninvasive means to assess cortical excitability and the efficacy of neuroplastic mechanisms in humans. Recently, cortical hyperexcitability, as indexed by the TMS resting motor threshold (RMT), has emerged as a potentially meaningful correlate of cognitive function in mild-to-moderate Alzheimer's disease (AD). Previous work has shown that RMT tends to be lower in AD patients than healthy controls and negatively associated with global cognitive dysfunction (lower RMT = greater dysfunction). It is unknown whether this relationship extends to older adults with Type-2 diabetes mellitus (T2DM) or mild cognitive impairment (MCI), who are at a higher risk of

developing AD.
Objective. The objective of the present study is to assess the relationship of RMT to measures of global cognitive function in patients with T2DM and those with MCI.
Methods. In a cross-cohort study, data were obtained from 18 patients with a diagnosis of probable amnestic MCI (mean ± SD age: 69.4 ± 9.3 years, 47% female) and 28 patients with T2DM (mean ± SD age: 65.8 ± 7.7 years, 43% female). Data included RMT (% of maximum stimulator output) and two measures of global cognitive function, the Mini Mental Status Examination (MMSE) and the Cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog).
Results. The MCI group performed significantly worse than T2DM on the MMSE (MCI: 25.8 ± 2.8; T2DM: 29.0 ± 1.0, $p < .001$) and the ADAS-Cog (MCI: 11.5 ± 4.4; T2DM: 6.0 ± 2.8, $p < .001$). RMT was significantly ($p = .012$) lower in MCI (58.8 ± 8.3) than T2DM (66.4 ± 11.4). Linear regression analyses yielded significant relationships between RMT and both MMSE ($p = .009$) and ADAS-Cog scores ($p = .009$), controlling for group. Specifically, lower RMT was associated with worse performance on both measures.
Conclusion. Lower RMT is associated with worse global cognitive function in individuals at risk of developing AD. Future longitudinal studies are needed to determine if cortical hyperexcitability, as indexed by TMS, can serve as a prognostic marker of cognitive decline in preclinical dementia.

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Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.17/III11

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant AG055653

Title: Eight-year longitudinal change in association cortical thickness: Progression from cognitively healthy to dementia

Authors: *S. L. WILLIS, P. R. ROBINSON, E. ULZIIBAATAR, T. J. GRABOWSKI, K. SCHAIE
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Abstract: Understanding the transition from cognitively normal status to a diagnosis of dementia and the risk factors predicting this transition is a major public health goal. This requires

longitudinal studies, following individuals over time. This study examined 8-year longitudinal change in cortical thinning in progression from cognitively healthy to dementia diagnosis. At baseline, all participants in the Seattle Longitudinal Study were nondemented (N=185; mean age = 16.3; 58% female; 31% APOE e4; and 42% hypertensive. Over 5 measurement occasions (8 years), N = 15 participants progressed to dementia. These participants were older, had higher proportion APOE e4, and hypertensive, but did not differ in education. Multivariate multilevel modeling was used to examine cross-sectional differences and longitudinal change in cortical thinning for 5 cortical composites (Frontal, Parietal, Temporal, Occipital, Cingulate). Using the Freesurfer suite, regions from the Desikan Parcelation were aggregated to form lobar composites of association cortex. Composites were modeled together at the whole brain level; regions within each composite were also modeled together. The modifying effects of APOE e4 and hypertension were examined. Results: Significant age differences (cross sectional) were found for all 5 composites. Dementing participants had thinner cortex at baseline in Frontal, Parietal, Temporal and Cingulate composites; and were more likely to be hypertensive (HB x Dementia) for these composites. For the Parietal composite and Parietal regions (inferior, precuneus), a faster rate of thinning occurred for participants progressing to dementia (Time x Dementia). No interactions of dementia status and APOE were found. These longitudinal findings extend prior cross-sectional reports between cortical thinning and progression to dementia.

Disclosures: P.R. Robinson: None. **E. ulziibaatar:** None. **T.J. Grabowski:** None. **K. Schaie:** None.

Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.18/III12

Topic: H.02. Human Cognition and Behavior

Support: R01 AG050523

Title: Age-related neural dedifferentiation extends beyond visual cortex and is driven by less reliable neural activation

Authors: *M. SIMMONITE[1], K. E. CASSADY[1], H. C. GAGNON[1], P. S. LALWANI[1], S. F. TAYLOR[2], D. H. WEISSMAN[1], R. D. SEIDLER[3], T. A. POLK[1]
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Abstract: According to the neural dedifferentiation hypothesis, age-related cognitive declines stem in part from reductions in the distinctiveness of neural representations; that is, neural activity associated with different stimulus categories becomes less distinguishable with age and

behavioral performance suffers as a result. Almost all previous studies have investigated age-related dedifferentiation in the visual cortex, using visual tasks. Increasing evidence however, suggests that dedifferentiation may be a more general feature of the aging brain, present in other brain regions. In the present study, we used 3T functional MRI to investigate age-related dedifferentiation not only in the visual cortex during a visual task (oddball detection during face and house blocks), but also in the auditory cortex during an auditory task (oddball detection during speech and music blocks), in somatosensory cortex during a somatosensory task (oddball detection during vibrotactile stimulation to fingers of the left and right hand), and in motor cortex during a motor task (directed movement of left and right hand). Participants were 21 young adults (aged 18 to 29) and 24 older adults (aged 65 +), who completed all four tasks. Activation patterns across different blocks within the same conditions were correlated (within-condition correlation, a measure of reliability) as were activation patterns across blocks from different conditions (between-condition correlations, a measure of dissimilarity). Neural distinctiveness was defined as the difference between the mean within- and between-condition correlations, averaged over all such pairwise comparisons. We found age-related reductions in neural distinctiveness in the visual, auditory and motor cortices, but not somatosensory cortex. In visual and auditory cortex, these effects were driven by age-related differences in within-condition correlations, not between-condition correlations. Additionally, neural distinctiveness in each brain region was not significantly correlated with distinctiveness in the other regions after correcting for multiple comparisons. These findings indicate that age-related reductions in neural distinctiveness extend beyond the visual cortex, and may be driven primarily by age-related reductions in the reliability of neural activity.

Disclosures: M. Simmonite: None. **K.E. Cassady:** None. **H.C. Gagnon:** None. **P.S. Lalwani:** None. **S.F. Taylor:** None. **D.H. Weissman:** None. **R.D. Seidler:** None. **T.A. Polk:** None.

Poster

515. Human Cognition and Behavior: Cognitive Aging I

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.19/III13

Topic: H.02. Human Cognition and Behavior

Support: NIH grant R01 NR014810

Title: Decline in functional connectivity between resting state networks after total knee arthroplasty with general anesthesia in older adults

Authors: *H. HUANG, C. HARDCASTLE, J. TANNER, H. PARVATANENI, C. PRICE, M. DING
Univ. of Florida, Gainesville, FL

Abstract: Our previous work has shown that functional connectivity within each of the three major resting state networks (RSNs), including default mode network (DMN), salience network (SN) and central executive network (CEN), declines after total knee arthroplasty with general anesthesia in older adults. In this study we examined the changes in functional connectivity between the three RSNs before and after surgery. Particular emphasis was placed on the impact of pre-surgery cognitive status on pre- to post-surgery changes in internetwork functional connectivity. Participants included 69 non-demented older individuals (average age: 68.7, 36 women) who elected for unilateral total knee arthroplasty surgery and 65 non-surgery controls (average age: 68.4, 37 women) matched on age, sex, education, and race. 13 surgery patients and 10 controls met the criteria for mild cognitive impairment (MCI). Resting state fMRI scans were acquired before surgery and within 48 hours after surgery (a pseudo surgery date was defined for each control). Pre-surgery and post-surgery functional connectivity between DMN, SN and CEN was computed and compared. The following results were found. For patients, the magnitude of functional connectivity between DMN and SN declined significantly after surgery. Comparing effect size, relative to patients without MCI, patients with MCI exhibited more pronounced DMN-SN functional connectivity decline (d=1.5 for MCI versus d=0.7 for non-MCI). There were no significant changes in DMN-CEN and SN-CEN internetwork functional connectivity. For controls, there were no significant changes in any of the internetwork functional connectivities. These results suggest that (1) DMN-SN functional relationship, one of the most important in the brain, is vulnerable to the disruption of major surgery and (2) impaired cognition is a major risk factor.

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Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.20/III14

Topic: H.02. Human Cognition and Behavior

Support: NSERC Discovery
Fonds de Recherche Quebec - Santé
Ontario Graduate Scholarship

Title: Little effect of computerized cognitive training or expectations in healthy older adults

Authors: *S. RABIPOUR, C. MORRISON, J. CROMPTON, M. PETRUCELLI, M. GERMANO, A. POPESCU, P. S. R. DAVIDSON
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Abstract: Computerized cognitive training is becoming increasingly popular and practical, holding promise for both patients and healthy individuals. Nevertheless, basic questions remain about the benefits of such programs, and about the degree to which expectations might influence training and transfer. Here we examined the potential transfer effects of a commercial cognitive training program (*Activate*) in a 5-week double blind, randomized placebo-controlled trial. We recruited 99 healthy older adults 59-91 years of age (*M*=68.87, *SD*=6.31; 69 women), randomly assigning them to either the intervention or an active control program (Sudoku and n-back working memory exercises). We subdivided both groups into high and low expectation priming conditions, to probe for effects of participant expectations on training and transfer effects. We assessed transfer using standard cognitive and neuropsychological tests, and self-reports of psychosocial function. The majority (88%) of participants completed the training, with positive feedback about their experience. Moreover, participants in all groups were largely optimistic about outcomes at baseline ($t_{(86)} \leq 3.97$, $p<0.0001$, Cohen's $d \geq .86$). Expectation ratings indicated that our expectation priming effectively increased or decreased participant expectations at the outset ($F_{(1,83)} \geq 7.32$, $p \leq .008$, $\eta_p^2 \geq .081$). Yet, transfer of training was minimal in all groups. Also minimal were any effects of expectations on training and transfer: results suggested that, if anything, the low expectation priming groups had higher scores on several transfer tests before and after training. Interestingly, participants in the active control groups reported significantly higher enjoyment ($F_{(1,83)} = 7.48$, $p=.008$, $\eta_p^2=.083$) and lower boredom ($F_{(1,83)}=9.42$, $p=.003$, $\eta_p^2=.102$), compared to the *Activate* groups. Our results suggest that such cognitive training interventions are feasible and enjoyable, but - using the current parameters - unlikely to improve cognitive function or psychosocial wellbeing.
Keywords: Aging; Executive function; Expectation; Cognitive

Disclosures: S. Rabipour: None. **C. Morrison:** None. **J. Crompton:** None. **M. Petrucelli:** None. **M. Germano:** None. **A. Popescu:** None. **P.S.R. Davidson:** None.

Poster

515. Human Cognition and Behavior: Cognitive Aging I

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 515.21/III15

Topic: H.02. Human Cognition and Behavior

Title: The effect of cardiovascular risk factors on fMRI activations to multi-tasking in healthy older adults

Authors: *S. QIN[1], C. BASAK[2]
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Abstract: Cardiovascular risk factors, such as high blood pressure (BP) and high Body Mass Index (BMI), have been associated with sharp age-related declines in executive functions in

normal aging. Past neuroimaging studies have identified age-related differences in brain activation patterns, as well as differences in brain-behavior relationship, between healthy older adults and younger adults during executive function tasks. It is possible that high cardiovascular risks in older adults contribute to these age-related differences in brain activations. The current study was aimed to examine the effects of cardiovascular risks on age-related differences in brain activation patterns in task-related regions during multi-tasking. A multi-tasking paradigm used in our prior study (Nashiro, Qin, O'Connell & Basak, 2018) was used, where a hybrid design allowed examination of both sustained (global switch cost: block design) and transient (local switch cost: event-related design) activations during different types of executive controls. Twenty seven younger and forty older adults were recruited. Older adults were then assigned to either high risk (20) or low risk (20) category based on a composite score of BP and BMI. Differences in activation patterns between high risk older adults and younger adults, and between high risk older adults and low risk older adults were examined in whole brain group contrasts. Preliminary results from block design analyses showed that high risk older adults had a) increased activation compared to low risk older adults in the paracingulate gyrus, and b) increased activation compared to younger adults at the posterior cingulate cortex. Increased activations in high risk older adults from these two regions were not related to task performance, and did not overlap with task-sensitive regions. Taken together, our results suggest that high cardiovascular risk results in both non-compensatory over-activation and disrupted brain-behavior relationships in healthy older adults.

Disclosures: S. Qin: None. **C. Basak:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

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Program #/Poster #: 516.01/III16

Topic: H.02. Human Cognition and Behavior

Support: TOYOTA Motor Corporation
RIKEN Research Funds for Data Assimilation

Title: Modeling the individual brain dynamics by a data assimilation approach

Authors: *T. SASE[1,2], K. KITAJO[2]
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Abstract: The human brain yields rhythms—which, in fact, originate from the underlying nonlinear dynamical system. Their properties, such as the interaction between different rhythms, spontaneously vary; i.e., the brain has the potential for making transitions among multiple

oscillatory states of the large-scale network. Those states can be referred to as the metastable states from a dynamical systems point of view (Tognoli & Kelso, 2014). The dynamics of such a state is likely to move into another one by small fluctuations, resulting in spontaneous transitions successively. Recently, we have shown the first experimental evidence that metastable phase-amplitude coupling (PAC) dynamics in the human brain is associated with the autism spectrum [Sase & Kitajo, The 47th Annual Meeting of Neuroscience, 2017]. This previous study has suggested that the following elements are necessary to model the resting human brain: slow and fast oscillators, connectivity with PAC, fluctuations, and metastability.
Based on this suggestion, in this study, we aim to generate individual models for the resting human brain by a data assimilation (DA) approach. The present DA study consists of: (I) Generating a universal model for the resting human brain among individuals; (II) Developing an adjoint method for the model; and (III) Applying the method to the model combined with the resting-state electroencephalography (EEG) data.
To generate the universal human brain model, in stage (I), we propose a methodology starting from a general system for metastable PAC systems driven by fluctuations. This system was reduced to (i) the small-amplitude system using the reductive perturbation method, (ii) the coupled phase oscillators system at a microscopic level, (iii) its macroscopic version derived from the Ott-Antonsen ansatz, and (iv) the coupled phase oscillators system at a macroscopic level, in turn. The reduced system was applied to the proposed DA method, and then, the individually specific parameters were estimated.
We conclude that the resting-state EEG-DA framework, proposed here, has the potential for unraveling individual differences. In the future, the present DA study should be validated by our previous data-driven study.

Disclosures: T. Sase: None. **K. Kitajo:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

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Program #/Poster #: 516.02/III17

Topic: H.02. Human Cognition and Behavior

Support: NIH R01MH110630
NICHD T32HD007475

Title: "Thin slice" functional connectome fingerprinting

Authors: *L. BYRGE, D. P. KENNEDY
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Abstract: In many domains, individual identity can be predicted using only a fraction of all possible diagnostic information, such as from a partial fingerprint or DNA segment or from a brief glimpse at a facial expression or gait. We now know that individual identity can be predicted using functional connectomes – correlation matrices among fMRI time series spanning the whole brain or cortex. However, whether individual identity can be predicted from a "thin slice" of a functional connectome has not yet been systematically explored. We analyzed functional connectomes constructed from Human Connectome Project resting-state fMRI scans (4 14 min. scans per subject, TR=720ms, *N*=883) preprocessed using ICA-FIX+GSR and various (901) parcellations. We used connectomes from half the subjects to determine the diagnostic value of each functional connection ("edge") based on the ratio of across-subject variability and within-subject variability. Using the remaining scans, we then attempted to "fingerprint" – to predict individual identity on the basis of maximal similarity among connectomes – using various subsets or "thin slices" of the complete connectome. First, we attempted to identify individuals using slices comprised of only the connectome edges with highest diagnostic value, increasing the slice size until ceiling identification accuracy (>99%) was reached. For all but the coarsest parcellations, ceiling accuracy was obtained using a remarkably tiny fraction of the complete connectome: under 0.25% of the connectome (and only 45 edges for the 360 ROI "Glasser" parcellation) was sufficient to accurately identify individuals. The most diagnostic edges were largely located in frontoparietal regions consistent with other reports. However, nearly all edges had some diagnostic value. We thus asked whether the edges with highest diagnostic value were required for high identification accuracy. Using the Glasser parcellation, we found accuracy above 98% for slices comprised of the 26th percentile of diagnostic value (e.g. without using the most diagnostic 25% of the connectome) and for larger slices from which the frontoparietal network (Yeo parcellation) was entirely excluded. Finally, we also obtained 98% accuracy using randomly-selected slices as small as 400 edges (0.7% of connectome). Our results indicate that while individual variability may be particularly *concentrated* in the frontoparietal regions previously reported, uniqueness in functional coupling is far more diffusely distributed throughout the brain than previously appreciated, with both practical and conceptual implications for thinking about the detection and sources of uniqueness in the brain.

Disclosures: L. Byrge: None. **D.P. Kennedy:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

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Topic: H.02. Human Cognition and Behavior

Support: NIH NICHD P50 HD052117
NIH NICHD R21 HD081437

NARSAD Young Investigator Award (JAC)
Start-up funds from University of Texas at Austin (JAC)

Title: Identifying twin pairs by classifying variability in whole-brain functional connectivity

Authors: *D. V. DEMETER[1], L. E. ENGELHARDT[1], R. MALLETT[1], M. A. ROE[1], T. NUGIEL[1], M. E. MITCHELL[1], J. JURANEK[4], K. P. HARDEN[1,2], E. M. TUCKER-DROB[1,2], J. A. LEWIS-PEACOCK[1,3], J. A. CHURCH[1,3]
[1]Psychology, [2]Population Res. Ctr., [3]Imaging Res. Ctr., Univ. of Texas at Austin, Austin, TX; [4]The Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX

Abstract: Multivoxel pattern analysis (MVPA) of fMRI data can provide insight into individual differences in functional brain network organization. Capitalizing on the increased sensitivity and specificity of machine learning methods, resting-state functional connectivity (rsfc) studies have predicted age, clinical diagnosis, and heritability. Can this approach be extended to identify a unique biomarker for a specific individual? The current study tested this using a novel application of MVPA to rsfc data to classify patterns of pairwise connectivity between a priori nodes distributed throughout the whole brain. This approach successfully matched pairs of school-aged twins by identifying heritable variance in rsfc patterns.
Methods: Three analysis sets were defined after strict motion censoring methods. The first test set consisted of 9 monozygotic (MZ) twin pairs (10.5 to 13.8 years old, M=11.04) and the second test set consisted of 10 dizygotic (DZ) twin pairs (9.4 to 13.2 years old, M=11.95). Our validation set consisted of 12 non-related individuals (9.8 to 17.2 years old, M=12.84) with two scans collected either six months or one year apart. Support vector machine MVPA and leave-one-out cross validation was used to first validate our methods and then to test individual whole-brain rsfc pattern variance. To increase sensitivity to individualized patterns over time, each resting-state timecourse was chunked into smaller samples to provide multiple instances of the rsfc signal for each individual. A vector of correlation values between all regions of interest (ROIs) in a 264 ROI set was then used for feature selection, model training, and testing. The robustness of this analysis was evaluated by parametrically varying the chunk size and feature selection threshold.
Results: Final model settings included 10 rsfc segments (40 sec each) using the top 5% of ANOVA-selected features. Models that included whole-brain connectivity between all ROIs performed better than those restricted to within-network connections. MZ twins were accurately identified based on their co-twin with 62% accuracy ($p < .001$, chance = 0.125) and DZ twins were identified with 27% accuracy ($p < .001$, chance = 0.10). In the validation set, an individual's second scan was identified from training a model on their first scan with 99% accuracy ($p < .001$, chance = 0.10).
We find the patterns of whole-brain measures of rsfc in fMRI are highly stable within individuals and are also heritable with a decrease in similarity from MZ to DZ co-twins. This novel analysis approach has the potential to increase accuracy in studies that aim to identify individual and group differences in resting-state fMRI.

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Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.04/III19

Topic: H.02. Human Cognition and Behavior

Support: NIMH grant K01MH099232 (AJH)

Title: Metabolic cost of structural hubs in the human connectome

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Abstract: The brain is expensive to build and maintain, incurring outsized material and metabolic costs for its size relative to the rest of the body. It has been proposed that brain organization balances cost and advantageous topological properties that enable higher communication efficiency. Network studies across species and modalities identify core sets of highly connected "hub" brain regions that are critical for efficient neuronal signaling and communication. These candidate "hub" regions tend to be mutually and densely interconnected, forming a "rich club". Due to its density and spatial layout, the rich club constitutes a costly feature of brain architecture, which may be offset by significant functional benefits that it confers to the overall brain network. Recent work in the mouse connectome uncovered a distinctive transcriptional profile of neural hubs, characterized by co-expression of oxidative metabolism genes (Fulcher & Fornito, 2016). The current study seeks to extend these findings by determining whether structural hubs in the human connectome also show enriched expression for genes regulating neuronal metabolism. In this ongoing project, topological characteristics of structural network organization were established in a large community sample using graph theory measures. Brain white matter structural connectivity was examined using diffusion magnetic resonance imaging (dMRI) data in 6,988 generally healthy individuals aged 40-70 years from the UK Biobank. We demonstrate that hub regions, being more mutually and densely interconnected, exhibit both central (i.e. playing a vital role in neural communication) and costly (i.e. exhibiting long distance anatomical projections) attributes of network organization. Ongoing analyses using gene transcription data from the Allen Human Brain Atlas, as well as follow-up investigations using genome-wide association (GWA) data from the UK Biobank, aim to identify

if a transcriptional signature for genes regulating metabolic processes is associated with topologically central, but costly hub connectivity in the human brain. Results from this large community cohort provide a current best estimate and one of the most extensive topological characterizations of structural network organization in the human connectome.

Disclosures: R. Chin: None. **K.M. Anderson:** None. **M.A. Collins:** None. **A. Yendiki:** None. **A.J. Holmes:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

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Program #/Poster #: 516.05/III20

Topic: H.02. Human Cognition and Behavior

Support: NINDS Grant R25NS09098
NIH Grant R37MH066078

Title: The influence of genetics on individual differences in neural activation patterns in the visual and frontoparietal communities

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Abstract: Individual differences in brain function play an important role in executive control, and are linked to general cognitive ability as well as characteristics in the areas of personality and emotion processing. These differences arise from both genetic and environmental influences and enable further understanding of how varying complex cognitive traits arise. By collecting task fMRI and behavioral data for monozygotic (MZ) twins, dizygotic (DZ) twins, siblings (SIB), and unrelated people, the Human Connectome Project (HCP) allows investigation of the degree to which genetics shapes these differences. This study compared activation similarity patterns in the FrontoParietal and Visual networks for 766 participants across these subject groups. Activation similarity was correlated for the N-back task under conditions of high or low working memory load and across two object stimulus categories. If heritability plays a substantial role in determining neural activation, groups of higher genetic similarity should have more similar activation patterns. Indeed, in both the FrontoParietal and Visual networks, MZ twins showed a higher similarity than DZ twins or siblings, and DZ twins and siblings showed a higher similarity than unrelated participants. Furthermore, this correlation is emphasized under conditions of higher cognitive load in the FrontoParietal network. As such, this study demonstrated that heredity is correlated to neural activation in both examined communities. This

provides evidence that genetic influences play a substantial role in the neural basis of individual differences, and may ultimately help to lay the foundation for task-related brain activation to be considered as an endophenotype for psychiatric or neural disorders.

Disclosures: Y. Courtney: None. **J.A. Etzel:** None. **T.S. Braver:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

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Topic: H.02. Human Cognition and Behavior

Support: NIH R01MH110630 (Kennedy)
NICHD T32HD007475 (Byrge)
Indiana University Research Funding (Kennedy)

Title: Idiosyncratic community organization of cortical functional networks in Autism Spectrum Disorder

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Abstract: Neuroimaging studies of the functional connectome in Autism Spectrum Disorder (ASD) have suggested generally abnormal patterns in various functional systems (e.g., default network, saliency network). However, systematic exploration of the system-level community organization has been quite limited, and findings at the group level have been largely inconsistent across the few studies that do exist. Given the enormous biological heterogeneity underlying ASD, an emerging perspective is that individuals with ASD will exhibit heterogeneous alterations of brain organization (Byrge, Dubois et al., 2015; Hahamy et al., 2015) that may not be well represented by group-level analyses. Here, we take this perspective in exploring individual, idiosyncratic variations of the community organization of the functional connectome in ASD, using densely sampled resting-state fMRI data acquired from 19 individuals with ASD and 28 matched controls. Two 16-minute scans were acquired from each individual, allowing for assessment of test-retest reliability of system-level organization. We used a multi-scale community detection algorithm for each scan to get a series of community structures from coarse to fine partition resolutions. We then derived an agreement matrix for each individual by combining each partition resolution together, thus defining an individual's multi-scale community organization, and allowing comparison within and across individuals. For both groups, agreement matrices were highly self-similar across scan 1 to scan 2, to the point of serving as a "connectome fingerprint", and indicating reliable within-subject measurement in both ASD and control individuals. However, the lower between-subjects similarity within the

ASD group suggested an idiosyncratic community organization. We further mapped the community agreement to a canonical network partition, and found that the functional systems with abnormal agreements were indeed more prevalent and more diverse in ASD. These findings suggest that system-level alterations can be reliably observed in ASD, and that group-level analyses seeking common alterations may be misguided and have limited utility. Future studies with larger samples may be able to subtype individuals based on their shared patterns of system-level abnormality, perhaps reflecting different underlying neuropathological mechanisms in ASD.

Disclosures: Y. He: None. **L. Byrge:** None. **O. Sporns:** None. **D. Kennedy:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

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Program #/Poster #: 516.07/III22

Topic: H.02. Human Cognition and Behavior

Support: DFG GE2777/2-1
DFG Gu227/16-1
DFG BE4045/26-1

Title: Microstructure of the human corpus callosum is modulated by genetic variation in PLP1 and CNTN1: A neurite orientation dispersion and density imaging (NODDI) study

Authors: *S. OCKLENBURG[1], C. ANDERSON[2], W. M. GERDING[3], C. FRAENZ[5], C. SCHLÜTER[4], P. FRIEDRICH[5], M. J. RAANE[4], L. ARNING[4], J. T. EPPLEN[4], O. GUNTURKUN[6], C. BESTE[7], E. GENC[8]
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Abstract: The corpus callosum is the brain's largest commissural fiber tract and is crucial for interhemispheric integration of neural information. Despite the high relevance of the corpus callosum for several cognitive systems, the molecular determinants of callosal microstructure are largely unknown. Recently, it was shown that genetic variations in the proteolipid 1 gene *PLP1* and the contactin 1 gene *CNTN1* were associated with differences in interhemispheric integration at the behavioral level. Since interhemispheric integration of neuronal information is the main function of the corpus callosum, it can be assumed that variation in these genes might affect callosal microstructure. To investigate this question, we used an innovative new diffusion

neuroimaging technique called neurite orientation dispersion and density imaging (NODDI). NODDI uses a multi-shell high-angular-resolution diffusion imaging protocol and features a three-compartment model distinguishing intra-neurite, extra-neurite and cerebrospinal fluid environments. Here, we used it to quantify axonal and neurite morphology in subsections of the corpus callosum, and to link them to genetic variation in *PLP1* and *CNTN1*. In a cohort of 263 healthy human adults, we found that polymorphisms in both *PLP1* and *CNTN1* were significantly associated with callosal microstructure. Importantly, we found a double dissociation between gene function and neuroimaging variables. Our results suggest that genetic variation in the myelin-related gene *PLP1* impacts white matter microstructure in the corpus callosum, possibly by affecting myelin structure. In contrast, genetic variation in the axon-guidance related gene *CNTN1* impacts neurite density in the corpus callosum.

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Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.08/III23

Topic: H.02. Human Cognition and Behavior

Title: Neurotransmitter model of temperament traits

Authors: *I. TROFIMOVA
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Abstract: This presentation reviews findings in neurochemistry that link temperament traits to complex relationships between neurotransmitter systems. Temperament traits, i.e. biologically based individual differences, are observable not only in humans, but also in animals and very young children, i.e. in pre-cultural individuals. Specialization between neurotransmitter systems underlying temperament traits is analyzed here from a functional ecology perspective that considers the structure of adult temperament corresponding to the structure of human activities. The roles of monoamine neurotransmitters (serotonin, dopamine, noradrenalin), as well as the roles of acetylcholine, neuropeptides and opioid receptor systems in the regulation of specific dynamical properties of behavior will be discussed. The functional differentiation within neurochemical systems is compared to models in kinesiology and neurophysiology that investigated key stages of human actions. Parallels to main models of temperament are summarized within the neurochemical Functional Ensemble of Temperament (FET) model. The FET framework allows having both, a common taxonomy for biologically based traits in healthy individuals and for taxonomies of mental illnesses. Temperament and mental illness are

considered to be variations along the same continuum of imbalance in the neurophysiological regulation of behavior. The presentation will give examples of how the FET framework can be used in psychiatry and clinical psychology.

Disclosures: I. Trofimova: None.

Poster

516. Human Cognition and Behavior: Individual Differences

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Program #/Poster #: 516.09/III24

Topic: H.02. Human Cognition and Behavior

Support: R01DA034685
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F32AG047686

Title: Dopaminergic mechanisms underlying normal variation in trait anxiety

Authors: *A. S. BERRY[1], R. L. WHITE, III[2], D. FURMAN[3], J. R. NASKOLNAKORN[3], V. D. SHAH[3], M. DESPOSITO[3], W. J. JAGUST[3]
[1]E O Lawrence Berkeley Natl. Lab., Berkeley, CA; [2]Univ. of California San Francisco, San Francisco, CA; [3]Helen Wills Neurosci. Inst., Univ. of California Berkeley, Berkeley, CA

Abstract: Trait anxiety has been associated with altered activity within corticolimbic pathways connecting the amygdala and rostral anterior cingulate cortex (rACC), which receive rich dopaminergic input. Current pharmacological interventions for clinical anxiety primarily target serotonergic and GABAergic neurotransmitter systems. However, early lines of research emphasized a role of dopamine in the pathophysiology of anxiety (Taylor et al., 1982), which have recently been reinvigorated (e.g. Kienast et al., 2008). To date, little work has examined the conjoint influence of endogenous dopamine function and corticolimbic functional connectivity on trait anxiety in humans. We sought to address this by examining inter-individual variability in dopamine release, fMRI resting-state amygdala-rACC functional connectivity, and trait anxiety in healthy adults (n = 31; 18-25 years old, mean = 21.42, standard deviation = 2.08, 20 female). We estimated dopamine release by contrasting the [^{11}C]raclopride PET measure of D2/3 receptor binding with D2/3 receptor binding following oral methylphenidate administration. We demonstrate for the first time that normal variation in trait anxiety is associated with individual differences in dopamine release in amygdala and rACC. Analysis of correlations among the three measurements revealed greater dopamine release in amygdala and rACC was associated with lower trait anxiety (r = -.43, bootstrapped 95% confidence interval = [-.66, -.11]), and lower resting amygdala-rACC functional connectivity (r = -.38 [-.65, -.01]). Further, dopamine release mediated the influence of functional connectivity on anxiety (unstandardized indirect effect =

4.19 [0.24, 12.14]). These data support a model by which elevated functional connectivity reduces dopamine release within the amygdala and rACC to produce higher trait anxiety within normal individuals.

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Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.10/III25

Topic: H.02. Human Cognition and Behavior

Support: CNI Innovation Grant

Title: Investigating the role of GABA and glutamate on dorsal anterior cingulate activity associated with hypnosis

Authors: *D. D. DESOUZA[1], K. STIMPSON[1], L. BALTUSIS[2], M. GU[3], R. HURD[3], H. WU[2], D. C. YEOMANS[4], N. WILLIAMS[1], D. SPIEGEL[1]
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Abstract: Background: Hypnosis is the oldest form of Western psychotherapy and serves as a powerful evidence-based tool in the treatment of many disorders. Hypnotizability is a stable trait over time, suggesting neurophysiological factors underlying hypnotic responsiveness. We previously demonstrated differential functional brain activity in high vs. low hypnotizable individuals during hypnosis compared to rest. Specifically, highly hypnotizable participants had increased resting-state functional connectivity between the dorsolateral prefrontal cortex and dorsal anterior cingulate cortex (dACC), and showed decreased dACC activity during hypnosis. Brain activity, as measured by the blood-oxygen-level-dependent (BOLD) signal, has been shown to be specifically coupled with neural activity. Neurochemical processes including the cycling of neurotransmitters such as GABA and glutamate, the major inhibitory and excitatory neurotransmitters of the central nervous system respectively, regulate neuronal activity. Studies have demonstrated a negative relationship between GABA concentration and BOLD signals and a positive correlation between glutamate and BOLD signals. **Rationale:** While it is clear that the dACC plays an important role in hypnosis, the relationship between dACC neurotransmitters in hypnotic response remains to be determined. **Objective:** To determine the relationship between GABA and glutamate in the dACC and measures of hypnotizability. **Methods:** 20 healthy participants with varying levels of hypnotizability as assessed by the Hypnotic Induction Profile (HIP) were recruited to undergo magnetic resonance imaging (MRI) and completed standardized

questionnaires to assess depression/anxiety (DASS-21), absorption (Tellegen Absorption Scale), and dissociation (Dissociative Experiences Scale). The MRI session included the following scans: T1-weighted anatomical, MEGA-PRESS spectroscopy to assess GABA and glutamate measures with a voxel of interest over the dACC, resting-state fMRI. **Results:** 1. a significant positive relationship was observed between dACC GABA measures and HIP scores (R- 0.590, p= 0.016). 2. dACC glutamate measures were negatively associated with the absorption subscale of the dissociative experiences scale (R= -0.584, p=0.011). **Conclusion:** We provide evidence for significant relationships between GABA and glutamate measures in the dACC and measures of hypnotizability. Having an understanding of these relationships provide a putative neurobiological basis for individual differences in hypnotizability and can inform our understanding of treatment response to this growing psychotherapeutic tool.

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Poster

516. Human Cognition and Behavior: Individual Differences

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Title: Genetic variants of MAOA influence oscillatory EEG & ECG activity in response to aggression-inducing stimuli

Authors: *S. IM[1,2,3], J. JEONG[1,4], G. JIN[1,3], J. YEOM[1,3], J. JEKAL[1,3], S.-I. LEE[1,3], S. LEE[1,3], Y. LEE[1,3], J. CHO[1,3], D. KIM[1,3], C. MOON[1,2], C.-H. LEE[1,3]
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Abstract: The monoamine oxidase A (MAOA) gene, which encodes an enzyme that breaks down monoamine neurotransmitters, is associated with human physiology and aggressive behavior. Genetic variation in upstream variable tandem repeats (uVNTR) of the *MAOA* promoter is believed to contribute to individual differences in aggression at the transcription level. However, research on the relationship of *MAOA* uVNTR with molecular change, neural activity, and psychological indices of aggression has reported inconsistent findings. Intriguingly, significant difference in *MAOA* allelic frequencies exist across ethnic groups as well as the

information of their sequences is insufficient. Therefore it is necessary to provide complete sequence analysis of *MAOA* uVNTR and its effects at multiple levels of human biology. Here, we identified three alleles of *MAOA* uVNTR in the Korean population: predominantly 3.5R and 4.5R plus the rare 2.5R. Functional promoter fusion assay demonstrated that the 3.5R allele has more efficient transcription than the 4.5R allele, while the 2.5R allele has the highest efficiency. This finding implies differential molecular effects of *MAOA* uVNTR on the neurobiological response to aggression. Our neurobiological studies revealed oscillatory changes in electroencephalogram and electrocardiogram patterns under aggression stimuli as novel functional phenotypes of *MAOA* uVNTR genotypes. Specifically, hemi- or homozygous 4.5R carriers with low *MAOA* transcriptional efficiency showed greater oscillatory variability of the γ wave from the prefrontal/frontal cortex and larger changes in heart rate. This suggests extended explanations on a neurobiological characteristics related to aggression in regard to *MAOA* variants. Our findings provide novel genetic insight into *MAOA* functions, which offer grounds for the various human socio-emotional mechanism in healthy individuals.

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Poster

516. Human Cognition and Behavior: Individual Differences

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.12/III27

Topic: H.02. Human Cognition and Behavior

Title: Implicit and explicit risk taking on the balloon analogue risk task and its relationship with positive personality characteristics in working adults

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Abstract: Many are the choices in face of risks in the organizational dynamic environment, especially when involving structure review, with changes of leadership and teams. Positive individual characteristics as optimism, hope and self-efficacy seem to contribute in this process (Seligman & Csikszentmihalyi, 2000). Despite this, little is known about how these characteristics relate to risk-taking, mainly when implicit and explicit levels of cognitive processing are considered. Thus, the aim of this study was to investigate the relationship between

risk-taking and positive characteristics of personality in an uncertainty organizational context. The sample was composed of 97 adults (average age=37 years old; 46% women), all employees from global companies involved in merging processes and that completed the Balloon Analogue Risk Task - BART (Lejuez et al., 2002). Besides BART, questionnaires accessing optimism (Bastianello, Pacico, & Hutz, 2015), hope (Bastianello, Pacico, & Hutz, 2015) and self-efficacy (Pacico, Ferraz & Hutz, 2015) were applied. The hypothesis was that individuals with higher levels of optimism, hope and self-efficacy would show higher propensity to implicit risk-taking (captured through the latency in pumping the balloons) and explicit (measured by the latency in collecting money). Consistent with the hypothesis, the results pointed out a positive relationship between implicit risk-taking and hope (r= .235; p < .05), indicating that the greater the hope, greater was the risk assumed at an automatic level. Also, was observed a positive relationship between explicit risk-taking and self-efficacy (r= .229; p < .05), supporting the notion that the self-efficacy is associated with planned processes. Additionally, leaders and non-leaders differed in time spent for total risk-taking, when implicit and explicit risk-taking were analyzed altogether (U= 637; p<.05), demonstrating that leadership positions seem to play a role in the way people deal with risks in organizations. The lower hierarchical level employees showed greater implicit risk-taking (H= 11,11; p< .05), in comparison with upper-level employees. In addition, it was observed a positive relation between explicit risk-taking and years of services (H= 10,44; p < .05), pointed that for longer time of services, longer was the planning to deliberate about the risk. The findings corroborate with the dual-process model, once they present risk-taking results at implicit and explicit levels. Also adds to the emerging fields of organizational neuroscience and positive psychology indicating relations between risk-taking and positive personality characteristics.

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Poster

516. Human Cognition and Behavior: Individual Differences

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Program #/Poster #: 516.13/III28

Topic: H.02. Human Cognition and Behavior

Support: JST-CREST

Title: Social networking service talk about your personality and resting-state brain network

Authors: *K. MORI, M. HARUNO
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Abstract: Social networking service (SNS) is the essential communication tool in the current life. The central problem of SNS in social science is whether SNS have good or bad mental effect. Past studies have offered mixed evidence about the good and bad side of SNS use. In the current study, we try to show the SNS mental effect using the framework of SNS neuroscience. We examined the relationship between twitter, one of the major SNS, behavior and psychological personality, brain resting state network. The results indicated that tweet by oneself is associated with negative personality / high IQ, whereas reply with others is associated with positive personality / free will. In line with the personality emotion, tweet by oneself includes more negative / less positive words and reply with others includes more positive / less negative words. Further, tweet by oneself can be predicted by resting nucleus accumbens functional connectivity network implying the addiction of tweet behavior. Our findings thus reveal positive and negative association of SNS and well-being, and the brain mechanism of SNS usage.

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Poster

516. Human Cognition and Behavior: Individual Differences

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Title: Linking resting state connectivity with attachment styles

Authors: *M. NANNI, A. KRAUSE[1], L. COLIC[2], V. BORCHARDT[3], M. LI[4], B. STRAUSS[5], A. BUCHHEIM[6], D. WILDGRUBER[7], P. FONAGY[8], T. NOLTE[8], M. WALTER[9]
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Abstract: Psychometric research has identified stable traits that predict inter-individual differences in relationship and attachment behavior. Avoidance and anxiety (AV/AX) scales

have been developed to quantitatively assess these traits. However, neural mechanisms corresponding to the proposed constructs reflected in av/ax are still poorly defined. The ventral medial orbito-frontal cortex (vmOFC) is implicated in social approach network (SAN) function, and lateral orbitofrontal cortex (lOFC) is related in subserving emotion regulation on social processing . In this study, we examined whether functional connectivity between these regions predicts components of these scales. We employed resting-state functional connectivity and av/ax scores assessed by a personality questionnaire. Participants completed a resting state run and the Experiences in Close Relationships Questionnaire (ECR-R). Using resting-state BOLD, we assessed correlations between structures of SAN (Fig. 1) and those related subserving emotion, establishing single subject connectivity summary scores. Summary scores were correlated with components of av/ax scores. Results demonstrate a novel correlation between AV and resting-state connectivity between vmOFC and lOFC (Fig. 2), implying that spontaneous synchrony between social approach processing regions may play a role in defining personality characteristics related to attachment.

Figure 1. Regions of interest. Social approach network: Ventral tegmental area (red) ventral-medial orfitofrontal cortex (green), hypotalamus (yellow), , striatum (blue). Emotion regulation: dorso-lateral prefrontal cortex (orange), lateral orbitofrontal cortex (fuchsia)

LOFC-VMOFC RSFC

Figure 2. Bivariate correlation of significants associations between lOFC-vmOFC RSFC r=-0.5655 p<0.002 Bonferroni corrected (8 ROIs and 2 subscales)

Disclosures: A. Krause: None. **L. Colic:** None. **V. Borchardt:** None. **M. Li:** None. **B. Strauss:** None. **A. Buchheim:** None. **D. Wildgruber:** None. **P. Fonagy:** None. **T. Nolte:** None. **M. walter:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.15/III30

Topic: H.02. Human Cognition and Behavior

Title: Brain network predictors of TMS-induced changes in cognitive control performance

Authors: *C. L. GALLEN, T. P. ZANTO, A. GAZZALEY
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Abstract: Previous research has demonstrated a critical role for the right inferior frontal junction (rIFJ) in cognitive control processes, such as selective attention and working memory (WM). In a previous study, we perturbed rIFJ function with TMS during a selective attention, delayed recognition task and observed a decrease in WM accuracy (Zanto et al., 2011). However, this

and other brain stimulation studies have shown variability in responses across individuals. Recent work has shown that baseline properties of brain networks predict cognitive control gains after long-term cognitive interventions, such as through video games and exercise. It remains poorly understood, however, whether brain network properties can similarly predict behavioral changes associated with TMS.

Here, we examined the relationship between network properties and TMS-induced changes in behavior during a selective attention WM task for color and motion. TMS-related changes in behavior were quantified from previous work showing that repetitive rIFJ TMS decreased WM accuracy during the remember color (ignore motion) condition. Network properties were quantified from a similar task performed during fMRI scanning in a baseline session. We created a focal 'segregation' metric that quantifies the balance of a region's connectivity to others in its own network, compared to that of another network. Given the importance of fronto-parietal (FP) and visual network interactions during the WM task, we focused on rIFJ segregation between FP and visual networks ('rIFJ segregation'). Larger rIFJ segregation values reflect higher connectivity between rIFJ (TMS target) and the rest of the FP network.

Greater rIFJ segregation was predictive of larger TMS-induced behavioral changes during remember color and not remember motion. Importantly, a bottom-up control metric focusing on V4 segregation was not related to behavioral changes. In addition to individual differences in TMS susceptibility, participants also exhibited variability in rIFJ-V4 structural connectivity. Individuals with cortico-cortical structural connections between rIFJ and rV4 (~60%), primarily along FP tracts, had larger rIFJ segregation during remember color. Additionally, greater integrity of this tract was related to larger rIFJ segregation.

These results demonstrate that individuals with greater rIFJ segregation have larger TMS-related behavioral changes and, further, that these individuals have greater integrity of FP tracts connecting rIFJ and rV4. More generally, these findings suggest that properties of brain networks can predict susceptibility to TMS-induced changes in cognitive control performance.

Disclosures: C.L. Gallen: None. **T.P. Zanto:** None. **A. Gazzaley:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.16/III31

Topic: H.02. Human Cognition and Behavior

Title: Identifying distinct alpha band oscillatory dynamics in the EEG as targets for rhythmic transcranial magnetic stimulation (rTMS)

Authors: *M. K. GOLA[1], J. WAGNER[2], J. A. ONTON[4], K. MURPHY[3], S. MAKEIG[3]
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Abstract: Associations between cognitive performance and spontaneous modulations of oscillatory neuronal activity in the alpha frequency range have been established in a number of studies (Klimesch, 1999, Haegens, 2014). Recently it has been suggested that alpha oscillations can be reinforced using rhythmic transcranial magnetic stimulation (rTMS) to improve health and cognition. If the effects of rTMS are mediated by phase-coupling (entraining) endogenous oscillatory brain activity to the externally applied electromagnetic stimulus, immediate as well as long lasting effects of rTMS may thereby depend on the matching the stimulation frequency and phase to the individual's natural brain dynamics (Ziemann & Siebner 2015). To tune rTMS therapy to the frequency and phase of each subject's brain dynamics, optimized individual peak frequency and phase detection are essential. Cortical alpha oscillations typically have a peak power value (between 8 Hz and 12 Hz) that has often been claimed to be a single, stable and heritable neurophysiological ''trait" marker reflecting anatomical properties of the brain and linked to each individual's personality and cognitive capacity. However, growing evidence suggests that the alpha peak frequency is actually volatile on short time scales, may depend on cognitive state, and can differ between cortical source areas. Many studies of EEG spectral dynamics measure power in pre-defined frequency bins. To better understand the functional roles of brain local field dynamics, more flexible, data-driven models of spectral dynamics are desirable. Here, we attempt to characterize the alpha frequency modulations occurring in continuously recorded EEG data during rest, to determine the inter-relationship of observed alpha band features in source-resolved EEG activities (Onton & Makeig, 2009). Multi-channel EEG data are linearly decomposed using independent component analysis (ICA) into maximally independent component (IC) processes. Then IC log spectrograms are jointly decomposed into source-resolved modes, independent modulators (IMs). Such processes might reflect coordinated actions of modulatory factors, for example thalamocortical feedback loops and/or brainstem-based neuromodulatory systems. Better understanding the landscape of alpha band dynamics may help identify and target distinct alpha oscillatory brain networks for stimulation.

Disclosures: M.K. Gola: None. **J. Wagner:** None. **J.A. Onton:** None. **K. Murphy:** None. **S. Makeig:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.17/III32

Topic: H.02. Human Cognition and Behavior

Title: The utility of off-the-shelf EEG devices for the study of psychoactive substance use in non-laboratory settings

Authors: *J. DREO[1], D. SAKIć[2], Z. PIRTOŠEK[2]
[1]Fac. of Medicine, Univ. of Ljubljana, Ljubljana, Slovenia; [2]Chair of Neurology, Fac. of Medicine, Univ. of Ljubljana, Ljubljana, Slovenia

Abstract: Since the early 2010s several mobile, inexpensive, consumer-grade EEG devices have entered the market. These devices seem to be opening new avenues for neuroscientific research into areas that, for a multitude of reasons, might not be compatible with traditional laboratory environments. These reasons might include: the rarity of the events we wish to observe, the unwillingness of participants to visit labs, the privacy concerns of participants, or the unsuitability of laboratory environments for experiences that only lend themselves to more informal settings. We pragmatically tested the utility of one consumer-grade EEG device (Emotiv, Insight) for the use in neuroscientific field-work, namely observing the effects of psychoactive drug use on EEG activity. Based on NIH data, illicit drug use seems to be increasing. Given this trend, more and better research into this area of human experience is clearly indicated. Since most recreational psychoactive substances have very complex and individual-specific effects on the psychology of their users, elucidating their underlying neurophysiological effects must also be subject-specific. Due to their often-illicit nature and resulting legal issues, studying phenomena related to psychoactive drug use is severely limited in traditional laboratory settings. Additionally, and understandably, many participants are quite reluctant to relinquish their anonymity by coming to a public lab for neuroscientific testing. In order to address these concerns, we opted to observe psychoactive drug use where it usually occurs - in the homes of the users. We did not induce our participants towards drug use and we did not incentivize them in any way. We simply circulated notices that an EEG study of psychoactive drug use is underway and that any interested parties may discretely contact us if they wish to have their experiences recorded at their homes. We therefore only observed events that would have taken place anyway. Great care was taken to ensure the privacy of all recordings. Participants were recorded for a total of 45 min while watching a nature documentary (Planet Earth, BBC). The first 5 min served as a baseline, after which participants inhaled cannabis with the aid of a vaporizer. Preliminary findings on 8 individuals (of 20 planned) show that the subjects' subjective experiences track the changes in their EEGs. EEG spectra showed a shift to lower frequencies and a higher total power. There were, however, great inter-individual differences in EEG responsivity, which also correspond to different reported psychological effects. We conclude that this kind of observational field-neuroscience is a promising avenue of research.

Disclosures: J. Dreo: None. **D. Sakić:** None. **Z. Pirtošek:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.18/III33

Topic: H.02. Human Cognition and Behavior

Support: NIH NIA 2RF1AG038465-06

Title: Connectome based predictive modeling predicts individual differences in processing speed in health young adults

Authors: *P. LI[1], H. HE[2], Y. STERN[4], Y. GAZES[3], C. G. HABECK[3]
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Abstract: Processing speed as a core cognitive ability plays a key role in everyday life and differs significantly across individuals. Here we used a recently developed method by Rosenberg et al. (2016) and Shen et al. (2017) to predict individual differences in processing speed based on resting-state functional connectivity. 128 healthy young adults aged 20-35 years were included in the current study. Each subject underwent 10 minutes resting state fMRI scan. Neuropsychological tests included digit symbol, trail making test A, and Stroop test. The index of processing speed was the mean of the zscores for digit symbol accuracy, stroop color accuracy score, and trail making test A reaction time. The last measure was inverted such that higher score denotes better performance.The following steps were performed to apply the connectome-based predictive modeling. First, each subject's whole brain was parcellated into 264 network nodes based on a recently developed functional atlas. For each subject, a mean time course was calculated for each node by averaging BOLD signals from all of its component voxels at each time point. Pearson correlations were computed among all pairs of 264 nodes. The Pearson correlation coefficients were Fisher-Z transformed to generate symmetric 264*264 connectivity matrices. Leave-one-out cross-validation was used in which the data was divided into a training and a testing set. Partial correlations between each edge in the connectivity matrices and processing speed were calculated across subjects. The resulting r values were thresholded at $p<0.01$ for feature selection and separated into positive and negative tails based on the correlation sign.A single summary statistic, network strength, was calculated to define each subject's degree of connectivity in the positive and negative tails. Positive and negative network strengths were calculated by summing the edge strength from a subject's connectivity matrix in the positive and the negative tail. A simple linear regression model was built to predict processing speed based on the network strengths of each subject in the training set. Then, the same model was validated on the subjects in the testing set. Results showed that the positive and

the negative network strengths both significantly predicted novel subjects' processing speed.Edges that predicted individual differences in better processing speed consisted of edges within the default mode network and of edges between the default mode network and other networks. Edges within the visual network and edges between the visual and the default mode network and with the somatosensory network predicted worse processing speed.

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Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

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Program #/Poster #: 516.19/III34

Topic: H.02. Human Cognition and Behavior

Support: NSERC
Oculus Research

Title: Narrative context and gaming experience moderate presence and cybersickness in virtual reality

Authors: *S. KENNY, S. WEECH, M. BARNETT-COWAN
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Abstract: Minimizing an observer's experience of bodily discomfort (cybersickness) and maximizing the sense of truly 'being there' in a simulated environment (presence) are important considerations in order to take advantage of the potential offered by the virtual reality (VR) medium. We explore the possibility that experimental manipulations of presence can lead to decreased reports of cybersickness. Specifically, we examine whether a top-down intervention based on enriched narrative context can increase the personal relevance and believability of the VR environment, protecting against cybersickness that arises from multisensory conflict. In a laboratory experiment, we randomly assigned 20 volunteer university students to a minimal- or enriched- narrative context between-subject condition prior to exploring a high-quality interactive VR environment for a 7-minute session. After the play session, we acquired self-report measures of presence and cybersickness using the Player Experience of Needs Questionnaire and the Simulator Sickness Questionnaire. We found evidence that these percepts are inversely correlated, and that experimental manipulation of narrative reduced reports of cybersickness. To replicate and extend the generalizability of these findings, we conducted a second experiment using the same methodology in a public research setting. Over the course of one week, we collected a comprehensive set of data including demographics, gaming experience, player engagement, and task performance from 153 visitors to a public museum. We replicated the finding that participants who reported high presence also tended to report lower sickness

severity. Highlights of the results include an interaction between narrative context and video game experience: Those who reported playing video games less than five hours a week (non-gamers) reported higher sickness severity if they were assigned to the minimal-narrative context condition than the enriched-narrative condition. On the other hand, those who played games regularly were unaffected by the narrative context manipulation. In addition, the association between presence and sickness was stronger for non-gamers than regular gamers. These results show the potential for top-down modulation of susceptibility to sickness for non-gamers in particular, who may have less exposure to experiences that generate multisensory conflict compared to regular gamers.

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Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.20/III35

Topic: H.02. Human Cognition and Behavior

Title: Mechanisms of skill improvement across 100 sessions of an online attention training game

Authors: *O. CLAFLIN
Lumos Labs, San Francisco, CA

Abstract: One largely unexplored question in the field of cognitive training is how individual differences manifest during learning of a cognitive task. Understanding individual differences may enable more sophisticated trainers in the future including timely and customized guidance or supplementary specialized training. Previous studies of cognitive training have used correlative methods among relatively small sample sizes to infer at the broader population trends. Here, we used a large, observational dataset comprising of over 50,000 Lumosity participants who completed 100 sessions of a cognitive trainer (Highway Hazards) to shed light on the stages of task learning during cognitive training. Participants spanned from 13 to 90 years of age (median of 46) and across different education levels. By breaking down our participant's microbehaviors across their first 100 sessions of learning (with participants achieving half of their eventual performance gains by approximately session 20), we characterize several different mechanisms of skill acquisition during the different stages of learning.

Disclosures: **O. Claflin:** A. Employment/Salary (full or part-time):; Lumos Labs. 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.; Lumos Labs. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lumos Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lumos Labs. F. Consulting Fees (e.g., advisory boards); Lumos Labs.

Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.21/III36

Topic: H.02. Human Cognition and Behavior

Support: BYU MRI Research Facility Seed Grant

Title: Individual variation in the cortical response to word predictability in naturalistic reading

Authors: *B. T. CARTER[1], S. G. LUKE[2]
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Abstract: Lexical predictability is the degree to which the linguistic features of a word can be predicted based on prior experience. How these predictions are made and the regions of the brain responsible for making these predictions are not well understood. Prior studies have shown lexical predictability is inversely related to gaze duration. Gaze duration is defined as the time spent viewing a word and can be used to assess cognitive effort. Changes in gaze duration are associated with lexical predictability. Cortical regions demonstrating activity associated with changes in gaze duration and lexical predictability are likely involved in the behavioral response to words and serve as potential indicators of reading proficiency. 41 participants with normal or corrected to normal vision, and no history of reading or learning disability were recruited. Participants were presented with 54 standardized paragraphs of text from Luke & Christiansen (2016). Eye movements were recorded via an Eyelink 1000 plus long range MRI eye tracker at 1000 Hz. fMRI was performed concurrently. Eye movement data were co-registered with fMRI data. fMRI analysis was performed using Analysis of Functional NeuroImages (Cox, 1996) and a group structural model was created using Advanced Normalization Tools (Avants, Tustison, & Song, 2011). The ideal hemodynamic response function was modeled with one binary regressor (fixation onset), and two parametric regressors coding for lexical predictability and gaze duration. This was contrasted with the baseline response function. 15 functional regions of interest were then identified at the group level and individual participant statistics were calculated for each region. A linear mixed-effects model was applied to fixation duration and lexical predictability. Slopes were extracted for each participant and correlated with the

maximum activation observed in each ROI. The hemodynamic response in the following regions was significant (df = 39, $\alpha < 0.05$, $|r| > 0.308$): the right anterior cingulate gyrus (r = 0.327), right posterior cingulate gyrus (r = 0.423), left middle frontal gyrus (r = 0.309), and right posterior insula (r = 0.417). This exploratory study highlights regions of interest for further investigation of linguistic function and skill. Individuals with greater overall sensitivity to word predictability, as revealed by eye tracking, showed a more negative hemodynamic response during reading within these regions. This association indicates these regions may be related to prediction, experience and the development of reading. Future research should focus on how this activity changes with development of reading skill.

Disclosures: B.T. Carter: None. **S.G. Luke:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

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Program #/Poster #: 516.22/III37

Topic: H.02. Human Cognition and Behavior

Support: Tohoku University Research Institutes Ensemble Grant for young researchers
The Fukuhara Fund for Applied Psychoeducation Research

Title: Neural correlates underlying the individual difference of positive psychological effect by remembering nostalgic memories

Authors: *K. OBA[1], M. BARTHEL[2], K. ABE[1], K. HIRANO[1], R. ISHIBASHI[1], R. NOUCHI[1], R. KAWASHIMA[1], M. SUGIURA[1]
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Abstract: It has been revealed that remembering nostalgic memory has positive psychological effects on self-esteem and mood (Wildschut et al., 2006). However, it is also the truth that there are individual differences on the effect of reminiscence (Fry 1991). Despite the amount of literatures reporting positive psychological effect by remembering memories, underlying psychological and neural mechanisms of this individual difference remain unknown. In the present study, we investigated the neural correlates underlying the change in self-esteem by remembering nostalgic memory using functional MRI (fMRI). Right-handed healthy students (n=29, 21.08±1.18 years old, 16 males) participated in this study. All participants gave written informed consent prior to the experiment. This study was approved by the institutional review board in the Tohoku University. Prior to the experiment, we collected 24 pictures that could remind nostalgic memories such as elementary school days, or 24 pictures for ordinary memories such as shopping at the supermarket. During fMRI scanning, participants saw these pictures for fourteen seconds each, remembered autobiographical memories and rated the nostalgia feeling

by Likert scale (1-4). Immediately before and after the remembering task, they answered the state self-esteem (SSE) questionnaire (Abe and Konno 2007). In the fMRI data analysis, we first compared the brain activity between the high (3 and 4) and low (1 and 2) nostalgia conditions (high vs low contrast) based on each participants' rating. Then, to investigate the neural correlates underlying the individual difference of SSE change, we performed regression analysis between SSE change (post minus pre) and brain activity (high vs low contrast). The behavioral data showed that there was no significant change in SSE before and after the task in the sample ($t(28) = 2.05$, $p = 0.40$). However, there were individual differences as some participants' SSE increased ($n = 16$), some decreased ($n = 11$), and some showed no change ($n = 2$). In the fMRI analysis, we identified a region covering left lateral parietal and medial parietal areas, which includes precuneus, that activated in correspondence with the individual difference of the SSE change ($p<0.001$ at voxel level and $p<0.05$ FWE corrected at cluster level). Previous study has shown the positive correlation between the precuneus activity and state self-esteem changed by positive social feedback (Eisenberger et al., 2011). Considering this finding, the present result suggests a possibility that there is a process mediating positive psychological effect which is common in both nostalgia and social feedback and is implemented on the precuneus.

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Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.23/III38

Topic: H.02. Human Cognition and Behavior

Title: Music preferences are radically idiosyncratic yet internally consistent

Authors: *S. SPIVACK, W. ERSLY, N. SPILKA, I. PASSMAN, S. PHILIBOTTE, P. WALLISCH
New York Univ., New York, NY

Abstract: To what degree do our subjective appraisals of reality correspond with those of other people? To investigate this question, we exposed a large sample of participants to a diverse selection of songs and compared ratings both between and within listeners to compute the inter-rater reliability and internal consistency of musical preferences. We found that there is low agreement between individuals but that ratings are highly consistent within individuals. We conclude that music taste is highly idiosyncratic yet stable, which renders music attractive as stimulus material for psychological research.

Disclosures: S. Spivack: None. **W. Ersly:** None. **N. Spilka:** None. **I. Passman:** None. **S. Philibotte:** None. **P. Wallisch:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.24/III39

Topic: H.02. Human Cognition and Behavior

Title: Personality, as it manifests in the temporal fine structure of musical appraisal judgments

Authors: I. PASSMAN[1], N. H. SPILKA[1], S. SPIVACK[2], S. J. PHILIBOTTE[3], *P. WALLISCH[4]
[1]New York Univ., New York, NY; [2]New York Univ., Brooklyn, NY; [3]Dept. of Psychology, [4]Ctr. Neural Sci., New York Univ., New York, NY

Abstract: What can we learn about human cognition from the way in which people interact with music? Our prior research suggests that the appraisal of musical stimuli reflects that human cognition is highly complex and idiosyncratic. This research focused on summary measures of appraisal, whereas here we were interested in the temporal fine structure of appraisal judgments in response to musical stimuli. To explore this topic, we presented music selected from a set of representative songs to over 600 participants and recorded their instantaneous appraisals throughout each song. Doing so, we were able to answer the following questions: 1) How long does it take for an individual's preference towards a song to stabilize after stimulus onset? 2) What is the influence of significant musical/sonic changes on appraisal throughout the song? 3) Which of these changes are idiosyncratic and can be related to individual personality and which are universal? We also related appraisal updating behavior to how engaging a particular song is and to measures of personality such as conscientiousness. Finally, with respect to these questions, we explored the role of the human voice in music and investigated whether vocals make songs more memorable. We conclude that most people respond to songs as they would to other auditory textures, but that this response is modulated by the personality characteristics of individuals.

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Poster

516. Human Cognition and Behavior: Individual Differences

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Topic: H.02. Human Cognition and Behavior

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NIH Grant DP2MH103909
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NIH Grant 1P50MH106435
Kent and Liz Dauten
Ellison Foundation

Title: Deep dynamic phenotyping of the individual: Daily life event analysis using actigraphy from wearable devices

Authors: *H. RAHIMI EICHI[1], G. COOMBS III[1], J.-P. ONNELA[2], J. T. BAKER[3,1,4], R. L. BUCKNER[1,5,4]
[1]Harvard Univ., Cambridge, MA; [2]Harvard T.H. Chan Sch. of Publ. Hlth., Cambridge, MA; [3]McLean Hosp., Belmont, MA; [4]Harvard Med. Sch., Cambridge, MA; [5]Massachusetts Gen. Hosp., Cambridge, MA

Abstract: Wearable devices are commonly available to record activity of individuals and provide information about their lifestyle and daily activity levels. There are several existing software technologies bundled with wearable devices, which are tailored to provide standard biometrics such as sleep and footsteps. To detect and categorize different life-related activities of individuals such as walking, running, exercise and sexual activity in addition to standard sleep and activity level measures, here we apply data-driven analysis to the raw data recoded by actigraphy wristband devices and validate them with other objective GPS measures as an analytical platform for deep dynamic phenotyping of the individual. For this purpose, actigraphy data of 74 college students (for 57-250 days with 30Hz sampling rate) and 10 individuals with bipolar disorder or schizophrenia spectrum (for 100-300 days with 20Hz sampling rate) are collected using low cost wristband devices. One-minute bin frequency spectrum of the actigraphy signal is deployed along with moving window analysis to detect sleep epochs (sleep onset, wake time, and quality of sleep) differentiated from watch-off intervals. Moreover, correlation-based clustering of the frequency spectrums is utilized to identify the most commonly repeated activities of the individual during the day. The daily behavioral map based on actigraphy clustering is evaluated by a previously developed daily map based on the most visited GPS locations collected using Beiwe, a research platform for smartphone-based digital phenotyping (Torous et al., 2016 *JMIR Ment Health*). The annotated in-house data collection

shows that the algorithm detects the sleep epochs, bedtime and wake time accurately. Moreover, this algorithm provides visual representation of sleep interruptions such as bathroom trips or in-bed sleepless minutes. Furthermore, the algorithm shows that the daily color-coded map of the most repeated activities such as walking, running, exercise and sexual activity are consistent with the separately collected GPS locations; such that the walking activity is at the transition time between locations, exercise is at the same location and same time of the week, and sexual activity can be detected as vigorous activities at the sleeping location with a trip to the bathroom afterwards. In conclusion, frequency-based analysis of the raw actigraphy data provides an accurate objective indicator of an individual's life events such as sleeping, walking, running, exercise, and even sexual activities.

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Poster

516. Human Cognition and Behavior: Individual Differences

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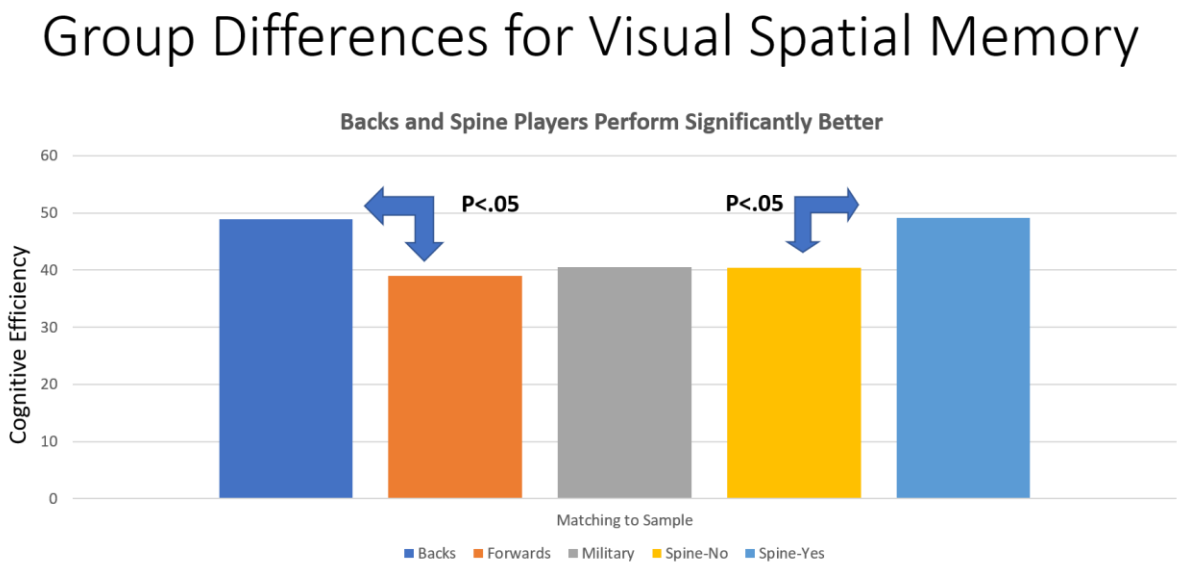
Program #/Poster #: 516.26/III41

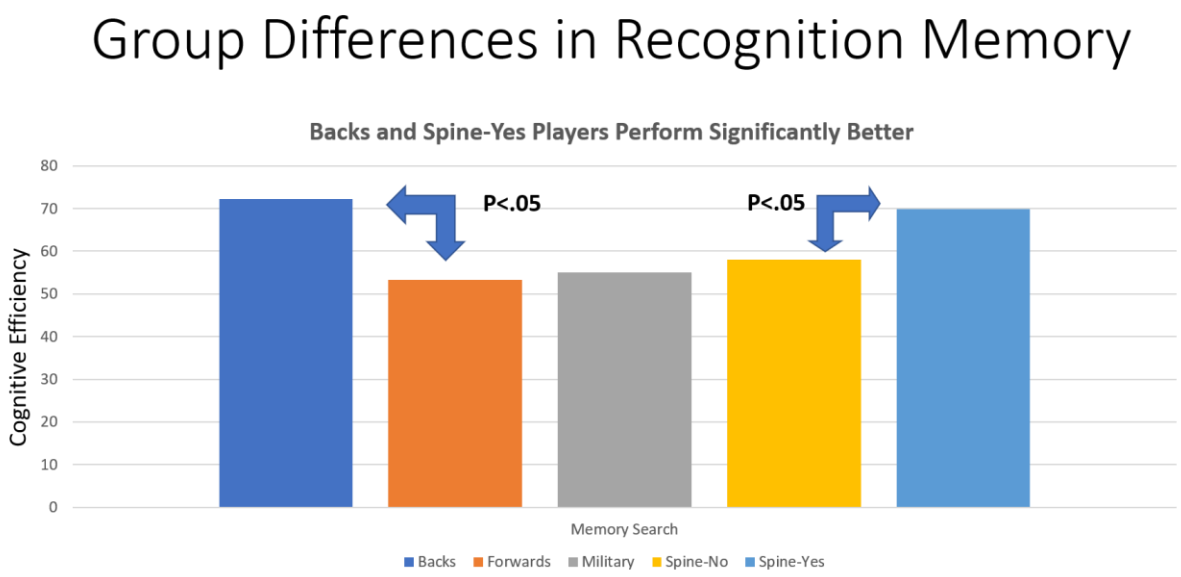
Topic: H.02. Human Cognition and Behavior

Title: Neurocognitive measures dissociate elite athletes in rugby league by position

Authors: *T. F. NUGENT III, S. L. MILLER, A. A. KRUSE, D. BACH
Platypus Inst., San Diego, CA

Abstract:





Rugby league is a full contact sport played internationally known for its fast action, player strength and decision making under stressful situations. Prior to the 2017 Men's Rugby League World Cup, a professional national league team underwent a series of cognitive assessments as part of an exploratory investigation into understanding the elite brains of professional athletes. 26 male players were subjected to a series of tests while instrumented with EEG. Data was collected for both neurophysiological brain-based metrics (workload, engagement, distraction), self-reported surveys on sleep, stress, and game performance anxiety, as well as more traditional behavioral measures through neuropsychological test batteries. Test batteries were selected for

cognitive metrics associated with high levels of performance in the sporting domain, such as visual spatial processing, executive function, reaction time, procedural reaction time and more. Data was collected and presented to both the team management and players to provide insight into cognitive levels of performance and how this could be related to their overall performance during rugby league play. When the players were grouped by position (forwards vs backs) we found significant difference for a match to sample task, memory search task, and fear of failure assessment ($p<.05$). These findings will lead to tailored training to improve cognitive performance of athletes, with longitudinal tracking of both their behavioral and cognitive outputs.

Disclosures: T.F. Nugent III: None. **S.L. Miller:** None. **A.A. Kruse:** None. **D. Bach:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.27/III42

Topic: H.02. Human Cognition and Behavior

Support: NASA 80NSSC17K0021
NASA NNX11AR02G
NSBRI SA02802

Title: The effects of 30 days of bed rest with elevated carbon dioxide on cognitive performance

Authors: *J. LEE[1], Y. E. DE DIOS[2], N. E. GADD[2], I. S. KOFMAN[2], J. J. BLOOMBERG[3], A. P. MULAVARA[2], R. D. SEIDLER[1]
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Abstract: Exposure to microgravity and elevated CO_2 as a result of residing in a confined compartment such as the International Space Station (ISS) may lead to neural structural and functional alterations in astronauts. In this study, evaluation of cognitive performance was carried out in 11 healthy participants (M=6, mean ± SD age: 33.91 ± 8.03 yr) who were exposed to 0.5% CO_2 concentrations over a 30 day period while in −6° head-down tilt bed rest (CO_2+ HDBR), simulating several conditions of the ISS including elevated CO_2, axial body unloading, and fluid shifts towards the head. Neurocognitive assessments of spatial working memory and visuomotor skills were administered on average 7 days before, 7 and 29 days during HDBR. The assessment results of the CO_2+ HDBR group were compared to that of 15 HDBR subjects (all males, mean ± SD age: 31.23 ± 5.07 yr) without 0.5% CO_2 exposure (CO_2 - HDBR) assessed on average 8 days prior, 8 and 50 days during HDBR, obtained for a separate spaceflight analog study. A significant group by time effect was observed for digit symbol substitution test

performance, where the CO_2+ HDBR group showed decreased task completion time with no change in accuracy. These findings are in line with a previous shorter duration HDBR study with increased CO_2 concentration. Behavioral improvements may be related to hypercapnia-induced cerebrovascular reactivity that favors brain regions such as the cerebellum and the visual cortex, areas that are involved in digit symbol substitution test performance. Results from the current study will help us better understand the mechanisms underlying neurocognitive changes occurring with spaceflight.

Disclosures: J. Lee: None. **Y.E. De Dios:** None. **N.E. Gadd:** None. **I.S. Kofman:** None. **J.J. Bloomberg:** None. **A.P. Mulavara:** None. **R.D. Seidler:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.28/III43

Topic: H.02. Human Cognition and Behavior

Support: Estonian Research Council Personal Post-doctoral Research Funding project PUTJD654
Fonds de recherche du Québec – Santé (FRQS) foreign post-doctoral training award CIHR

Title: Neurobehavioural correlates of obesity are largely heritable

Authors: *U. VAINIK[1,2], T. BAKER[3], M. DADAR[1], Y. ZEIGHAMI[1], A. MICHAUD[1], Y. ZHANG[1], J. C. G. ALANIS[4], B. MISIC[1], D. L. COLLINS[1], A. DAGHER[1]
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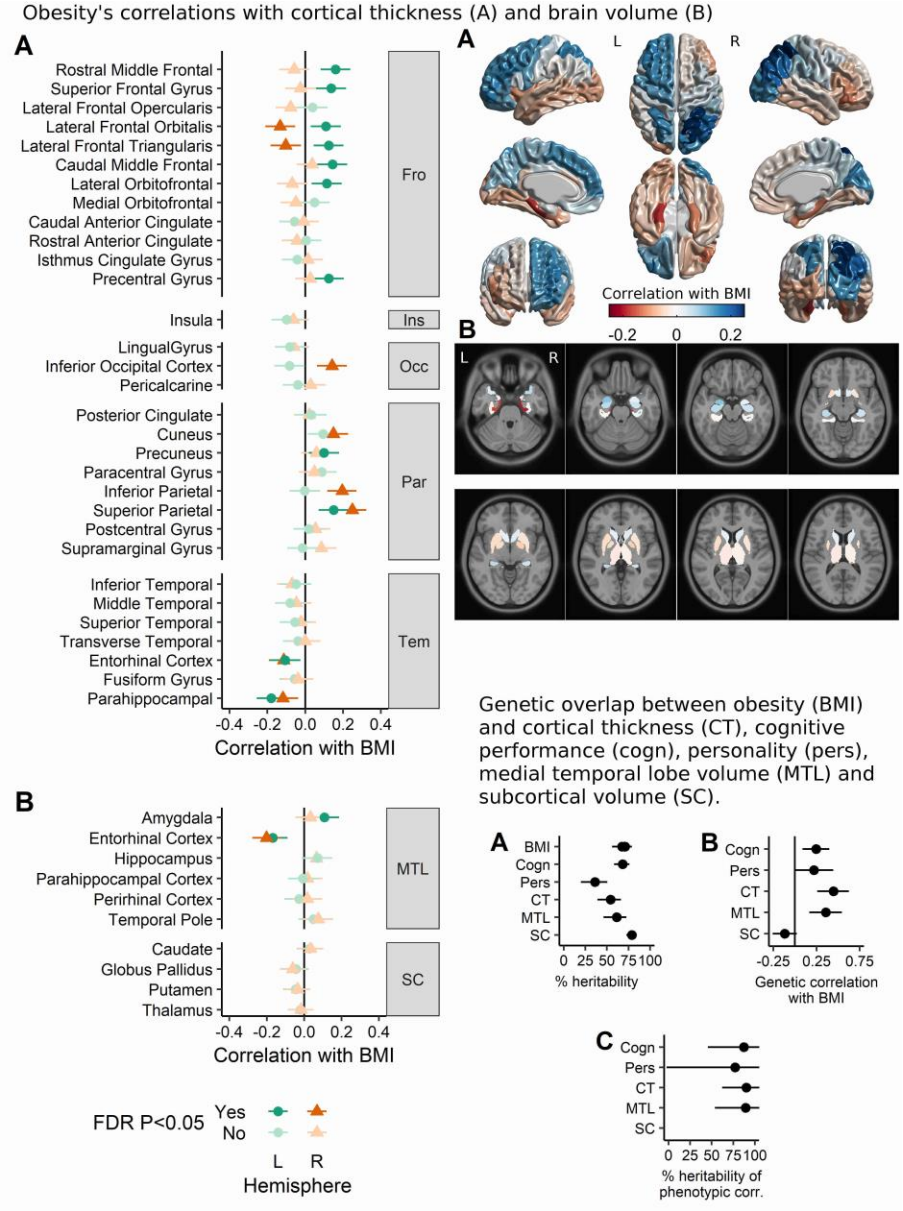
Abstract: Recent molecular genetic studies have shown that the majority of genes associated with obesity are expressed in the central nervous system. Obesity has also been associated with neurobehavioural factors such as brain morphology, cognitive performance, and personality. Here, we tested whether these neurobehavioural factors were associated with the heritable variance in obesity measured by body mass index (BMI) in the Human Connectome Project (N=895 siblings). Phenotypically, cortical thickness findings supported the “right brain hypothesis” for obesity. Namely, increased BMI associated with decreased cortical thickness in right frontal lobe and increased thickness in the left frontal lobe, notably in lateral prefrontal cortex. In addition, lower thickness and volume in entorhinal-parahippocampal structures, and increased thickness in parietal-occipital structures in obese participants supported the role of visuospatial function in obesity. Brain morphometry results were supported by cognitive tests,

which outlined obesity's negative association with visuospatial function, verbal episodic memory, impulsivity, and cognitive flexibility. Personality-obesity correlations were inconsistent. We then aggregated the effects for each neurobehavioural factor for a behavioural genetics analysis and demonstrated the factors' genetic overlap with obesity. Namely, cognitive test scores and brain morphometry had 0.25 - 0.45 genetic correlations with obesity, and the phenotypic correlations with obesity were 77-89% explained by genetic factors. Neurobehavioural factors also had some genetic overlap with each other. In summary, obesity has considerable genetic overlap with brain and cognitive measures. This supports the theory that obesity is inherited via brain function, and may inform intervention strategies.



Disclosures: U. Vainik: None. **T. Baker:** None. **M. Dadar:** None. **Y. Zeighami:** None. **A. Michaud:** None. **Y. Zhang:** None. **J.C.G. Alanis:** None. **B. Misic:** None. **D.L. Collins:** None. **A. Dagher:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.29/III44

Topic: H.02. Human Cognition and Behavior

Support: Wellcome Trust grant number 538149
European Research Council NEUROCODEC, 309865

Title: Individual differences in social punishment of unfair individuals and groups

Authors: *M. EL ZEIN, C. SEIKUS, L. DE-WIT, B. BAHRAMI
Univ. Col. London, London, United Kingdom

Abstract: In the last few decades, research on collective decisions has mainly focused on whether they are better or worse than individual decisions, but rarely on the motives that drive individuals to engage in group decisions. Besides improving accuracy, an important and less explored motive for individuals joining collectives is *shared responsibility* for decision outcomes. It can protect them against negative consequences of decisions especially if they trigger punishment (unfair behaviors, crimes), as individual punishment often decreases when shared among group members. Following the reasoning that groups share responsibility for harmful decisions, we predicted that a group would be punished less than an individual for the same decision. We tested this hypothesis by investigating social punishment in two well-known cooperation games: (1) the ultimatum and (2) the dictator game with third party punishment). In each game, one (individual condition) vs three (group condition) proposers made offers to a recipient in several rounds In the ultimatum game, recipient could reject (i.e. costly social punishment as proposers and recipients are left with nothing) or accept the offer. In the dictator game, a third party would incur a cost to punish the proposer(s) for their unfair offer. 81 healthy human participants (40 females, mean age=23.7±4.9) took part in the study. To investigate individual differences in social punishment of groups and individuals, questionnaires measuring social value orientation, political orientation, and psychopathy traits were collected from all participants. Punishment of individual and group proposers increased gradually with offers' unfairness. Critically, groups were punished less than individuals who made the same unfair offers. Punishment across all offers varied as a function of social value orientation and political orientation: the more prosocial and liberal recipient or third-party participants were more likely to administer punishment. Punishment difference between groups and individuals was only observed for individuals who scored low on psychopathy traits. Social punishment in

cooperation games reflecting sensitivity to others' unfairness relate to individual differences in political views and pro-sociality. The results importantly confirm our hypothesis that groups benefit from decreased punishment demonstrating a most useful motive to join collectives: shared responsibility. Finally, this decreased punishment for groups co-varied with psychopathy traits highlighting interesting individual differences in judgments of individuals vs groups.

Disclosures: M. El Zein: A. Employment/Salary (full or part-time):; Wellcome Trust. **C. Seikus:** None. **L. De-Wit:** None. **B. Bahrami:** None.

Poster

516. Human Cognition and Behavior: Individual Differences

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 516.30/III45

Topic: H.02. Human Cognition and Behavior

Title: The songs of my people: Appraisal differences of popular music as a function of ideology

Authors: *C. F. MYERS[1], S. SPIVACK[1], N. H. SPILKA[1], S. J. PHILIBOTTE[2], I. PASSMAN[1], P. WALLISCH[3]
[2]Dept. of Psychology, [3]Ctr. Neural Sci., [1]New York Univ., New York, NY

Abstract: Music powerfully engages brain and mind, yet remains largely underutilized as experimental stimulus material. Here, we wondered how ideological differences manifest in terms of musical preferences. To explore this question, we studied a large sample of research participants by exposing them to a representative corpus of musical stimuli while also eliciting their ideological position. Doing so, we found that ideological differences are linked to specific signatures of musical appraisal - there are significant genre-based differences in self-reported listening behavior as well as appraisal differences in how people with different ideological affiliations experience the music when listening to it. This effect is strong: ideology can be used to predict whether an ambiguous stimulus in terms of valence - e.g. country music - is experienced as aversive or enjoyable. As political preferences affect aesthetic judgments, we conclude that ideological positions are more deeply rooted than suggested by a discourse model of political exchange.

Disclosures: S. Spivack: None. **N.H. Spilka:** None. **S.J. Philibotte:** None. **I. Passman:** None. **P. Wallisch:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.01/III46

Topic: H.03. Schizophrenia

Support: Brain and Behavioral Research Foundation (NARSAD) Young Investigator Grant
NCATS UL1TR000427
NIH Grant T32 GM007507

Title: Shared brain microstructure across genetic models of schizophrenia and autism spectrum disorder

Authors: *B. R. BARNETT[1], C. P. CASEY[2], M. TORRES-VELÁZQUEZ[3], S. Y. YI[2], J.-P. J. YU[4]
[2]Neurosci. Training Program, [3]Biomed. Engin., [4]Radiology, [1]Univ. of Wisconsin, Madison, Madison, WI

Abstract: Autism spectrum disorder (ASD) is a complex and genetically heterogeneous neuropsychiatric disease affecting as many as 1 in 68 children. Large scale genetic sequencing of individuals along the autism spectrum has uncovered several genetic risk factors for ASD; however, understanding how, and to what extent, individual genes contribute to the overall disease phenotype remains unclear. Recent work has also uncovered strong evidence for the unanticipated genetic and neurostructural convergence of several psychiatric diseases including ASD, schizophrenia, and major depression. DISC1 is one such gene that stands at the intersection of numerous psychiatric diseases. As with other genetic variants that have been shown to confer an increased risk for disease, the balanced chromosomal t(1;11)(q42.1;q14.3) translocation of the DISC1 gene has been implicated in several psychiatric illnesses including schizophrenia, autism spectrum disorder, and major depressive disorder. Neuroimaging studies of ASD and schizophrenia have revealed a wide spectrum of structural and functional perturbations that are thought to reflect, in part, the complex genetic heterogeneity underpinning both diseases. These perturbations, in both preclinical models and clinical patients, were identified in preclinical genetic models and clinical patients as compared to control subjects; however, few studies have explicitly explored the intrinsic differences between the models themselves. To better understand the degree and extent to which individual genes associated with ASD and schizophrenia differ in their contribution to global measures of neurite density and white matter structural integrity, diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI) was acquired from three novel rat genetic models of ASD (Fmr1, Nrxn1, and Pten) and from a novel Disc1 knockout rat model of schizophrenia. DTI parameters of fractional anisotropy, mean, axial, and radial diffusivity and NODDI parameters of

neurite density and neurite orientation were measured and compared. Our findings demonstrate unexpected convergence in brain structures across all four genetic models and buttresses an emerging understanding of neurostructural phenotypic convergence in psychiatric disease.

Disclosures: B.R. Barnett: None. **C.P. Casey:** None. **M. Torres-Velázquez:** None. **S.Y. Yi:** None. **J.J. Yu:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.02/III47

Topic: H.03. Schizophrenia

Support: NIMH Grant MH090067

Title: Gene therapy reverses physiological and behavioral deficits in a rodent model of schizophrenia

Authors: *J. J. DONEGAN, A. M. BOLEY, D. J. LODGE
Pharmacol., Univ. of Texas Hlth. Sci. Ctr. At San Antonio, San Antonio, TX

Abstract: Schizophrenia is a devastating psychiatric disorder characterized by positive symptoms, like delusions and hallucinations, negative symptoms, like social withdrawal, and cognitive deficits. The dopamine hypothesis of schizophrenia suggests that enhanced activity in the mesolimbic dopamine system underlies symptoms of the disorder. Yet, no primary pathology exists in the dopamine system of schizophrenia patients and antipsychotic medications, which target dopamine receptors, only alleviate positive symptoms. This has led to the suggestion that the pathology lies in upstream brain regions, such as the ventral hippocampus (vHipp). Schizophrenia patients display hippocampal hyperactivity and our lab has shown that vHipp hyperactivity underlies increased dopamine cell activity and schizophrenia-like symptoms in the methylazoxymethanol acetate (MAM) rodent model. The increase in vHipp activity is thought to be caused by a deficit in inhibitory GABAergic interneurons. Therefore, we hypothesized that using gene therapy to restore GABAergic signaling in the vHipp would reverse schizophrenia-like deficits in the MAM model. A lenti virus expressing the α5 subunit or α1 subunit of the $GABA_A$ receptor under the control of the CAMKII promoter was injected into the vHipp and rats were allowed 6 weeks recovery before behavioral testing and *in vivo* extracellular recordings were performed. We found that MAM-treated rats had an increase in pyramidal cell firing rate in the vHipp compared to saline-treated controls. This aberrant firing was completely normalized in rats that received the virus to over-express the α5 subunit but not those that received the α1 subunit. To model positive symptoms, we measured latent inhibition and found that MAM-induced deficits in latent inhibition were attenuated by over-expression of the α5, but not the α1,

subunit of the $GABA_A$ receptor. Latent inhibition requires dopamine signaling; and over-expression of the α5, but not the α1, subunit also normalized dopamine cell activity in the ventral tegmental area. Next, using the attentional set-shifting test, we measured two forms of cognitive flexibility disrupted in schizophrenia, reversal learning and extradimensional set-shifting. We found that the MAM-induced deficits in reversal learning were not affected by over-expression of either the α1 or the α5 subunit while extradimensional set-shifting deficits were attenuated by both subunits. Together, these results suggest that gene therapy to restore GABAergic signaling in vHipp pyramidal neurons may be an effective treatment strategy to target multiple symptom domains of schizophrenia.

Disclosures: J.J. Donegan: None. **A.M. Boley:** None. **D.J. Lodge:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.03/III48

Topic: H.03. Schizophrenia

Support: NIH Grant MH097997
VA grant MIRECC

Title: Nuclear paraspeckle lncRNA, Neat1 is an epigenetic modulator of oligodendroglial function with suppressed transcription in schizophrenia

Authors: *P. L. KATSEL[1], P. ROUSSOS[2], M. PLETNIKOV[3], P. FAM[2], V. HAROUTUNIAN[4], S. NAKAGAWA[5], T. HIROSE[5]
[1]Dept Psych, Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Icahn school of medicine at Mount sinai, New York, NY; [3]Johns Hopkins Univ., Baltimore, MD; [4]Director, Neurobio. Labs., Bronx, NY; [5]Hokkaido Univ., Sapporo, Japan

Abstract: Oligodendrocyte (OLG)/myelin - related abnormalities are strongly corroborated observations in the pathophysiology of schizophrenia. The cause(s) of these abnormalities is unknown. Noncoding RNAs (ncRNAs) are important part of multifaceted transcriptional complexes participating in neurogenic commitment and regulation of post-mitotic cell maturation and function. A long ncRNA, NEAT1, is a structural component of paraspeckles, subnuclear bodies in interchromatin regions that may control activity of developmental enhancers of OLG fate specification. Gene expression studies of multiple cortical regions from individuals with schizophrenia showed strong downregulation of NEAT1 levels compare to controls. Evaluation of "quaking-Qk" mice which exhibit demyelination and $NEAT1^{-/-}$ mice revealed that NEAT1 loss is strongly associated with decrease of number of OLG lineage cells in the frontal cortex. To gain insight into biological processes affected by deficiency of NEAT1

expression we analyzed RNA-Seq data from frontal cortex of NEAT1$^{-/-}$ mice. Analyses of differentially expressed gene signature from NEAT1$^{-/-}$ mice reveal a significant impact on processes related to OLG differentiation and RNA post-transcriptional modification. We present evidence of coexpression of SOX10 and NEAT1 in OLG nuclei, and show enrichment of OLG specific transcripts in NEAT1 purified chromatin isolates (ChIRP) from human frontal cortex. Reduced nuclei retention of Qki isoform 5 in NEAT1$^{-/-}$ mice shed light on possible mechanism(s) responsible for reduced expression of OLG proteins and support strong involvement of NEAT1 in the mechanisms underlining myelin deficit in schizophrenia.

Disclosures: P.L. Katsel: None. **P. Roussos:** None. **M. Pletnikov:** None. **P. Fam:** None. **V. Haroutunian:** None. **S. Nakagawa:** None. **T. Hirose:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.04/III49

Topic: H.03. Schizophrenia

Title: Psychopathology in a 15q13.3 microdeletion mouse model to probe mechanisms for early intervention

Authors: K. D. BORNEMANN, M. HEIL, S. JAEGER, *J. R. NICHOLSON, N. SCHUELERT, H. ROSENBROCK, V. MACK
Boehringer Ingelheim Pharma GmbH & Co.KG, Biberach, Germany

Abstract: Rodent models for rare gene copy number variants, which confer high risk for psychiatric diseases such as schizophrenia (SCZ), are attractive to test new therapeutic concepts. With a particular focus on early pathophysiology as e.g. observed in patients with clinical high risk for psychosis, we explored biomarkers of cortical network synchrony and GABAergic interneuron function in the Df(15q13)/+ mouse model. This mouse line carries a deletion in chromosome 7, which corresponds to the human chromosome 15q13.3 region, comprising six genes linked to psychiatric risk. As shown by others, we could reveal a reduced density of parvalbumin-positive interneurons (PVI) in the prefrontal cortex (PFC) of young adult mice, indicative of impaired cortical excitatory-inhibitory (E/I) balance and network synchronization. The deficits in PVI density were accompanied by reduced size of perineuronal nets (PNN), which are crucial for PVI function and protection against oxidative stress. To address neurophysiological consequences linked to cortical pathology, we are about to assess changes in network synchrony and sensory processing by in vivo electroencephalography in the PFC and auditory cortex. We aim for monitoring translational biomarkers that have been reported to be abnormal in several psychiatric diseases, such as event-related potentials and γ oscillation (evoked power and inter-trial coherence). Taken together, the Df(15q13)/+ mouse might serve as

a preclinical model for early psychiatric pathophysiology and, thereby, offers the possibility to probe therapeutic concepts aimed at early intervention in the disease progress.

Disclosures: K.D. Bornemann: None. **M. Heil:** None. **S. Jaeger:** None. **J.R. Nicholson:** None. **N. Schuelert:** None. **H. Rosenbrock:** None. **V. Mack:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.05/III50

Topic: H.03. Schizophrenia

Support: Action on Hearing Loss
National Institute of Mental Health

Title: Hearing loss, auditory sensorimotor gating deficits, and cortical interneuron abnormalities in a mouse model of 22q11.2 Deletion Syndrome

Authors: *J. F. LINDEN[1], F. A. ZINNAMON[2], F. G. HARRISON[1], S. S. WENAS[1], A. F. MEYER[1], Q. LIU[3], K. H. WANG[3]
[1]Univ. Col. London, London, United Kingdom; [2]Univ. Col. London and Natl. Inst. of Mental Hlth., Bethesda, MD; [3]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: The chromosomal microdeletion that causes 22q11.2 Deletion Syndrome (22q11DS) confers a 25-30% risk of developing schizophrenia. An estimated 40-70% of patients with 22q11DS also have hearing loss, mostly from otitis media (OM). In the *Df1/+* mouse model of 22q11DS, similar rates of hearing loss and OM occur (Fuchs et al. *PLoS One* 2013) and have been shown to arise from haploinsufficiency of the *TBX1* gene within the minimum 22q11DS deletion region (Fuchs et al. *Hum Mol Genet* 2015). However, the relationship between hearing loss and susceptibility to schizophrenia-relevant brain and behavioural abnormalities in 22q11DS is unknown. Here we report a link between hearing loss, deficits in auditory sensorimotor gating, and abnormalities in parvalbumin-positive auditory cortical interneurons in a mouse model of 22q11DS.
Using the auditory brainstem response (ABR), we found that 60% of *Df1/+* mice had hearing loss in one or both ears. However, suprathreshold cortical auditory evoked potentials (AEPs) were similar in *Df1/+* and WT mice. The ratio between AEP P1-N1 or N1-P2 amplitude and ABR wave I amplitude was significantly higher in *Df1/+* mice with hearing loss than in WT mice or *Df1/+* mice without hearing loss, suggesting a compensatory increase in central auditory gain in *Df1/+* mice with hearing loss.
Behavioural measures similarly revealed an influence of hearing loss. Acoustic startle response (ASR) thresholds were significantly higher in *Df1/+* than WT mice. Prepulse inhibition (PPI) of

ASR was reduced in *Df1/+* mice relative to WT for prepulse cues with fixed sound level, as has previously been reported elsewhere. However, we found that there was no significant difference in PPI between *Df1/+* and WT mice when the prepulse cue sound level was adjusted to be constant relative to the startle threshold for each animal.
Finally, in immunohistochemical studies, we found that the density of parvalbumin-positive (PV+) interneurons in the auditory cortex was significantly reduced in *Df1/+* compared to WT mice. This abnormality arose primarily in *Df1/+* mice with hearing loss, suggesting cortical compensation for loss of input.
Overall, the findings indicate that *Df1/+* mice have reduced hearing sensitivity and elevated startle thresholds, but also increased central auditory gain and reduced density of PV+ inhibitory interneurons in auditory cortex. Moreover, PPI of acoustic startle in *Df1/+* and WT mice differs for prepulse cues of fixed sound level, but not when the cue level is adjusted relative to startle threshold. Thus, the findings suggest a complex interaction between hearing loss and auditory brain and behavioural abnormalities in 22q11DS models.

Disclosures: J.F. Linden: None. **F.A. Zinnamon:** None. **F.G. Harrison:** None. **S.S. Wenas:** None. **A.F. Meyer:** None. **Q. Liu:** None. **K.H. Wang:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.06/III51

Topic: H.03. Schizophrenia

Support: MRC G0902166
MRC MR/J004367/1
Brain & Behavior Research Foundation 23306
EUFP7 607616FP7

Title: Transcriptomic analysis of neurons derived from psychiatric patients carrying a t(1;11) translocation, and a corresponding mouse model

Authors: *K. MILLAR[1], S. T. O'SULLIVAN[2], M. BONNEAU[2], P. GAUTIER[2], Y. SINGH[3], H. S. TORRANCE[2], D. L. MCCARTNEY[2], S. M. ANDERSON[2], H. VOLKMER[4], M. LOOS[5], K. L. EVANS[2], C. A. SEMPLE[2], S. CHANDRAN[6], M. DIDIER[7], D. J. PRICE[8], D. J. PORTEOUS[2]
[1]Univ. of Edinburgh, Edinburgh, United Kingdom; [2]MRC Inst. of Genet. and Mol. Med., Edinburgh, United Kingdom; [3]CeGaT, Tuebingen, Germany; [4]The Univ. of Tuebingen, Tuebingen, Germany; [5]Sylics, Amsterdam, Netherlands; [6]The Univ. of Edinburgh, Edinburgh, United Kingdom; [7]Sanofi, Chilly-Mazarin, France; [8]Univ. Edinburgh, Edinburgh, United Kingdom

Abstract: A chromosomal translocation linked to schizophrenia in a large Scottish family disrupts the DISC1 gene. To identify translocation-induced disease pathways we have carried out RNASeq analysis of induced pluripotent stem cell (IPSC)-derived cortical neurons from translocation family members, and of brain cortex from a corresponding mouse model that recapitulates the effects of the translocation upon DISC1 expression. The set of dysregulated genes in the human cortical neurons is enriched for matches to genes whose expression is altered by independent DISC1 mutations in IPSC-derived human neurons. A substantially overlapping set of genes is dysregulated in both human cortical neurons and mutant mouse cortex. Moreover, gene ontology and pathway analysis predict largely the same major dysregulated functions in both datasets, including excitatory synapse dysfunction. Multiple putative schizophrenia genes identified through recent large-scale genome-wide association and copy number variant studies are dysregulated in the human cortical neurons and mutant mouse cortex. These sets of dysregulated putative schizophrenia genes highlight defective synapse function and plasticity as likely disease pathways. Altogether these observations indicate that i) many of the gene expression changes in the human cortical neurons are due to disruption of DISC1, ii) DISC1 disruption may act as a trigger for common shared disease pathways in schizophrenia, and iii) defective excitatory synapse function and plasticity due to the translocation may be a disease mechanism.

Disclosures: K. Millar: None. **S.T. O'Sullivan:** None. **M. Bonneau:** None. **P. Gautier:** None. **Y. Singh:** None. **H.S. Torrance:** None. **D.L. McCartney:** None. **S.M. Anderson:** None. **H. Volkmer:** None. **M. Loos:** None. **K.L. Evans:** None. **C.A. Semple:** None. **S. Chandran:** None. **M. Didier:** A. Employment/Salary (full or part-time):; Sanofi. **D.J. Price:** None. **D.J. Porteous:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.07/III52

Topic: H.03. Schizophrenia

Support: NIH R01 MH075916-05
NIH 5P50MH096891-03

Title: Src deficient mice demonstrate behavioral and electrophysiological alterations relevant to schizophrenia

Authors: O. MELNYCHENKO[1], K. R. WARD[2], C.-G. HAHN[3], *R. E. FEATHERSTONE[1], S. J. SIEGEL[1]
[1]Psychiatry and Behavioral Sci., USC, Los Angeles, CA; [2]Psychiatry, Univ. of Pennsylvania, Philadelphia, PA; [3]Dept Psychiat, Univ. Pennsylvania Sch. Med., Philadelphia, PA

Abstract: While much evidence suggests that hypofunction of the *N*-methyl-D-aspartate glutamate receptor (NMDAR) hypofunction is a primary cause of schizophrenia (SCZ), little is known about the molecular basis of NMDAR dysfunction. Sarcoma tyrosine kinase (Src) serves as a hub for signaling mechanisms affecting GluN2 phosphorylation, and can be disrupted by convergent alterations of various schizophrenia susceptibility pathways. Src signaling is reduced in post mortem tissue from schizophrenia patients, despite increased MK-801 binding and NMDA receptor complex expression in the postsynaptic density (PSD), suggesting that Src dysregulation may be a primary mechanism responsible for reduced glutamate signaling in schizophrenia (Banerjee et al. 2015). Despite evidence for a central role of Src in NMDAR signaling, little is known about how reductions in Src activity might regulate phenotypic changes relevant to schizophrenia. As such, the current study sought to characterize behavioral, electrophysiological and anxiety related phenotypes in mice heterozygous for the Src *Acl* gene (Src+/- mice). Male and female Src+/- mice were compared with litter mate controls on a series of behavioral and EEG related measures relevant to schizophrenia. Src+/- mice demonstrated decreased sociability and working memory relative to Src+/+ (WT) mice while no significant differences were seen on locomotive activity and anxiety. In relation to WT mice, Src+/- mice showed decreased P20 and N40 event related potential (ERP) amplitudes, decreased mismatch negativity (MMN) and decreased evoked gamma power, which was only present in males. Decreased MMN was reversed following a single administration of the mGluR5 antagonist MPEP (2-Methyl-6-(phenylethynyl)pyridine). Src+/- mice express behavioral, cognitive, and electrophysiological phenotypes, consistent with those seen in patients with SCZ. This data indicates that Src+/- mice are a promising model for the negative symptoms of schizophrenia.

Disclosures: O. Melnychenko: None. **K.R. Ward:** None. **C. Hahn:** None. **R.E. Featherstone:** None. **S.J. Siegel:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.08/III53

Topic: H.03. Schizophrenia

Support: JSPS KAKENHI Grant Number JP18K15354

Title: Behavioral phenotype of glyoxalase 1 knockout mice

Authors: *K. SUZUKI, K. TORIUMI, Y. HORIUCHI, M. MIYASHITA, M. ITOKAWA, M. ARAI
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Abstract: Schizophrenia is considered to be a heterogeneous psychiatric disorder, since symptom and severity seen in patients with schizophrenia varies widely among individuals. Recently, we found a characteristic group in which patients exhibit high plasma pentosidine, one of advanced glycation end products (AGEs), and depletion of serum vitamin B_6, known as a scavenger of AGEs. Schizophrenic patients in the group account for approximately 20%. Furthermore, we found several schizophrenic patients with novel heterozygous frameshift and missense mutations in Glyoxalase 1 (*GLO1)* gene with 40-50% and 15-20% reduction of enzymatic activity, respectively. GLO1 is one of enzymes to detoxify reactive carbonyl compounds such as methylglyoxal, preventing the eventual formation of AGEs. However, the association between GLO1 deficit and schizophrenia development remains unclear.
In order to evaluate effects of GLO1 deficits on behavior, we generated *Glo1* knockout (KO) mice and assessed their behavioral phenotypes. In the open field test, *Glo1* KO mice showed less locomotor activity compared with wild-type (WT), but no significant difference in time spent in the center zone. Furthermore, *Glo1* KO mice showed shortened immobility time in the forced-swimming test and exhibited remarkable reduction in the acoustic startle response, resulting in enhanced prepulse inhibition. *Glo1* KO mice showed no changes in the Y maze test and the social interaction test. Additionally, in order to assess stress vulnerability of *Glo1* KO mice, we performed social avoidance test after chronic social defeat stress, but we have not detected significant difference between WT and KO mice so far.
These results suggest that GLO1 deficits induce some behavioral changes. However, the behavioral deficits observed in *Glo1* KO mice were not typical schizophrenia like-behaviors. As it is widely accepted that not only genetic but also environmental factors play key roles in development of schizophrenia, further experiments using more suitable and gene-environment interaction models, such as *Glo1* mice fed with VB6-deficient diet, will be needed in the future.

Disclosures: K. Toriumi: None. **Y. Horiuchi:** None. **M. Miyashita:** None. **M. Itokawa:** None. **M. Arai:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.09/III54

Topic: H.03. Schizophrenia

Support: NIH Grant MH103775

Title: Behavioral flexibility of male and female rats in the MAM animal model of schizophrenia

Authors: *M. GHASEMZADEH, D. KRAVTSOV, L. KELBLE
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Abstract: Schizophrenia is a neurodevelopmental disorder with distinct abnormal behaviors and cognitive deficits. Since the MAM neurodevelopmental animal model (E17 gestational methylazoxymethanol acetate administration) displays some anatomical and neurochemical deficits associated with schizophrenia, we examined the performance of the MAM-treated animals (Sprague-Dawley rats) in behavioral cognitive tasks to evaluate the extent and nature of the deficits in this model. Rats were bred on site and MAM (22 mg/kg, ip) or saline (1 ml/kg, ip) was administered on gestation day 17. Male and female offspring were housed 3-4 per cage and were provided with enrichment. All efforts were made to eliminate sources of stress in these animals during development and behavioral testing. We examined adult male and female rats (PND > 90) for performance in behavioral flexibility using an automated operant procedure. Since MAM animals show abnormal development of prefrontal cortex, we employed strategy set-shifting and reversal learning tasks to examine their performance. Adult female and male MAM rats performed as well as controls in initial learning of a response or a visual-cue. However, both adult female and male MAM rats displayed a deficit in visual-cue to response strategy shift by requiring a higher number of trials to achieve criterion. In addition, both adult female and male MAM rats demonstrated impairment in reversal learning of a discrimination task. Notably, the deficits in behavioral flexibility in MAM rats became more prominent as the relative difficulty in type of strategy shift and reversal learning increased. In other studies, adult MAM rats displayed decreased level of anxiety, higher social interaction, and augmented locomotor response in a novel environment. In order to examine the developmental nature of behaviors displayed by adult MAM rats, we examined the male and female rats during adolescence (PND 35-45). The adolescent MAM rats (male and female) responded with higher locomotor activity in a novel environment, which continued through adulthood. In an open field arena, adolescent rats (male and female) spent more time in the center of the arena compared to the saline-treated animals. In addition, adolescent MAM animals (male and female) spent more time on the open arm of the elevated plus maze compare to saline-treated rats which continued into adulthood. The overall pattern of behaviors displayed by the MAM developmental animal model is suggestive of a deficit in cognitive flexibility and behavioral inhibition and may be a useful model in examining the neuronal basis of these abnormalities in mental disorders.

Disclosures: M. Ghasemzadeh: 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.; AviMed Pharmaceuticals, LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AviMed Pharmaceuticals, LLC. **D. Kravtsov:** None. **L. Kelble:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.10/III55

Topic: H.03. Schizophrenia

Support: JSPS Grant 17K13965

Title: Neonatal blockade of NR2A-containing NMDA receptors induces schizophrenia-like behavior in adult rats

Authors: *H. FURUIE, H. KUNIISHI, M. YAMADA
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Abstract: N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor subtype, plays pivotal roles in brain development. Chronic neonatal blockade of NMDA receptors causes various behavioral abnormalities similar to those observed in schizophrenia in adulthood, and it is suggested that these effects are due to the neurodevelopmental interference. NMDA receptors are composed of NR1 and NR2A-D and/or NR3A-B subunit, and NR2A- and 2B-containing receptors are principally expressed in the postnatal rodent forebrain. However, differential roles of NR2A and NR2B- containing NMDA receptors in the postnatal brain development are unknown. To address this issue, we compared the effects of neonatal treatment with an NR2A-preferring antagonist PEAQX, an NR2B-selective antagonist ifenprodil, and a non-selective NMDA receptor antagonist MK-801 on the expression of schizophrenia-like behavior in adulthood.
Seventy-nine male pups obtained from 14 female Wistar-Imamichi rats were used in the experiments. On postnatal day (PND) 7, pups were randomly assigned to four treatment conditions. From PND 7 through 20, they were administered one of the following four drugs twice per day: PEAQX (10 mg/kg), ifenprodil (7.5 mg/kg), MK-801 (0.4 mg/kg), or saline. Rats were weaned at PND 28 and housed in groups of 2 or 3 rats per cage. At PND 70, the rats were tested in the prepulse inhibition (PPI) test, the social interaction test, the spontaneous alternation test, and the MK-801-induced locomotor test.
Interestingly, PEAQX-, ifenprodil- and MK-801-treated rats showed equivalent PPI compared with SAL-treated control. On the other hand, PEAQX- and MK-801-treated rats exhibited greater startle response when compare to SAL- and ifenprodil-treated rats. PEAQX- and MK-801-treated rats also showed significantly lower spontaneous alternation ratio than SAL- and ifenprodil-treated rats. Furthermore, neonatal PEAQX treatment increased sensitivity to locomotor-stimulating effect of acute MK-801 challenge. In conclusion, our results suggest that NR2A-containing NMDA receptor is essential for normal brain development during neonatal

period, and the blockade of this receptor in this period induces schizophrenia-like behavior in adulthood.

Disclosures: H. Furuie: None. **H. Kuniishi:** None. **M. Yamada:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.11/III56

Topic: H.03. Schizophrenia

Support: MOST 105-2628-B-002 -004 -MY3

Title: Phenotypic characterization of mice lacking exons 4-13 of Disc1 gene

Authors: *P. SIOW, L.-J. LEE
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Abstract: Schizophrenia is a chronic mental disorder that affects a person's feeling, thoughts, and behaviors. One of the candidate susceptibility gene related to the pathogenesis of this disease is *Disrupted-in-Schizophrenia 1* (*DISC1*). We have established a *Disc1* mutant mouse line in which the exons 4 to13 were deleted by the expression of *Emx1-Cre* in the excitatory neurons of the forebrain. Both homozygous (Homo) and heterozygous (Het) forebrain-specific *Disc1* knockout (Fb*Disc1* KO) mice were apparently normal with no significant physical impairment. Behavioral examinations were then conducted. In the open field test, mice of all three genotypes (wildtype, WT, Het and Homo) behaved similarly in distance travelled and time spent in central and peripheral regions. In the novel object recognition test, Homo mice displayed impaired short-term recognition memory, while WT and Het mice had comparable performances . In the elevated plus maze test, Homo mice spent more time in the open arms than WT and Het mice and no difference was noticed between WT and Het groups. In the forced swim test, no significant difference was found among the three genotypes. Our preliminary results showed behavioral abnormalities in Homo Fb*Disc1* KO mice in cognition and emotional aspects while Het mutants seemed to be normal.

Disclosures: P. Siow: None. **L. Lee:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.12/III57

Topic: H.03. Schizophrenia

Support: KAKENHI 21390329
KAKENHI 16K07210

Title: Maternal infection alters methylome of schizophrenia loci in female brain

Authors: *Z. YU[1], K. UENO[2], R. FUNAYAMA[1], M. SAKAI[3], C. ONO[1], K. NAKAYAMA[1], M. NAGASAKI[1], H. TOMITA[1]
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Abstract: Schizophrenia is a severe and relatively common mental disorders, affecting approximately 1% of the world's population. Maternal infection during pregnancy has been considered a plausible risk factor for schizophrenia. Although differential DNA methylation at CpG is a well-characterized epigenetic hallmark for schizophrenia, the mechanisms is unknown.Here we use murine maternal viral infection schizophrenic model, after behavioral evaluations of offspring from polyriboinosinic-polyribocytidilic acid (poly I:C)- and phosphate-buffered saline (PBS)-treated pregnant mice, prefrontal contextual gene expression and DNA methylation profiling were analyzed. Female offspring show more methylated CpG sites, as well as higher levels of *Dnmt1*mRNA expression.DNA hyper-methylation that contribute to genes transcript reduction was observed in poly I:C-treated female offspring along with more striking schizophrenia like behavior than PBS-treated females, but not males. Poly I:C significantly induced *Dnmt* expression in female offspring of poly I:C treated dams. Neuron and synapse-relevant genes were significantly over-represented among poly I:C affected genes in females, whereas no specific category of genes was over-represented in males. An in-depth investigation of astrocyte marker gene showed significant hyper-methylation DNA and reduced gene expression in female offspring of poly I:C-treated dam and female schizophrenia patients postmortem tissues.Present results not only generated gender different genome-wide DNA methylation, but also identified new candidate genes for maternal infection during pregnancy which may affect neuron and glia cell development. Our study suggest that based on significant gender difference in genome-wide DNA methylation profiling, and provide a breakthrough in elucidating the pathogenesis of schizophrenia via studies into gender differences in the susceptibility.

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Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.13/III58

Topic: H.03. Schizophrenia

Support: NIMH grant P50 MH103222 Silvio O. Conte Centers for Translational Mental Health Research

Title: Maternal immune activation in rats blunts brain cytokine and kynurenine pathway responses to a second immune challenge in early adulthood

Authors: *S. M. CLARK[1], F. M. NOTARANGELO[2], X. LI[1], S. CHEN[2], R. SCHWARCZ[2], L. TONELLI[1]
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Abstract: Maternal immune activation (MIA) with the viral mimic poly (I:C) provides an established rodent model for studying schizophrenia (SZ) and other human neurodevelopmental disorders. Postnatal infections are additional risk factors in SZ and may cumulatively contribute to the emergence of pathophysiology. Underlying mechanisms may involve metabolites of the kynurenine pathway (KP) of tryptophan degradation, which is readily induced by inflammatory stimuli. In the present study, the expression of selected cytokines and KP enzymes, and the levels of selected KP metabolites, were evaluated in the brains of MIA offspring following a second, acute immune challenge with lipopolysaccharides (LPS) on postnatal day (PND) 35 (adolescence) or PND 60 (early adulthood). Peripheral measures of kynurenine (KYN) and kynurenic acid (KYNA) were also determined in the plasma. Assessed in adolescence, MIA did not alter the expression of pro-inflammatory cytokines (except TNF-α) or KP metabolite levels compared to controls, but substantially reduced the expression of the anti-inflammatory cytokines IL-4 and IL-10 and influenced the expression of two of the four KP enzymes examined (IDO1 and TDO2). LPS treatment caused distinct changes in central expression of pro- and anti-inflammatory cytokines, as well as KP enzymes in MIA offspring, with no effect on KP metabolites compared to control rats. Additionally, while LPS increased plasma KYN levels, there was no effect on peripheral KYNA. Several of these effects were blunted in MIA offspring receiving LPS on PND 60. Notably, LPS caused a significant reduction in brain kynurenine levels in these animals. Of relevance for SZ-related hypotheses, these results indicate that MIA leads to an increasingly defective, rather than overactive, regulation of cerebral KP metabolism during the postnatal period.

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Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.14/III59

Topic: H.03. Schizophrenia

Title: NFAT5 regulates psychotomimetic behaviors of mice through modulating brain dopaminergic neurotransmission

Authors: *S. KIM[1], H. PARK[2], Y. KIM[1], Y. AHN[3], H. KWON[4]
[1]Dongguk Univ. Intl. Hosp., Ilsandong-Gu, Goyang-Si, Gyeonggi-Do, Korea, Republic of; [2]Dept. of Biomed. Sciences, Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of; [3]Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of; [4]Ulsan Natl. Inst. of Sci. and Technol., Ulsan, Korea, Republic of

Abstract: Nuclear factor of activated T-cells 5 (NFAT5), also known as tonicity enhancer element binding protein (TonEBP), is the osmosensitive transcription factor, which plays a crucial role in protection of renal medullary cells against hyperosmotic stress, urinary concentration, the adaptive immune response. NFAT5 is expressed abundantly in the brain, while the functions in nervous systems have not been understood yet. We examined the role of NFAT5 on the behaviors in terms of mood and psychotomimetic domains and the behavios-related regulatory mechanisms. NFAT5 heterozygote (+/-) mice did not show significant differences compared to wild type (WT) mice in forced swim test, sucrose preference test, and open field activity. When chronic unpredictable stress (CUS) has been applied, WT mice demonstrated depression-like behavioral phenotypes, while NFAT5 (+/-) mice showed attenuated response to CUS compared to WT. The reponse to cocaine injection was also in NFAT (+/-) mice compared to WT. While overexpression of TonEBP gene in mice striatum using adenovirus iuduced the increased behavioral response to cocaine. The dopamine level was reduced in the striatum of NFAT5 (+/-) mice compare to WT. NFAT5 gene knockdown using siRNA showed reduced expression of dopamine decarboxylase and tyrosine hydroxylase genes. The findings suggest the important role of NFAT5 gene in dopamine neurotransmission and related psychotomimetic behaviors in the brain.

Disclosures: S. Kim: None. **H. Park:** None. **Y. Kim:** None. **Y. Ahn:** None. **H. Kwon:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.15/III60

Topic: H.03. Schizophrenia

Support: NARSAD Independent Investigator Award
USU URCO Fellowship

Title: Impaired latent inhibition in NrCAM-deficient mice exposed to chronic stress

Authors: C. K. BROWN, 84322[1], C. V. BUHUSI[2], *M. BUHUSI[1]
[1]Dept. Psychology, [2]Interdisciplinary Program in Neurosci., Utah State Univ., Logan, UT

Abstract: Schizophrenia is a neurodevelopmental disorder characterized by abnormal processing of information and attentional deficits. Schizophrenia has a high genetic component but is precipitated by environmental factors, as proposed by the 'two-hit' theory of schizophrenia. One of the top candidate genes related to vulnerability to schizophrenia is NrCAM, with essential roles in neuronal connectivity and function. Here we compared latent inhibition as a measure of learning and attention, in NrCAM-deficient mice, and their wild-type littermates, under no-stress and chronic stress conditions. Freezing behavior in response to pre-exposed and non-pre-exposed stimuli paired with foot shocks was analyzed to assess latent inhibition. Analyses indicated a main effect of pre-exposure (F(1,36)=37.24, p < 0.01), a pre-exposure x stress interaction (F(1,36)=5.24, p < 0.05), and a pre-exposure x stress x genotype interaction (F(1,36)=4.28, p < 0.05). Post-hoc analyses showed that all unstressed mice as well as the wild-type stressed mice showed latent inhibition (p < 0.01); in contrast, NrCAM-deficient mice did not show latent inhibition after chronic stress (p > 0.05). Differences in activation in brain regions associated with latent inhibition - such as the prefrontal cortex and nucleus accumbens - were identified using c-Fos immunostaining. These results provide strong support for a 'two-hit' (genes x environment) effect on latent inhibition in NrCAM-deficient mice, and identify NrCAM-deficient mice as a model of schizophrenia-like learning and attention impairments.

Disclosures: C.K. Brown: None. **C.V. Buhusi:** None. **M. Buhusi:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

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Program #/Poster #: 517.16/III61

Topic: H.03. Schizophrenia

Support: NIMH Grant MH090067

Title: Adolescent stress induces a schizophrenia-like phenotype in a rodent model of susceptibility

Authors: *S. M. PEREZ[1], D. J. LODGE[2]
[1]Pharmacol., [2]UTHSCSA, San Antonio, TX

Abstract: Factors that contribute to the development of schizophrenia include both, genetic and environmental conditions. Rodent models are used to recapitulate various aspects of the disease; however, to our knowledge there are no models routinely used to examine schizophrenia susceptibility. Here, we employ the use of a verified gestation disruption model, the methylazoxymethanol acetate (MAM) E17 model, to produce a model of susceptibility to circuit level alterations and behavioral deficits consistent with those observed in schizophrenia. Specifically, first filial generation (F1) MAM-treated rats were mated to produce second filial generation (F2) offspring. We have previously demonstrated that only a proportion (~30%) of F2 MAM-treated rats display a schizophrenia-like phenotype, defined as an increase in ventral tegmental area (VTA) dopamine neuron population activity. This aberrant dopamine neuron activity has been previously attributed to hyperactivity in the ventral hippocampus (vHipp). Thus, we posit that the F2 generation MAM rats provide a model of susceptibility whereby the effect of environmental risk factors can be investigated. We now examine the effect of adolescent stress (a known risk factor for psychiatric disease) in this model and report that a significantly greater proportion of F2 MAM-treated rats (~70%) displayed a schizophrenia-like phenotype, determined by dopamine neuron electrophysiology, following adolescent stress (predator odor). Indeed, this was correlated with increases in the firing rates of vHipp putative pyramidal neurons. Taken together, these data provide mechanistic insights into how adolescent stress may contribute to the pathophysiology of psychiatric diseases, such as schizophrenia.

Disclosures: S.M. Perez: None. **D.J. Lodge:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

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Program #/Poster #: 517.17/III62

Topic: H.03. Schizophrenia

Support: NIH 1R01A9053588-01

Title: The mPTP-regulating protein cyclophilin D contributes to oxidative stress in a developmental rodent model of schizophrenia

Authors: *A. J. PHENSY[1], K. A. LINDQUIST[4], D. BAIRUTY[2], K. RAPOLU[3], K. KING[3], H. DU[5], S. KROENER[6]
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Abstract: Cognitive deficits are a major predictor for clinical outcome in schizophrenia; however, current treatments are ineffective in treating these deficits. Pathological changes in NMDAR signaling and a loss of GABAergic parvalbumin interneurons (PVI) in the PFC and hippocampus appear to be crucial to the development of network dysfunction and the emergence of cognitive deficits. The loss of PVI is an important biomarker in post-mortem studies of schizophrenia; however, the mechanisms behind this loss are still unknown. The fast-spiking PVI have high metabolic needs which render them susceptible to periods of oxidative stress. Excessive stress can activate cyclophilin D (CypD), which alters the mitochondrial membrane permeability and results in reduced ATP production, as well as an efflux of reactive oxygen species (ROS) and calcium from the mitochondrial matrix into the cytosol, further increasing oxidative stress and eventually disrupting neuronal development and function. Perinatal blockade of NMDA receptors with ketamine induces a persistent schizophrenia-like phenotype in adult mice, which includes deficits in cognition, as well as positive and negative symptoms. These changes correlate with reduced PVI immunoreactivity and increased levels of mitochondrial-derived ROS in PVI of the PFC. Here, we examined if genetic deletion of CypD (via ablation of the *Ppif* gene) can protect against ketamine-induced loss of PVI and the development of behavioral deficits. CypD knockout (CypD-KO) and wild-type (CypD-WT) mice were treated with ketamine (30mg/kg) on postnatal days (PND) 7, 9, and 11. In adult animals (PND 60-90) we then assessed behavioral alterations in a battery of cognitive and memory tasks. In addition, we used immunohistochemistry to measure changes in PVI expression in the PFC after PND 90. Our data show that CypD-KO animals are protected from PVI loss, as well as deficits in attentional set-shifting, novel-object recognition, and social interaction that result from perinatal

ketamine exposure. Thus, CypD activation and subsequent mitochondrial ROS release may provide a novel mechanism that contributes to the pathological changes in schizophrenia.

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Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 517.18/III63

Topic: H.03. Schizophrenia

Support: Ministério da educação

Title: Behavioral and electrophysiological characterization of a post-weaning isolation model of schizophrenia

Authors: *L. ANDREOLI, E. MORYA
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Abstract: There is still a lot to learn about the physiopathology of mental disorders, among them, schizophrenia, but recent studies suggest an involvement of mesolimbic and mesocortical structures. This work aims to investigate behavioral characteristics and electrophysiological interaction of mesolimbic and mesocortical activity in a post-weaning isolation animal model of schizophrenia. This project used 20 Wistar rats to analyze behavioral differences between healthy controls and post-weaning isolated rats as a model for schizophrenia and 16 rats to study electrophysiology. Animals performed three behavioral tasks: (1) socialization, (2) prepulse inhibition (PPI) and (3) novel object recognition (NOR) while recorded in videos with the Cineplex software (80 Hz, Plexon Inc, USA). In all tasks, the animals assigned to electrophysiology studies went through local field potentials (1 kHz, Plexon Inc, USA) and spike activity recording (40 kHz, Plexon Inc, USA). Animals in electrophysiology group went through stereotaxic neurosurgery for microelectrode arrays implant (32 channels, tungsten wire of 50 um diameter) in five areas: ventral tegmental area (VTA), amygdala (AMG), nucleus accumbens (NACC), hippocampus (HIPC) and pre-frontal cortex (PFC). Our preliminary analysis evaluated if there were behavioral differences between GC and SCZ groups to investigate the electrophysiological mechanisms of such differences through firing rate and power spectral density analysis. SCZ animals interacted socially more time ($U = 12$, $p = 0.050$) and more frequently ($U = 6$, $p = 0.008$) then GC animals. There was no statistical difference in exploration time on new ($t(12.68) = 0.142$, $p = 0.889$) or old ($t(18) = -1.536$, $p = 0.142$) object between SCZ and GC groups and there was no difference on PPI startle response in any type of pulse between SCZ and GC (pulse1: $t(17) = -0.177$, $p = 0.862$, pulse2: $t(17) = 0.540$, $p = 0.596$, pulse3: $t(17) = -$

0.410, p = 0.687, pulse4: t(17) = 0.483, p = 0.635). Our preliminary data showed two units in PRL and NACC of GC animals and seven units in SCZ animals in PRL and VTA correlated to social interaction. Additionally, VTA neurons were related to objects exploration (both new and old) in NOR task and NACC neuron were related to tone presentation in PPI test. These results are important towards an increase in the comprehension of the physiopathology of schizophrenia and, in consequence, to assist in creating new therapies and technologies to assist people affected by the disorder.

Disclosures: L. Andreoli: None. **E. Morya:** None.

Poster

517. Schizophrenia: Animal Models: Developmental

Location: SDCC Halls B-H

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Program #/Poster #: 517.19/III64

Topic: H.03. Schizophrenia

Support: Sumitomo Dainippon

Title: Behavioral and microdialysis studies indicate E/I imbalance contributes to cognitive impairment, psychosis and deficit in social interaction in subchronic phencyclidine-treated mice

Authors: *H. Y. MELTZER[1], L. RAJAGOPAL[2], W. HE[4], M. HUANG[3]
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Abstract: E/I imbalance as a cause of cognitive impairment (CI), psychosis, and negative symptoms in schizophrenia (SCH) is based, in part, on the effects of phencyclidine (PCP), an NMDAR antagonist, in SCH patients and normal subjects. There is conflicting evidence concerning the role of $GABA_A$ receptors (R) and NMDARs in causing these behavioral disturbance and contributing to the efficacy of atypical antipsychotic drugs (APDs). We have now examined drugs affecting GABARs and other aspects of GABA interneuron activity and targets, alone and in combination with the atypical APD, lurasidone (Lur), in WT and scPCP-treated mice (7 days treatment and withdrawal for > seven days) to clarify the contribution of GABA and E/I balance to specific PCP-induced behavioral abnormalities. These include deficits in novel object recognition (NOR), reversal learning (RL), social interaction (SI), PCP- and amphetamine(AMP)-induced locomotor activity (LMA) in scPCP or WT mice. We used microdialysis to measure efflux of DA, NE, ACh, 5-HT, GABA, and glutamate (Glu) in mPFC, ventral HIP, or dorsal STR in awake, freely moving WT and scPCP-treated adult mice. Gabazine (GZ), a $GABA_A$ antagonist, did not rescue NOR, RL or SI. Lur alone, and the $GABA_A$ agonists, gaboxadol, the $alpha_5$-targeting $GABA_A$ agonists, AA29504, , and L655708, restored NOR, RL

and SI. Lur blocked PCP- and AMP-induced LMA in WT- and scPCP-treated mice. GZ enhanced AMP-induced LMA in WT and scPCP mice. GZ blocked PCP-induced LMA in scPCP mice but not in WT mice. GZ also blocked the effect of Lur to decrease PCP-induced LMA in scPCP mice, but had the opposite effect on PCP-induce LMA in scPCP mice in the absence of Lur. The combination of the classical $GABA_A$ antagonist, bicuculline, which we will show also may act like an agonist in the scPCP model, and Lur, enhanced cortical and dorsal hippocampal DA, Glu and especially GABA efflux whereas bicuculline alone or Lur alone had no effect on GABA efflux, in either region. Thus, enhancing GABA efflux was of benefit in rescuing cognitive deficits in the scPCP-treated mice. Cortical and hippocampal GABA efflux were positively correlated in scPCP-treated mice, but negatively correlated in the PFC of the WT mice. DA, GLU, and GABA efflux in PFC were significantly negatively correlated in WT mice, but not in scPCP-treated mice. These results are in accord with other data showing disrupted E/I balance in both mPFC and HIP in scPCP mice. They suggest the scPCP model is useful for studying E/I imbalance in schizophrenia and that Lur and other AAPDs are effective to restore E/I balance. Important differences between the AMP and PCP-models of psychosis are highlighted by these findings.

Disclosures: H.Y. Meltzer: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Allergan, Sunovion, Acadia,. **L. Rajagopal:** None. **W. He:** None. **M. Huang:** None.

Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.01/III65

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

Support: American Heart Association Postdoctoral Fellowship #16POST29680003

Title: Discovery of novel chemo-optogenetic actuators using a zebrafish behavior-based small molecule screen

Authors: *P. LAM[1], L. LEAVITT[2], A. R. THAWANI[3], M. J. FUCHTER[3], B. M. OLIVERA[2], R. T. PETERSON[1]
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Abstract: Optogenetics has proven to be a transformative approach to various fields of basic research, particularly in neuroscience. It allows a non-invasive, localized, and temporally selective optical modulation of selected cells within an animal. Chemo-optogenetic tools,

combining chemicals and optogenetics, have been under rapid development. An important aspect for future advancement in optogenetics/chemo-optogenetics is to identify and/or engineer light-driven proteins with novel properties. We have previously developed and characterized a novel high conductance light-controlled chemo-optogenetic system based of the Trpa1b/ligand pairing. With the goal of discovering novel chemo-optogenetic actuators of vertebrate protein targets, we have further developed and optimized a medium-throughput, semi-automated behavioral screening assay to identify novel photoactivatable ligands for endogenous targets. We conducted a pilot screen using 2000 compounds selected for their molecular photoswitch moieties such as acylhydrazones, azobenezene and stilbenes. From this screen, we identified several hits including two lead compounds that have novel and distinct light-induced biological properties, as determined by constellation pharmacology and gene specific knockout approaches. Discovery of novel optogenetic actuators that possess novel and unique properties will undoubtedly enhance our ability to dissect biological processes such as the complex neuronal network of the brain.

Disclosures: P. Lam: None. **L. Leavitt:** None. **A.R. Thawani:** None. **M.J. Fuchter:** None. **B.M. Olivera:** None. **R.T. Peterson:** None.

Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.02/III66

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

Support: T32 training grant

Title: Ablating inhibitory synapses with novel optogenetic tool

Authors: *A. BAREGHAMYAN[1], G. G. GROSS[2], W. ZHANG[3], R. E. CAMPBELL[3], D. B. ARNOLD[1]
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Abstract: We have generated a novel, recombinant, photo-activatable protein complex, with extremely low background activity in the dark. This system is based on the photocleavable protein PhoCl, whose amino acid backbone is cleaved following absorption of 400 nm light, causing a 13-mer peptide to be released from its C-terminus. Using mRNA display we have generated a 10 amino acid peptide (PhoCl binding peptide, Pbp) that binds with high affinity and specificity to the pocket that is created by release of the native C-terminus of PhoCl. Because there is virtually no cleavage of PhoCl in the dark, and because Pbp does not bind to uncleaved PhoCl there is negligible interaction between PhoCl and Pbp in the absence of light. To demonstrate the efficacy of this system we have targeted PhoCl to different subcellular locations such as to the Golgi, and shown that we can inducibly target protein fused to PBP to those

locations with light.
Furthermore, we have shown that using this system we can ablate inhibitory synapses in a light-dependent manner using a split version of the protein GFE3, which uses an E3 ligase targeted to inhibitory synapses to degrade Gephyrin. In the dark, ablation of Gephyrin by the PhoCL/GFE3 complex is undetectable, even when it has been expressed for over one week. This low level of background activity is remarkable given that existing photodimerization systems, when combined with split GFE3, caused almost complete elimination of inhibitory synapses in the dark. Because of its low background activation, even over long periods of time, we believe that this system will be practical for applications requiring photo-activation in vivo.

Disclosures: A. Bareghamyan: None. **G.G. Gross:** None. **W. Zhang:** None. **R.E. Campbell:** None. **D.B. Arnold:** None.

Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.03/III67

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

Support: DARPA W911NF-17-2-0036
Heritage Medical Research Institute
Jacobs Institute for Molecular Engineering for Medicine

Title: Acoustically targeted chemogenetics for noninvasive control of neural circuits

Authors: *J. O. SZABLOWSKI, A. LEE-GOSSELIN, B. LUE, D. MALOUNDA, M. SHAPIRO
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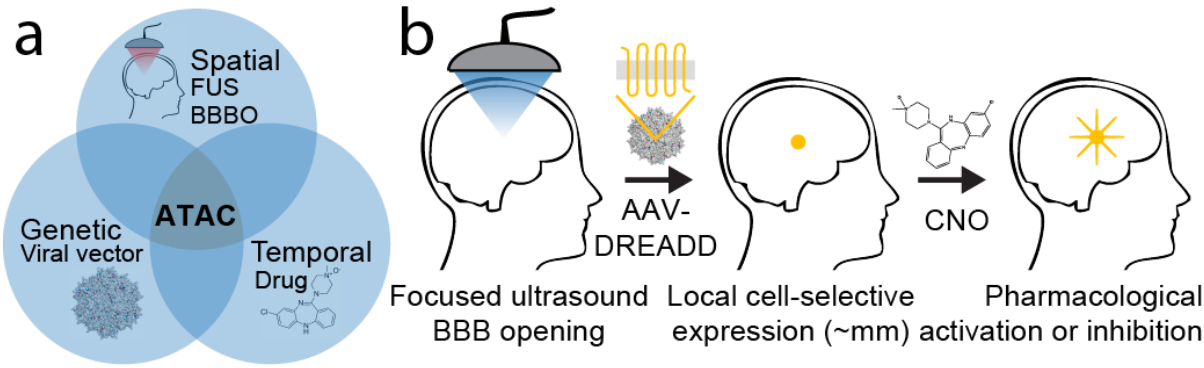
Abstract: Neuropsychiatric diseases often involve the dysfunction of specific neural circuits. Ideal treatment would involve noninvasive control of the right brain regions and cell-types at the right time. Existing treatments, including drugs and brain stimulators, modulate the activity of neural circuits, but are either not cell type-specific, lack spatial targeting, or require invasive procedures. Here, we introduce an approach to modulating neural circuits noninvasively with spatial, cell-type, and temporal specificity. This approach, called acoustically targeted chemogenetics, or ATAC, uses transient ultrasonic opening of the blood brain barrier (FUS-BBBO) to transduce neurons at specific locations in the brain with virally-encoded chemogenetic receptors. We used ATAC to noninvasively transduce and subsequently control hippocampus (HPC) and SNc/VTA in mice. For testing the activation, we expressed activatory DREADD (hM3Dq) in the HPC of mice and measured the accumulation of c-Fos. Neurons expressing activatory DREADD were 5.8-fold more likely to also show c-Fos accumulation ($p<1E-3$). To

show neuronal inhibition we evaluated ATAC mice with expression of inhibitory DREADD (hM4Di) throughout the HPC by a context fear conditioning protocol. Mice treated with saline had 2.4-fold higher context fear than those treated with CNO ($p<2E-5$), revealing that noninvasive inactivation of hippocampus prevents memory acquisition. All mice showed normal exploratory behavior the next day and responded to the sound cues equivalently ($p=0.22$), indicating lack of effects on response to painful shocks. The CNO injection alone had no significant effect on the context fear in mice with no FUS-BBBO or WT mice ($p=0.38$). To achieve sub-millimeter targeting precision we combined FUS-BBBO delivery with methods of intersectional genetics. We noninvasively transduced unilateral SNc/VTA region in mice with activatory DREADD (hM3Dq) to induce c-Fos activity with CNO ($p<1.1E-3$). With ATAC selected cells in brain regions of large animals could be placed under chronic pharmacological control.



Disclosures: J.O. Szablowski: None. **A. Lee-Gosselin:** None. **B. Lue:** None. **D. Malounda:** None. **M. Shapiro:** None.

Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.04/III68

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

Title: DART: A new way to revitalize behavioral neuropharmacology

Authors: *M. R. TADROSS[1], B. C. SHIELDS[1], E. W. KAHUNO[1], G. SCHILTZ[2], P. VAGADIA[2], J. IZQUIERDO-FERRER[2], A. REITZ[3], M. LOUGHRAN[3]
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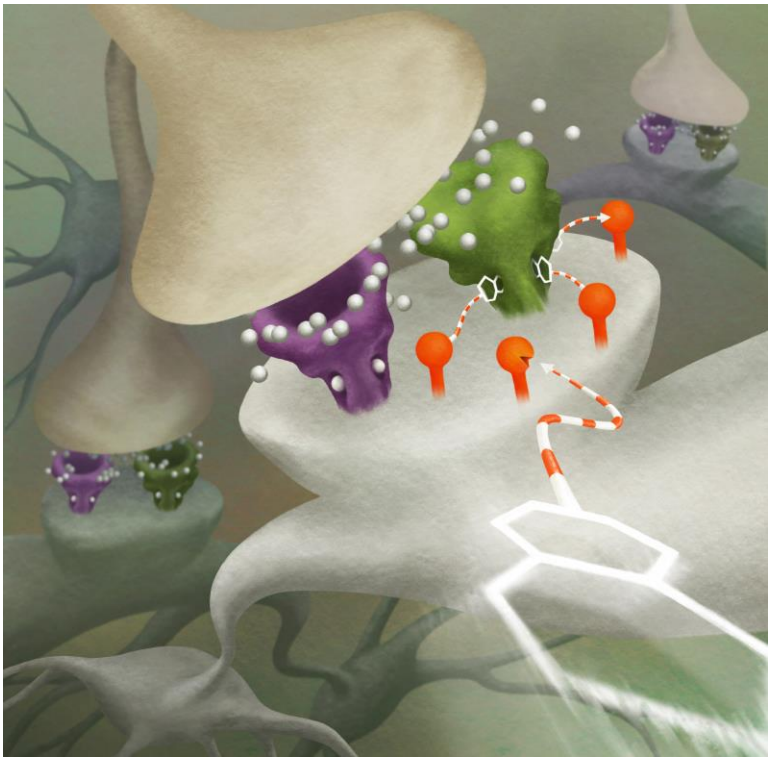
Abstract: The neuropharmaceutical revolution of the 1950's provided hope to millions that would have otherwise suffered in isolation. Since then, progress has largely stalled. A major

impediment to rational neuropharmaceutical advances can be attributed to a poor understanding of how drugs exert their effects at the circuit level; in particular, how behavioral effects of drugs are mediated by individual cell types in the brain. To address this gap, we developed DART (drugs acutely restricted by tethering), a system in which drugs home to a defined cell type. The method is simple, robust in behaving animals, and *unique* because it functions without mutation or overexpression of the targeted native receptor. *DART is the only method to date that can cell type-specifically map behavioral effects of clinical drugs.* Here, we will provide a progress report, highlighting recent technology advances, summarizing immediate future goals, and engaging with the neuroscience community to forge collaborations and shape future priorities.



Disclosures: M.R. Tadross: None. **B.C. Shields:** None. **E.W. Kahuno:** None. **G. Schiltz:** None. **P. Vagadia:** None. **J. Izquierdo-Ferrer:** None. **A. Reitz:** None. **M. Loughran:** None.

Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.05/JJJ1

Topic: F.04. Stress and the Brain

Support: R01 MH046729

P51-OD011132
ZIA000069

Title: Characterizing the expression and function of designer receptors exclusively activated by designer drugs (DREADDs) in the non-human primate

Authors: *S. MUELLER[1], J. A. OLER[1], P. H. ROSEBOOM[1], M. RIEDEL[1], E. FEKETE[1], J. L. GOMEZ[2], J. BONAVENTURA[2], M. MICHAELIDES[2], J.-F. PARE[3], A. GALVAN[3], R. KOVNER[1], M. KENWOOD[1], N. H. KALIN[1]
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Abstract: Anxiety disorders are the most prevalent form of psychiatric illness and constitute an ongoing major public health concern. Nonhuman primates (NHPs) are an ideal translational model for studying the underlying biological mechanisms of anxiety, as well as for developing treatment strategies for future clinical use. DREADDs (designer receptors exclusively activated by designer drugs) technology has the unique potential for pharmacologically manipulating neuronal activity in freely-moving animals for extended periods of time via systemic administration of selective DREADD-activating compounds. In pursuit of developing DREADDs as a tool in the NHP, we sought to validate the expression and functionality of DREADDs in the amygdala, a critical brain region with a central role in anxiety-related behaviors. Here we present data from 3 case studies where we performed viral vector delivery using intraoperative MRI. In subject 1 (*Macaca fascicularis*), which received dorsal amygdala injections of rAAV5-hSyn-hM4Di-mCherry, neuronal expression of DREADDs was quantified across 4.8 mm in the A/P plane surrounding the injection site. Average expression rates within a 2.5 x 2.5 mm region sampled ranged between 17-46%, with subregions near the center of the injection reaching as high as 100%. In two other subjects (*Macaca mulatta*), we injected rAAV5-hSyn-hM4Di-HA into the center of the amygdala (unilaterally in subject 2, and bilaterally in subject 3), and DREADDs expression was assessed 4 weeks later with *in vivo* [^{11}C]clozapine PET imaging. In subject 2, results demonstrated comparatively greater [^{11}C]clozapine binding in the injected amygdala as compared to the non-injected amygdala. In subject 3, bilateral amygdala binding was comparatively greater than pre-surgery baseline levels. Using *in vitro* autoradiography on tissue from subject 2, [^{3}H]clozapine binding was detected in the injected amygdala, with very little binding observed in the non-injected hemisphere. GTPγS exchange in the presence of clozapine also showed greater radio signal relative to baseline in the injected amygdala, suggesting that the expressed DREADDs receptors can functionally couple to the G-protein. In subject 3, electron microscopy using immunogold staining demonstrated that HA-tagged DREADDs localized almost exclusively to the cell membrane, suggesting cell surface expression. Together, these results provide evidence validating the expression and function of DREADDs in NHPs, setting the stage for more detailed behavioral experiments using DREADDs technology, as well as the systematic investigation of hypotheses related to the neural circuits that underlie primate anxiety.

Disclosures: S. Mueller: None. **J.A. Oler:** None. **P.H. Roseboom:** None. **M. Riedel:** None. **E. Fekete:** None. **J.L. Gomez:** None. **J. Bonaventura:** None. **M. Michaelides:** None. **J. Pare:** None. **A. Galvan:** None. **R. Kovner:** None. **M. Kenwood:** None. **N.H. Kalin:** None.

Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.06/JJJ2

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

Support: JSPS KAKENHI JP 17K11222

Title: Generation of glycine receptor alpha 4 knockout mice using high-efficient modified CRISPR-Cas9 protocol

Authors: *M. I. DARWISH[1], K. UNO[1], K. TAKAO[2], H. NISHIZONO[2]
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Abstract: Human glycine receptor α4 (GLRA4) was thought to be a pseudogene due to lack of transmembrane domain, but surprisingly it was recently reported that microdeletion at Xq22.2 including GLRA4 shows symptoms similar to Pelizaeus-Merzbacher disease (PMD). PMD is a hereditary disease that develops due to abnormalities in myelination in the central nervous system and the patient dies in infancy in most cases. To understand the biological role of glycine receptor α4 (Glra4) in cognitive brain functions and whether it is involved in X-linked syndromic intellectual disability, we disrupted Glra4 gene using a developed CRISPR/cas9 protocol for genome editing. Our optimized protocol shows many advantages compared to currently used genome editing protocols. First, we are using C57BL/6J frozen embryos instead of F1 hybrid embryos which will enable the researchers to shorten the time required for preparation of mice by around 2 years (backcrossing is not needed). Second, the genetic recombination rate is as high as 100%, and the mosaic mutation rate is low. Third, it is the first protocol showing that cryopreserved embryos are effective for the production of genetically modified mice. Using our protocol, we generated several lines of knockout and knock-in mice with high reproducibility. Glra4 Systemic knockout mice were generated by designing gRNA targeting exon 4 and introducing it into 1-cell stage embryos of C57BL/6J mice by electroporation. As a result, three lines of mice, namely, 11 bases deletion, five bases deletion, and one base insertion were produced due to the difference in the cleavage site by Cas9 protein. The sequences of F0 mouse and F1 mouse genome were analyzed and we found short truncated protein was expressed in all strains. It had an extracellular neurotransmitter-gated ion channel domain and a glycine binding site, but it lacked transmembrane and intracellular domains. Furthermore, the homozygous deletions of 11 bases and five bases were embryonic lethal. This is an unexpected result, as Glra4 is considered as a pseudogene in humans. Currently, behavioral analysis experiments of Glra4

knockout mice are being conducted. These results show that we developed an improved protocol, by using CRISPR/Cas9 system, which generated rapid, high efficient and non-mosaic mutant mice using cryo-embryo of inbred mice.

Disclosures: M.I. Darwish: None. **K. Uno:** None. **K. Takao:** None. **H. Nishizono:** None.

Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.07/JJJ3

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

Support: NIH PO1 MH64570
NIH RO1 MH104147
NIH T32 AI049815
NIH F31 MH113504

Title: Multiplex CRISPR/Cas9-based gene activation in cultured microglia

Authors: *P. MILLER-RHODES[1], H. A. GELBARD[2]
[2]Ctr. for Neurotherapeutics Discovery, [1]Univ. of Rochester Med. Ctr., Rochester, NY

Abstract: Next-generation sequencing technologies have vastly expanded our knowledge of factors that regulate the development and homeostasis of microglia. However, the generation of floxed mouse strains capable of achieving cell-specific gene knockout remains a significant bottle-neck in the investigation of such factors *in vivo*. Moreover, current *in vitro* approaches for studying gene function in cultured hematopoietic cells are limited by difficulties associated with expressing full-length cDNAs and/or generating knockout or knockdown cell lines. To circumvent these limitations, we developed a straightforward *in vitro* approach for studying gene function in cultured microglia that relies on recent advances in CRISPR/Cas9 technology. We stably expressed the CRISPR/Cas9 synergistic activation mediator (SAM) complex in the BV2 microglial cell line. When combined with a single guide RNA that targets a desired genomic promoter element, the Cas9-SAM complex activates gene transcription by recruiting endogenous transcriptional machinery to the targeted locus. To establish the utility of this reagent, we used this system to overexpress the transcription factor Mafb from the endogenous locus. Expression of Mafb-targeting sgRNAs resulted in an upregulation of Mafb mRNA and protein. Upregulation of Mafb via this method also resulted in increased expression of the putative Mafb target genes. We also describe a method for multiplex gene activation in BV2-SAM cells whereby tRNA-flanked sgRNAs are expressed in a single polycistronic transcript that is processed by tRNA processing enzymes upon expression in the target cell. Altogether, the reagents described here

can be used broadly to study the function of newly identified microglia-specific genes in the microglia-like BV2 cell line.

Disclosures: P. Miller-Rhodes: None. **H.A. Gelbard:** None.

Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.08/JJJ4

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

Support: National Science Center, Poland 2016/22/M/NZ2/00548

Title: Modeling Huntington's disease (HD) by Cas9-based HTT gene editing in isogenic patient-specific induced pluripotent stem cells (hiPSCs)

Authors: *P. LISOWSKI[1], B. MLODY[2], S. SINGH[2], H. TOBIAS[2], J. PRILLER[3], E. WANKER[2], R. KUEHN[2], A. PRIGIONE[2]
[1]iPS Cell Based Dis. Modeling Group, [2]Max-Delbrück-Center for Mol. Med. (MDC), Berlin, Germany; [3]Dept. of Neuropsychiatry, Charité-Universitätsmedizin, Berlin, Germany

Abstract: Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder characterized by a progressive loss of GABAergic medium spiny neurons (MSNs) in the striatum. The disease is caused by a mutation in the CAG repeat tract of the huntingtin gene HTT, which leads to an expanded polyglutamine stretch (polyQ) in the huntingtin protein HTT. The presence of 40 CAG repeats or more give rise to the disease, with longer repeats associated with more aggressive forms. In order to clearly dissect the impact of the disease-causing HTT mutation, we have taken an advantage of Cas9-based genome editing technology that allowed for generation of isogenic lines within the same nuclear background of the patients by manipulation of DNA repair pathways based on inhibition of the key NHEJ regulators and upregulation of the HDR proteins. As a results we generated (1) precisely corrected iPSC clones carrying a healthy length of CAG repeats by homologous recombination (HR) and (2) NHEJ mediated excision of the Q/P repeat region by reannealing of the DSB resulted into an in-frame HTT coding region lacking the N-terminal Q/P repeat and (3) to fast forward disease phenotype we generated iPSC isogenic clones with introduced 70 CAG repeats. Edited iPSC clones were differentiated into neurons of interest and subjected for the high-content screening (HCA).

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Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.09/JJJ5

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

Title: CRISPR/Cas9 engineered IDH1^{R132H}isogenic luciferase expressing cell models for *in vitro* and *in vivo* glioma studies

Authors: *F. TIAN[1], D. DIANA[3], J. FOULK[2], L. CHEN[2], M. ENUAMEH[3], S. JACOB[3], W. SHU[3]
[1]ATCC, Gaithersburg, MD; [2]ATCC, Manassas, VA; [3]ATCC Cell Systems, Gaithersburg, MD

Abstract: Isocitrate dehydrogenase (IDH) is a metabolic enzyme that converts isocitrate to a-ketoglutarate, which is involved in the control of oxidative cellular damage. The mutation affecting IDH1 amino acid 132 has been linked to grade II and III astrocytomas and oligodendrogliomas, and glioblastomas. IDH1 mutations result in the production of 2-hydroxyglutarate (2-HG), which acts as a-KG antagonist to competitively inhibit multiple a-KG-dependent dioxygenases, causing widespread changes in histone and DNA methylation and potentially promoting tumorigenesis. Although mutant IDH has been identified as a valid target for a new class of brain tumor therapeutics, there is a lack of well-established and characterized cell models containing IDH mutants. In this study, we sought to use the CRISPR/Cas9 gene editing technology to create an *in vitro* isogenic model harboring the IDH1^{R132H} mutation. To develop the most clinically relevant disease model we selected a commonly used glioblastoma cell line, U-87 MG, as the parental line to introduce the IDH1^{R132H} mutation. The precise point mutation knock in was confirmed via sequencing at the genomic and transcriptional levels. We tested the intracellular and extracellular levels of 2-HG to validate that the isogenic IDH1^{R132H} mutation confers gain-of-function to the mutant enzyme that is produced. Data indicated that IDH1^{R132H} U-87 MG isogenic cells exhibit a significant increase in cellular 2-HG levels and an elevated level of histone methylation compared to the parental cell line. Based on the *in vitro* model described above, we developed additional models for use in live-animal bioluminescence brain tumor imaging by introducing a stable luciferase reporter into the U-87 MG and the IDH1^{R132H} U-87 MG isogenic cell lines. Both relative and absolute bioluminescence signals within the cells were quantified. Data show that the U-87 MG-Luc2 cells emit $1.04x10^6$ photons/cell/sec and the IDH1^{R132H} U-87 MG-Luc2 cells emit $1.0x10^6$ photons/cell/sec. Moreover, the cells were injected into nude mice to establish tumors for *in vivo* live bioluminescence imaging. A subcutaneous flank tumor xenograft model and an intracranial glioblastoma orthotopic model were utilized in a study, and the *in vivo* live bioluminescence signal was quantified by Xenogen IVIS imaging system. Taken together, the U-87 MG luciferase-expressing cell line and the IDH1^{R132H} U-87 MG isogenic luciferase expressing cell

line are valuable tools for elucidating mechanisms involved in IDH-associated tumorigenesis, studying brain tumors in vivo, and screening anti-cancer compounds for drug discovery and development.

Disclosures: F. Tian: None. **D. Diana:** None. **J. Foulk:** None. **L. Chen:** None. **M. Enuameh:** None. **S. Jacob:** None. **W. Shu:** None.

Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.10/JJJ6

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

Title: Targeted insertion of polyA tracks with CRISPR-Cas9 allows titratable control of gene expression

Authors: *K. M. GAMBER[1], R. DELSTON[1], Y.-H. CHEN[2], X. CUI[2], L. A. ARTHUR[3], L. RYZHOVA[4], A. HARRINGTON[4], E. WEINSTEIN[1], S. DJURANOVIC[3], L. LIAW[4]
[1]Canopy Biosci., Saint Louis, MO; [2]Genome Engin. & iPSC Ctr., [3]Dept. of Cell Biol. and Physiol., Washington Univ. in St. Louis, Saint Louis, MO; [4]Ctr. for Mol. Med., Maine Med. Ctr. Res. Inst., Scarborough, ME

Abstract: Embryonic lethality following global knockout is a major obstacle in the study of essential genes. Embryonic lethality may be overcome with heterozygous knockout, however haploinsufficiency and related phenotypes may not necessarily result. The most common solution tends to be tissue-specific knockout via the cre-lox system, however this method is dependent upon the availability of tissue-specific promoters as well as cre-driver mice. Additionally, only gene function in the targeted tissue may be studied.
The observation that insertion of polyA tracks into the coding region of target genes results in predictable reduction of gene expression presents an opportunity to study hypomorphic mutations in essential genes. Furthermore, length of polyA tracks is inversely correlated with gene expression, allowing for the generation of multiple animal models with defined levels of gene knockdown. Animal models with defined, diverse, heritable levels of gene knockdown represent novel tools to study essential genes, model small molecule inhibition of a target, examine diverse expression of a biomarker representative of human patient populations, among many other potential applications.
Here we will give an overview of the polyA track system, demonstrate its function in in vitro systems and conservation amongst diverse model systems. We will demonstrate its use with CRISPR-Cas9 to target endogenous genes, and lastly will present our progress in the generation of mouse models.

Disclosures: K.M. Gamber: A. Employment/Salary (full or part-time):; Canopy Biosciences. **R. Delston:** A. Employment/Salary (full or part-time):; Canopy Biosciences. **Y. Chen:** None. **X. Cui:** None. **L.A. Arthur:** None. **L. Ryzhova:** None. **A. Harrington:** None. **E. Weinstein:** A. Employment/Salary (full or part-time):; Canopy Biosciences. **S. Djuranovic:** None. **L. Liaw:** None.

Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.11/JJJ7

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

Support: Stowers Institute for Medical Research

Title: Adenoviral vector mediated genetic interrogation and visualization of the olfactory sensory neurons

Authors: *Y. WU[1], R. YU[1,2]
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Abstract: The olfactory sensory neurons provide a good model of axon guidance study for their specific projection pattern and regenerative capacity. Classical method to study the system involves genomic targeting of the genes of interest in embryonic stem cells and fluorescent protein labeled olfactory receptor reporter mouse. An alternative approach using viral vectors is widely adapted in the central nervous system. However, the widely used adeno-associated viruses are limited by its loading capacity and by their transduction efficiency, especially for the olfactory sensory neurons. There is also a lack of standardized method to quantify the efficiency of the genetic manipulation *in vivo* using virus-based approaches. Here we present a set of adenovirus-based molecular toolkits to knockout, overexpress genes, or to visualize axon projection at single cell resolution. We validated the approaches in the mouse olfactory system. These tools potentially can be used for other cell types, providing utility to the broader neuroscience community.

Disclosures: Y. Wu: None. **R. Yu:** None.

Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.12/JJJ8

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

Support: U01MH109133

Title: Transposon-mediated cell type-specific enhancer profiling in the mouse brain

Authors: *A. CAMMACK[1], T. LAGUNAS[2], M. VASEK[2], A. MOUGDIL[2], M. WILKINSON[2], J. HE[2], M. SHABSOVICH[1], X. CHEN[2], M. HOODA[1], T. MILLER[1], J. DOUGHERTY[2], R. MITRA[2]
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Abstract: Enhancers are abundant and central controllers of gene transcription throughout the brain. Consequently, profiling these cis-regulatory elements across the genome has been instrumental in understanding gene regulatory networks. To date, this work has largely been accomplished through chromatin immunoprecipitation followed by high-throughput sequencing (ChIP-Seq) of histone modifications associated with active enhancers such as H3K27ac and H2K4me1. Enhancers display extensive tissue and cell type diversity, highlighting their importance in defining and maintaining cellular identity. While histone ChIP-Seq has been crucial in uncovering the importance of non-coding cis-regulators in the brain, it has been challenging to adapt this method for cell type-specific use *in vivo*. Here we present a novel methodology for mapping enhancer profiles in the mouse brain in a cell type-specific manner. By introducing the hyperPiggyBAC transposase (hypPB) and donor transposons via AAV9 directly to the postnatal day 1 (P1) mouse brain, we are able to achieve widespread transduction across the brain. HypPB, likely through interactions with enhancer-associated bromodomain proteins such as Brd4, inserts donor transposons near active enhancer sites throughout the genome, which are later read out with high-throughput sequencing. We show that hypPB insertion profiles are highly reproducible between mice and display a high concordance with the active enhancer mark H3K27ac. Finally, using a cre-dependent hypPB virus, we show utility of this tool in defining cell type-specific enhancer profiles in the brain without physical separation of cellular pools. This approach will enable important investigations into the non-coding regulatory networks of the brain and will provide valuable insights into brain development, homeostasis, and disease.

Disclosures: A. Cammack: None. **T. Lagunas:** None. **M. Vasek:** None. **A. Mougdil:** None. **M. Wilkinson:** None. **J. He:** None. **M. Shabsovich:** None. **X. Chen:** None. **M. Hooda:** None. **T. Miller:** None. **J. Dougherty:** None. **R. Mitra:** None.

Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.13/JJJ9

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

Support: Max Planck Florida Institute, Kwon Lab

Title: Temporally precise labeling of oxytocin sensitive neuronal populations

Authors: *N. L. MIGNOCCHI[1], H.-B. KWON[2]
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Abstract: Oxytocin (OXT) is a neuropeptide originating in the paraventricular nucleus (PVN) of the hypothalamus, with a role in influencing brain areas designed to process social stimuli, such as midbrain dopaminergic (DA) neurons in the ventral tegmental area (VTA). However, techniques to measure the extent and specificity of oxytocin modulation on a cellular level remain unavailable. *i*Tango2 is an optogenetic gene reporter technique designed to detect ligand-receptor interactions and is used to study specific neuromodulatory signals in a temporally precise manner. The present research study aimed to develop the OXT-sensitive iTango2 technique (OXT-iTango2) to distinctively measure the quantitative OXT modulation onto neuronal populations. Results demonstrated that this OXT-iTango2 was capable of allowing gene expression in a ligand- and light-dependent manner both *in vitro* cultured cells and *in vivo*. Thus, OXT-iTango2 will allow us to dissect neural circuits activated by OXT at high temporal resolution in behaving animals.

Disclosures: N.L. Mignocchi: None. **H. Kwon:** A. Employment/Salary (full or part-time):; Max Planck FL Institute.

Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.14/JJJ10

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

Support: VA-CDA Grant IK2RX002013

Title: Studying cortical circuitry using a retrograde trans-synaptic tracing system driven by a cortical layer-specific promoter

Authors: *J. LIM[1], D. JGAMADZE[1], J. A. WOLF[1,3], T. DUONG[2], J. MILLS[2], H. I. CHEN[1,3]
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Abstract: Introduction: Trans-synaptic neuronal tracing has become an essential tool for investigating brain circuitry and function. Glycoprotein-negative rabies virus (RABVdG) systems have been developed for monosynaptic retrograde tracing, and can be combined with genetic techniques to interrogate specific neural circuits. Much remains to be learned about how cortical circuits develop and how different areas of cortex communicate with each other. Layer V receives afferents from upper-layer cortex but is also involved in the propagation of horizontal activity. Here, we present a novel RABVdG system driven by the CTIP2 promoter that is capable of examining layer V-specific afferent connectivity. Methods: We constructed a plasmid expressing the CTIP2 promoter sequence followed by a fluorescent marker (mRuby). This construct was transfected into dissociated rat embryonic day 18 cortical neurons, and promoter specificity was evaluated with immunocytochemical and flow cytometry techniques using CTIP2 antibodies. In parallel, a polycistronic plasmid expressing a fluorescent marker (dsRed), the Rabies virus glycoprotein (G), and an avian leukosis virus receptor (TVA) under the CAG promoter was transfected into rat embryonic cortical neurons *in vitro* and then infected with RABVdG-GFP to confirm the viability of this tracing system. Subsequent steps involve replacing the CAG promoter in the polycistronic plasmid with the CTIP2 promoter and generating lentiviral vectors from this plasmid. Layer V-specific tracing can be validated in dissociated rat embryonic cortical neurons. **Results:** In rat cortical neurons transfected with CTIP2-mRuby, we found that nearly 70% of the mRuby+ cells were CTIP2+ by antibody staining. Rat cortical neurons transfected with CAG-dsRed-G-TVA were identified by fluorescence microscopy, and a network of GFP+ upstream monosynaptic partners were found surrounding these “starter cells” after RABVdG-GFP infection. Transduction of rat cortical neurons with lenti-CTIP2-dsRed-G-TVA should result in the generation of starter cells that are primarily CTIP2+, which would allow interrogation of the cortical-layer phenotype of neurons sending afferent inputs to layer V cells.Conclusion: Our results demonstrate the feasibility of using cortical layer-specific promoters to drive trans-synaptic tracing. This novel technology could be utilized to examine cortical connectivity both *in vitro* and *in vivo.* In particular, these tools could help map the evolution of cortical circuitry during fetal development and in cerebral organoids and elucidate the mechanisms by which transplanted neurons integrate with the host brain.

Disclosures: J. Lim: None. **D. Jgamadze:** None. **J.A. Wolf:** None. **T. Duong:** None. **J. Mills:** None. **H.I. Chen:** None.

Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

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Program #/Poster #: 518.15/JJJ11

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

Support: 1U19MH114830-01
R01DA036909

Title: Expanding the mouse genetic toolkit: New transgenic and viral strategies for cell-type specific investigations

Authors: E. SZELENYI[1], T. L. DAIGLE[2], L. SIVERTS[2], M. WALKER[2], G. LENZ[2], L. T. GRAYBUCK[3], R. LARSEN[2], L. MADISEN[2], S. YAO[2], A. H. CETIN[2], H. ZENG[4], B. TASIC[5]
[1]Transgenic Technol., [3]Mol. Genet., [4]Structured Sci., [5]Cell and Circuit Genet., [2]Allen Inst. for Brain Sci., Seattle, WA

Abstract: Ultimate understanding of brain function relies on the precise identification of its working parts and interrogation of the parts' functions. Towards this end, great leaps have recently been made in defining, through transcriptomic and epigenetic approaches, the rich diversity of neurons that encompass the nervous system. Taking advantage of this information and in combination with our established transgenic technology approaches, we report here the latest advancements in our mouse genetic tool repertoire designed for precise cell-type based studies. Overall, these new tools are more versatile, enable functional experiments, and offer simplified breeding schemes for fast research goal completion. Specifically, we will describe our most recent additions made to the previously engineered TIGRE locus. Our new Cre-dependent TIGRE2.0 reporters express viral-like levels of a variety of molecular tools, such as synaptic or nuclear targeted fluorescent proteins, an electron microscopy tag, genetically encoded calcium indicators (GECIs), genetically encoded voltage indicators (GEVIs), and new channelrhodopsin variants. In addition, we will describe the development of a new TIGRE2.0-based transgenic platform, which utilizes four different recombinases and has enabled the generation of Cre- and Flp-dependent reporter lines. Lastly, we will present data from a new and complementary viral-based approach to achieve cell-type specificity in our reporters, which utilizes enhancer elements identified via single cell ATACseq to drive expression of transgenes in restricted cortical layers. This approach circumvents transgenesis, and may enable reliable genetic access to diverse cell types in a minimally invasive manner due to the use of retro-orbitally delivered virus. Characterization for several reporter lines, viruses, and the latest additions to our Cre- and Flp-driver line suite of transgenics will be presented, and the challenges of their development and current work will be shared. In summary, our latest toolset will greatly benefit researchers by allowing for better labeling, monitoring and manipulation of broad and unique cell types, and by

extension neural circuits. This foundational work will therefore greatly accelerate the speed of attaining detailed mechanistic insight on brain function.

Disclosures: E. Szelenyi: None. **T.L. Daigle:** None. **L. Siverts:** None. **M. Walker:** None. **G. Lenz:** None. **L.T. Graybuck:** None. **R. Larsen:** None. **L. Madisen:** None. **S. Yao:** None. **A.H. Cetin:** None. **H. Zeng:** None. **B. Tasic:** None.

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518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.16/JJJ12

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

Title: Characterization and application of a genetically modified rat toolbox for neuron-specific activity modulation

Authors: *Z. LIU, G. ZHAO, A. BROWN, K. FORBES
Horizon Discovery, Saint Louis, MO

Abstract: Rats were once the most popular models for neuroscience research thanks to its higher intelligence and richer behaviors when compared to mice. The recent rapid progress of the CRISPR/Cas9-based gene editing technologies has made the creation of genetically modified rats relatively straightforward and paved the way for its return. We therefore initiated the efforts to create an optogenetic toolbox, consisting of about a dozen of knock-in rats including various neuron-type-specific Cre driver lines (such as CamKII-cre, VGAT-Cre and Parvalbumin-cre), Cre-activity-dependent excitatory and inhibitory opsin expression lines as well as a fluorescent protein-based Cre-activity reporter line a few years ago. Here we are going to update our continued efforts in characterizing this toolbox and showcase how it might be applied for basic research and drug development.

Disclosures: Z. Liu: A. Employment/Salary (full or part-time):; Horizon Discovery. **G. Zhao:** A. Employment/Salary (full or part-time):; Horizon Discovery. **A. Brown:** A. Employment/Salary (full or part-time):; Horizon Discovery. **K. Forbes:** A. Employment/Salary (full or part-time):; Horizon Discovery.

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518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.17/JJJ13

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

Title: Optimization of a GCaMP expression system for functional calcium imagining in the marmoset brain

Authors: *M. UEMURA, T. MATSUI, T. HASHIMOTO, T. MURAKAMI, K. KIKUTA, T. KATO, K. OHKI
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Abstract: Calcium imaging using genetically encoded calcium indicator (GECI) is a powerful technique to elucidate the brain function. The licencephalic brain of the common marmoset, *Callithrix jacchus*, provides a unique opportunity to apply modern optical approaches, such as calcium imaging, to the primate visual system. Although a pioneering system of adeno-associated virus (AAV) mediated GCaMP expression using Tet-off system was established in the marmoset brain (Sadakane et al., 2015), Thy1s-tetracycline transactivator (tTA) driven GCaMP6 expression level was still unsatisfactory and its expression was limited in a small subset of neurons expressing Thy1s. Moreover, in the previous calcium imaging studies using primates, neuronal expression of GCaMP was limited in a small region of cortex (typically 1 mm by 1 mm region). The licencephalic brain of the marmoset should allow imaging in a much larger field-of-view if GCaMP expression in such a large area is possible. In order to improve the calcium response in larger population of cells, fine optimization of GCaMP expression system was required. First we designed new AAV vectors which contain the tetracycline response element (TRE) promoter driving both GCaMP6 and tTA (TLoop system, Cetin and Callaway, 2014) or two in-tandem of GCaMP6. To further improve the expression, we inserted the chimeric intron, and replaced the woodchuck hepatitis post-transcriptional regulatory element (WPRE) with shortened WPRE, and human growth hormone polyadenylation (poly(A)) with the tandem arrangement of SV40 late poly(A) signal element. As expected, transduction of those new vectors and conventional Thy1s-tTA with AAV increased the GCaMP6 expression level in much larger population of cells in both mouse and marmoset brains. With our improved vectors, we were able to record reliable visual responses in the primary and other visual areas of the marmoset brain both with two-photon and wide-field calcium imaging. Furthermore, as a Tet driver, we constructed a single or tandem tTA transgene under the neuron specific and ubiquitous promoters instead of Thy1s, resulting GCaMP expression in a broader population of neurons and neurons with glial cells, respectively. Finally, we optimized the protocol for the virus injection and the window implantation to allow imaging in a large field-of-view containing multiple cortical areas. Taken together, our new GCaMP expression tools provide a unique

opportunity to apply calcium imaging to understand the information processing in the marmoset brain.

Disclosures: M. Uemura: None. **T. Matsui:** None. **T. Hashimoto:** None. **T. Murakami:** None. **K. Kikuta:** None. **T. Kato:** None. **K. Ohki:** None.

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518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.18/JJJ14

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

Support: 1RF1MH114106-01

Title: A light-inducible recombinase system for spatiotemporally controlled genomic modifications

Authors: *S. YAO[1], B. OUELLETTE[1], T. ZHOU[1], M. MORTRUD[1], S. CHATTERJEE[1], X. KUANG[2], T. L. DAIGLE[1], B. TASIC[1], Y. WANG[1], H. GONG[3], Q. LUO[3], S. ZENG[3], H. ZENG[1], A. H. CETIN[1]
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Abstract: The nervous systems are composed of diverse cell types that present distinct molecular, morphological and physiological features. To enable spatiotemporally controlled activation of individual neurons, we have developed a light-inducible recombinase system, in which the site-specific recombinases become active only upon light induction. We have verified in cultured cells that the expression of recombinase-dependent reporters can be effectively triggered by light induction, whereas reporter expression remains undetectable in the absence of light. In vivo expression of the light-inducible recombinases in the mouse brain can be successfully achieved using adeno-associated viral vectors. We demonstrated in live mouse brains that spatiotemporally controlled induction of light-inducible recombinases by one-photo or two-photo illumination can efficiently produce precise and strong labeling of individual neurons. Our toolbox of light-inducible recombinases will facilitate the functional and anatomical dissection of different cell types by enabling specific and efficient genomic modification at the single cell level.

Disclosures: S. Yao: None. **B. Ouellette:** None. **T. Zhou:** None. **M. Mortrud:** None. **S. Chatterjee:** None. **X. Kuang:** None. **T.L. Daigle:** None. **B. Tasic:** None. **Y. Wang:** None. **H. Gong:** None. **Q. Luo:** None. **S. Zeng:** None. **H. Zeng:** None. **A.H. Cetin:** None.

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518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

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Program #/Poster #: 518.19/JJJ15

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

Support: Swedish Research Council, 2014-3863
StratNeuro
Swedish Brain Foundation
NIH-KI doctoral program
Wellcome Trust (108726/Z/15/Z

Title: Interneuron diversity in the dorsal striatum revealed by single-cell RNA-sequencing: The Pthlh population

Authors: *A. B. MUÑOZ MANCHADO[1], C. BENGTSSON-GONZALES[1], A. ZEISEL[1], H. MUNGUBA[1], B. BEKKOUCHE[2], N. SKENE[1], P. LÖNNERBERG[1], J. RYGE[3], K. D. HARRIS[4], S. LINNARSSON[1], J. HJERLING-LEFFLER[1]
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Abstract: The striatum, the largest nucleus of the basal ganglia, plays an important role in motor planning, decision-making, motivation and reward. The most abundant striatal neurons are the Spiny Projecting Neurons (SPNs) that comprise 95% of the neuronal population. The remaining 5% are locally-projecting interneurons that although less in number play a key role in regulating the output from the striatum to the rest of the basal ganglia. Alterations in this circuitry can lead to neurological disorders as Parkinson's disease, Huntington's disease and others. Currently, the interneuron populations can be divided into several subtypes including the largest heterogeneous population expressing 5HT3a that we recently identified (Muñoz-Manchado *et* al., Cereb Cortex 26(1): 96-105, 2016). This study together with others, pointed towards that the diversity of interneuron subtypes has been underestimated. In order to elucidate this diversity we have taken advantage of a recent developed technique, such as the large-scale single-cell mRNA-sequencing (Zeisel, Muñoz-Manchado *et al*., Science 347(6226): 1138-42, 2015). We have performed a study of 4552 cells in the striatum covering a wide range of ages and using two different platforms to independently confirm our findings. To enrich for the interneuron population, besides CD1 wild-type mice, we have used two transgenic mouse lines, 5HT3a^{EGFP} and Lhx6^{cre}::R26R-tdTomato. As a result we have molecularly characterized all interneuron subpopulations and validate our findings with *in situ* hybridization and/or immunohistochemistry. In addition, we have revealed a *Cck*$^{+}$ interneuron population, and also a population of *Pthlh*$^{+}$ interneurons, which contains the cells expressing *Pvalb*. Interestingly, for

the largest interneuron populations we found additional internal structure shown as gradients of gene expression. For example, the *Pvalb*-expression within the Pthlh-population exists on a transcriptional gradient correlating with a dorso-medial to ventro-lateral axis. Using PatchSeq, we could confirm that this gradient is also correlated to the fast-spiking electrophysiological properties. Furthermore, we found significant molecular differences that correlated with differences in electrophysiological properties between developmentally, morphologically and functionally related *Pvalb*-expressing cells of the striatum and cortex.

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518. Tools and Techniques for Manipulation of Neurons and Circuits

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 518.20/JJJ16

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

Support: NIH-KI doctoral program

Title: Molecular/electrophysiological heterogeneity and circuit function of striatal Pvalb expressing cells revealed by PatchSeq

Authors: *C. L. BENGTSSON GONZALES[1], A. MUÑOZ MANCHADO[1], A. ZEISEL[1], H. MUNGUBA[1], B. BEKKOUCHE[1], N. SKENE[1], P. LÖNNBERG[1], J. RYGE[2], K. D. HARRIS[3], S. LINNARSSON[1], C. J. MCBAIN[4], J. HJERLING-LEFFLER[1]
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Abstract: *Pvalb* expressing fast-spiking basket cells across the telencephalon share the same developmental origin and have been considered a homogenous group with a canonical circuit function including feed-forward inhibition. Their unique high-frequency firing and dense local axonal arborization allows them to exhibit a strong somatic inhibition onto their target cells, making them crucial for fine-tuning the circuit output.
Using Striatal single-cell RNA-sequencing in combination with patch clamp recordings (PatchSeq) we reveal that striatal Pvalb-cells differ from their cortical and hippocampal counterparts, both in terms of molecular profiles and intrinsic properties. In addition, molecularly striatal Pvalb cells do not cluster into a discrete cluster but are found within a larger group of cells defined by the expression of *Pthlh*. Within this population *Pvalb* expression is detected in a gradient wise manner with a ventro-lateral bias. Using PatchSeq we showed that Pthlh-cells

exhibited another continuum of electrophysiological properties, correlated to *Pvalb* expression. Gradient like differences in both molecular profiles and intrinsic properties, raises the question if striatal *Pvalb*-high and low cells within the Pthlh-population could be states rather than discrete subtypes. This is determined by studying differences in their morphology and local connectivity, traits that are more stable than intrinsic properties and gene expression and therefore will change minimally between different states of a neuronal population.

Disclosures: C.L. Bengtsson Gonzales: None. **A. Muñoz Manchado:** None. **A. Zeisel:** None. **H. Munguba:** None. **B. Bekkouche:** None. **N. Skene:** None. **P. Lönnberg:** None. **J. Ryge:** None. **K.D. Harris:** None. **S. Linnarsson:** None. **C.J. McBain:** None. **J. Hjerling-Leffler:** None.

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518. Tools and Techniques for Manipulation of Neurons and Circuits

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Program #/Poster #: 518.21/JJJ17

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

Support: Volkswagen Foundation Freigeist fellowship (A110720)
ERC starting grant (678071—ProNeurons)

Title: Identification of novel neurogenic transcription factors driving neurogenesis in human stem cells

Authors: *V. BUSSKAMP[1], A. H. M. NG[2], A. KEMPE[1], K. LENK[1], E. ROJO[1], J. HOERSTEN[1], A. EUGSTER[1], A. DAHL[1], G. M. CHURCH[2]
[1]Ctr. for Regenerative Therapies, TU Dresden, Dresden, Germany; [2]Dept. of Genet., Harvard Med. Sch., Boston, MA

Abstract: There are more than 300 neuronal cell classes with an unknown number of subtypes in the human brain. However, access to high quality human tissue samples from donors is extremely limited. Therefore, one can bypass the shortage on human brain samples by programming somatic or human stem cells into neuronal-like cell types or by generating human brain organoids.
Elegant ways to obtain human neurons are transdifferentiating fibroblasts or inducing neuronal differentiation in stem cells. In comparison to many different neuronal induction techniques, the ectopic overexpression of neurogenic transcription factors (TFs) can result in rapid and homogeneous neurogenesis. Still, the set of neurogenic TFs, mostly inspired by *in vivo* development, only results in very few neuronal cell types. To expand the breadth and access of *in vitro* neuronal cell types, we conducted large-scale cell fate engineering to generate neurons from human induced pluripotent stem cells (iPSCs).

We created a comprehensive inducible human TF expression library within a lentiviral backbone to systematically screen TFs that differentiate human stem cells. Next, we tagged human iPSCs with a fluorescent reporter cassette driven by a human Synapsin promoter enabling us to identify neurons upon differentiation. We transduced this reporter line with lentiviral particles at different multiplicities of infections to obtain single and combinatorial integrations of the conditional TF constructs. Upon induction for four days, we sorted fluorescently labeled cells using FACS into single wells, extracted the RNA to perform both, single cell qPCR to identify the neurotransmitter identity and sequencing to reveal the overexpressed TFs.
By this unbiased neurogenic TF screening, we analyzed hundreds of individual neurons at single cell resolution, identified known but more importantly novel single TFs and TF combinations that drove human iPSCs into postmitotic neurons in just four days. We subject these neurons to in-depth characterization using transcriptomics as well as imaging and functional assays.
Our large-scale unbiased TF-mediated neuronal induction system at single cell resolution can pave the way towards the production of many human neuronal cell types *in vitro* useful for basic and biomedical approaches.

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Poster

518. Tools and Techniques for Manipulation of Neurons and Circuits

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Program #/Poster #: 518.22/JJJ18

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

Title: Automated phenotyping screen for mosquito larvicides

Authors: *D. B. SATTELLE[1], S. BUCKINGHAM[1], G. LYCETT[2]
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Abstract: Pyrethroid impregnated nets have halved the burden of malaria in the past decade but resistance threatens their future efficacy and the pipeline of new insecticides is short. We report the application of automated phenotyping to mosquito larvae. The INVertebrate Automated Phenotyping Platform (INVAPP) for use with 96-well plates combined with the algorithm Vectorgon provides a robust assay for *Anopheles gambiae* and *Aedes aegypti* larval motility. By this means the actions of chemical insecticides can be measured quickly and reliably. We illustrate how the assay is convenient for measuring dose-dependent actions of the insecticide deltamethrin on larval motility over time and use it to demonstrate that larval resistance to deltamethrin can be detected in both species. As proof-of-principle of its capacity for library-scale chemical screening we screened the Pathogen-Box library for novel candidate larvicides

from which Tolfenpyrad emerged as an effective larvicide. The system enables screening for novel and re-profiled chemicals as candidate larvicides.

Disclosures: D.B. Sattelle: None. **S. Buckingham:** None. **G. Lycett:** None.

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518. Tools and Techniques for Manipulation of Neurons and Circuits

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Program #/Poster #: 518.23/JJJ19

Topic: F.01. Neuroethology

Support: NIH Grant 1OT2OD025307
NIH Grant T32EB007509

Title: Selectively inhibiting small-diameter axons with glucose

Authors: *J. ZHUO[1], M. T. MCPHEETERS[1], E. D. JANSEN[5], S. J. LEWIS[2], H. J. CHIEL[3,1,4], M. W. JENKINS[2,1]
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Abstract: Neuromodulation has the potential to treat various diseases (e.g., rheumatoid arthritis, obesity, heart failure), but needs finer selectivity for more targeted treatments. Small-diameter fibers in the peripheral nervous system carry important sensory information crucial for altering organ function. Previously, we have shown that IR neuromodulation can preferentially modulate sensory peripheral nerves. We are actively studying the potential of small fiber modulation for further clinical applications. In our previous work, a mathematical analysis suggested that any modality acting primarily on the axonal surface (e.g., ion channels) would preferentially affect the small-diameter axons. Isotonic glucose solution primarily blocks ion channels on the axonal surface. Therefore, we hypothesize that isotonic glucose solution can also selectively inhibit small-diameter axons.
To test our hypothesis, we stimulated and recorded compound action potentials (CAP) from the pleural-abdominal connective of *Aplysia californica* (n = 3). This nerve's length allows the different component of CAPs with different conduction velocity to separate from each other. The nerve was placed across a triple-chamber platform, where the chambers are sealed from each other but the nerve could course through all three. Suction electrodes were placed on both ends of the nerve, one for electrical stimulation and a second for monopolar recording. The suction electrodes also stretch the nerve, allowing control of length and strain. The nerve was stimulated at 0.5 Hz and the CAPs were amplified before digitizing. *Aplysia* saline is placed in the two outer chambers while the middle chamber can be perfused with *Aplysia* saline or isotonic glucose

solution (10.21 w/v %). The width of the middle chamber is adjustable to vary the exposed length of the nerve in the solution. With *Aplysia* saline in the middle chamber and minimum exposure length (250 um), stimulation current threshold was determined to reliably evoke all CAP components. With glucose solution in the middle chamber, as the exposure length is increased from its minimum, recorded CAPs change from undistorted, to selective inhibition of small-diameter axons and eventually full block. Using the characterized selective inhibition exposure length, and by perfusing different solution in the middle chamber, we were able to inhibit small-diameter axons with isotonic glucose solution and restore the full CAP with *Aplysia* saline. This test was conducted at least 2 times per nerve and the response was stable and repeatable. These results support the hypothesis that isotonic glucose solution can also selectively inhibit small-diameter axons.

Disclosures: J. Zhuo: None. **M.T. McPheeters:** None. **E.D. Jansen:** None. **S.J. Lewis:** None. **H.J. Chiel:** None. **M.W. Jenkins:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.01/JJJ20

Topic: I.02. Systems Biology and Bioinformatics

Support: 5R24HD0008836 Eunice Kennedy Shriver National Institute of Child Health & Human Development to the Laboratory of Developmental Biology, University of Washington

Title: Proteomic profiling of extracellular vesicles from IL-1β stimulated human primary astrocytes by quantitative mass spectrometry

Authors: *Y. YOU[1], K. BORGMANN[3], S. STACY[3], A. GHORPADE[3], T. IKEZU[1,2]
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Abstract: Astrocytes are abundant glial cells in the central nervous system (CNS) that provide supportive neuronal functions. Increasing evidence has specified their critical roles in regulating neuronal activities in response to pro-inflammatory factors such as cytokines, amyloid-β peptides and lipopolysaccharides in infectious and neurodegenerative diseases. However, a greater understanding of underlying mechanisms and specific mediators during these processes is still emerging. Exosomes, typically 30-150nm extracellular microvesicles, are known to carry a large diversity of molecules such as proteins and RNA species that can modify the physiology of recipient cells. Here, we hypothesized that astrocyte-derived exosomal proteins are regulated

upon exposure to pro-inflammatory factors and are likely regulators of neuronal function and plasticity. We present a quantitative proteomics analysis of exosomes purified from human primary astrocytes with or without interleukin-1β (IL-1β) stimulation in vitro. Exosome-enriched fractions were purified by size-exclusion columns and the size distribution was determined by nanoparticle tracking analysis. Overall, a total of 539 common proteins were identified with an overlap of 89 proteins among ExoCarta Top100 proteins. Abundant molecules were specifically present in exosomes from IL-1β-stimulated astrocytes. Bioinformatics analysis shows that they are not only involved in activation of immune response and modulation of cell adhesions, but also regulating actin cytoskeleton, which could result in cytoskeletal reorganization of target cells. The exosomal proteins specific to resting astrocytes play a role in protein metabolism, cell growth and maintenance. Otherwise, 37 differentially expressed proteins (a cutoff of absolute fold change ≥1.5 and p value <0.05) from IL-1β stimulated exosomes were selected. Among them 35 proteins, most of them contribute to innate immunity and cytoskeleton organization. Finally, similar proteomic results were also obtained from exosomes derived from astrocytes cultured in exosome-depleted media with IL-1β stimulation, further validating the alteration of exosomal proteins in activated astrocytes, which can be transferred to regulate neuronal function and plasticity. Our findings will be helpful to elucidate the pathophysiological functions of astrocyte-derived exosomes in regulating neuronal networks and provide new insights into the diagnostics and therapeutics of inflammatory diseases.

Disclosures: Y. You: None. **K. Borgmann:** None. **S. Stacy:** None. **A. Ghorpade:** None. **T. Ikezu:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.02/JJJ21

Topic: I.02. Systems Biology and Bioinformatics

Title: PhosphoSitePlus as a resource to explore PTM-mediated signaling in neuronal physiology and disease

Authors: *J. M. KORNHAUSER[1], B. ZHANG[2], E. SKRZYPEK[2], B. MURRAY[2], V. LATHAM[2], V. NANDHIKONDA[2], P. V. HORNBECK[2], F. GNAD[2]
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Abstract: Protein post-translational modifications (PTMs) are critical events in cellular signaling that mediate a wide variety of biological processes. In the context of neuronal cells, PTMs regulate normal physiological functions including neuronal development and synaptic plasticity, and also play important roles in neurological and degenerative diseases states as well as cancers

of the nervous system.
PhosphoSitePlus (PSP) is an open, manually-curated online resource that aggregates comprehensive information about known sites of protein PTMs, including sites discovered in high-throughput publications. Curated information about each PTM site includes upstream signaling receptors and enzymes that catalyze the modifications, downstream consequences of the modification on protein function, and implication of the modification site for disease. Among the >400,000 individual PTM sites in PSP curated from over 22,000 published articles, over 100,000 have been observed in the context of either brain tissue or cells of CNS origin. PSP also curates information about protein modifications that are regulated in response to specific neurotransmitters, and observed in the context of CNS diseases. This aggregated data can be searched in flexible ways, and can be analyzed to illuminate signaling networks that are involved in specific neuronal responses and disease states.
Recently introduced updates to the PSP web interface enhance a users' ability to analyze PTMs in the context of mutations and sequence variants implicated in disease. A lollipop plot representing the linear protein sequence allows co-visualization of PTMs, their mutation frequencies in cancer, and somatic cancer mutations and disease polymorphisms neighboring the PTM sites. Among other ongoing enhancements, we are also currently improving methods for visualization of PTM quantification in large mass spectrometric studies, to facilitate the analysis of signaling network involved in neuronal physiological responses, therapeutic treatments, and disease processes.
PhosphoSitePlus: www.phosphosite.org

Disclosures: J.M. Kornhauser: A. Employment/Salary (full or part-time):; Cell Signaling Technology. **B. Zhang:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **E. Skrzypek:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **B. Murray:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **V. Latham:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **V. Nandhikonda:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **P.V. Hornbeck:** A. Employment/Salary (full or part-time):; Cell Signaling Technology. **F. Gnad:** A. Employment/Salary (full or part-time):; Cell Signaling Technology.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.03/JJJ22

Topic: I.02. Systems Biology and Bioinformatics

Support: China Precision Medicine Initiative (2016YFC0906300)

Title: Genetic and functional study of LAMA5 for its role in nicotine dependence

Authors: *F. RONGLI[1], M. D. LI[2]
[1]Zhejiang Univ., Zhejiang province, China; [2]Inst. NeuroImmune Pharmacol., Seton Hall Univ., South Orange, NJ

Abstract: Nicotine dependence (ND) is a common brain disorder that is extremely harmful to the individual and society. Heritability for ND is estimated to be 50%~60%. Although previous whole genome-wide association studies (GWAS) have indicated a number of genetic variants associated with ND, they could explain only a small proportion of heritability and most of these detected variants are not causative ones. In this study, we conducted a whole genome-wide exome genotyping study in the Mid-South Tobacco Case-Control (MSTCC) population, consisting of 1,656 smokers and 1,740 no-smokers, which revealed several genes of interest, such as *LAMA5* (laminin subunit alpha 5). We found that 6 common SNPs in *LAMA5* are significantly associated with smoking status and other 8 SNPs are significantly associated with FTND. To determine the involvement of *LAMA5* in the etiology of ND, we treated HEK293T cells with different nicotine concentrations (1μM, 10μM, 100μM) for 48 hours and found that the expression of *LAMA5* was significantly down-regulated by nicotine (p value <0.001 for all groups). Further, we showed that nicotine treatment enhanced HEK293T cells migration (p value <0.001), an indicator of contribution to neuronal plasticity and meditated drug memory and drug withdrawal. Subsequently, we used CRISPR/Cas9 technique to edit *LAMA5* gene, which indicated that knockout of *LAMA5* greatly enhanced cell migration and affected the expression of other members of laminin family which composed of heterotrimers with *LAMA5*. Consistently, we showed there existed significant interactions among variants in *LAMB2, LAMC2* and *LAMC1* with *LAMA5*. Combined with the findings from both genetic and functional studies, we concluded that *LAMA5* along with other members of the family are involved in etiology of ND and deserve to be further investigated.

Disclosures: F. Rongli: None. **M.D. Li:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.04/JJJ23

Topic: I.02. Systems Biology and Bioinformatics

Support: China Precision Medicine Initiative (2016YFC0906300)

Title: Sex-specific long non-coding RNA regulates genes expression in human depression

Authors: *Q. LIU[1], M. D. LI[2]
[1]Zhejiang Univ., Zhejiang, China; [2]Inst. NeuroImmune Pharmacol., Seton Hall Univ., South Orange, NJ

Abstract: Major depressive disorder (MDD) is a debilitating disease for public health, which affects 350 million individuals worldwide annually. Although it has been shown that the long non-coding RNAs (lncRNAs) play an important role in activating gene expression for various disorders, involvement of lncRNA in MDD is largely unknown. By performing differentially expression and co-expression network analysis, we found lncRNAs PACERR and BDNF-AS in female and HIF1A-AS2 in male, whose expression patterns are significantly associated with transcriptional profiles of MDD in human brain in a sex-specific manner. We showed that the PACERR and BDNF-AS ($p = 4.9 \times 10^{-4}$; $p = 1.4 \times 10^{-4}$), antisense lncRNA for *PTGS2* and *BDNF* ($p = 1.0 \times 10^{-6}$; $p = 2.7 \times 10^{-2}$), respectively, were significantly differentially expressed in female MDD patients compared with female healthy controls. We also found that the lncRNA of HIF1A-AS2, which is antisense for *HIF1A* ($p = 1.2 \times 10^{-5}$), were differentially expressed in male MDD patients compared with male healthy controls ($p = 8.4 \times 10^{-7}$). Interestingly, *BDNF*, *PTGS2* and *HIF1A* have all been implied to play critical roles in MDD and in several other physiological diseases. Our results also showed that the expression patterns of these lncRNAs were positively correlated with their host mRNAs. In addition, we detected 10 significantly enriched pathways (adjusted $p < 0.05$) in females and 7 in males, with only two pathways overlapped between males and females (i.e., Osteoclast Differentiation, NF-kappa B Signaling pathway). In sum, our findings highlighted the sexual dimorphism of the MDD mechanisms at the transcriptional level, providing novel insights into the regulation of three lncRNAs underlying the physiology of MDD.

Disclosures: Q. Liu: None. **M.D. Li:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

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Program #/Poster #: 519.05/JJJ24

Topic: I.02. Systems Biology and Bioinformatics

Support: China Precision Medicine Initiative 2016YFC0906300

Title: Integrative Genome-wide association analyses reveal the genetic link between smoking and schizophrenia

Authors: *Y. MA[1], M. D. LI[2]
[1]Zhejiang Univ., Hangzhou, China; [2]Inst. NeuroImmune Pharmacol., Seton Hall Univ., South Orange, NJ

Abstract: Prevalence of cigarette smoking is significantly higher in schizophrenia (SCZ) patients compared with general population. However, the underlying biological mechanisms of the comorbidity between smoking and SCZ are largely unknown. We sought to reveal shared

biological pathways in genome-wide association study (GWAS) data containing a total of 153,898 samples. By using gene-based analysis, 208 genes associated significantly with SCZ were common with that for smoking behaviors. With the pathway-based enrichment analysis for four gene-set datasets (i.e., KEGG, GO, BioCarta, and Reactome), we identified 175 significantly enriched pathways (q-value < 0.1) for SCZ, 172 for smoking quantity, 233 for ever smoking, 225 for former smoking, and 158 for age at smoking initiation. Importantly, we revealed 18 enriched pathways which were shared between SCZ and all five smoking phenotypes. By using multidimensional scaling to cluster these common pathways in terms of shared genes, we identified five clusters for these pathways: postsynaptic density, cadherin binding, dendritic spine, long-term depression, and axon guidance. To reveal the expression profiles in human brain of these common pathways, we performed a coexpression analysis. Among genes in these identified pathways, there were 1,443 genes coexpressed in six modules. After summarizing the mean expression level of genes in each module, we found there existed two distinct and dynamic expression patterns in brain regions and developmental stages. In sum, our results indicate that risk variants from GWAS data for SCZ and smoking aggregate in particular biological pathways, providing novel insights into the etiology of the comorbidity between SCZ and smoking behaviors.

Disclosures: Y. Ma: None. **M.D. Li:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

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Program #/Poster #: 519.06/JJJ25

Topic: I.02. Systems Biology and Bioinformatics

Support: Kids Brain Health Network
Canadian Institute for Health Research Post-doctoral Fellowship
NIH grant MH111099

Title: Cross-laboratory analysis of patch-seq datasets reveals shared features of within-cell type electrophysiological heterogeneity

Authors: *S. TRIPATHY, C. BOMKAMP, L. TOKER, O. MANCARCI, P. PAVLIDIS
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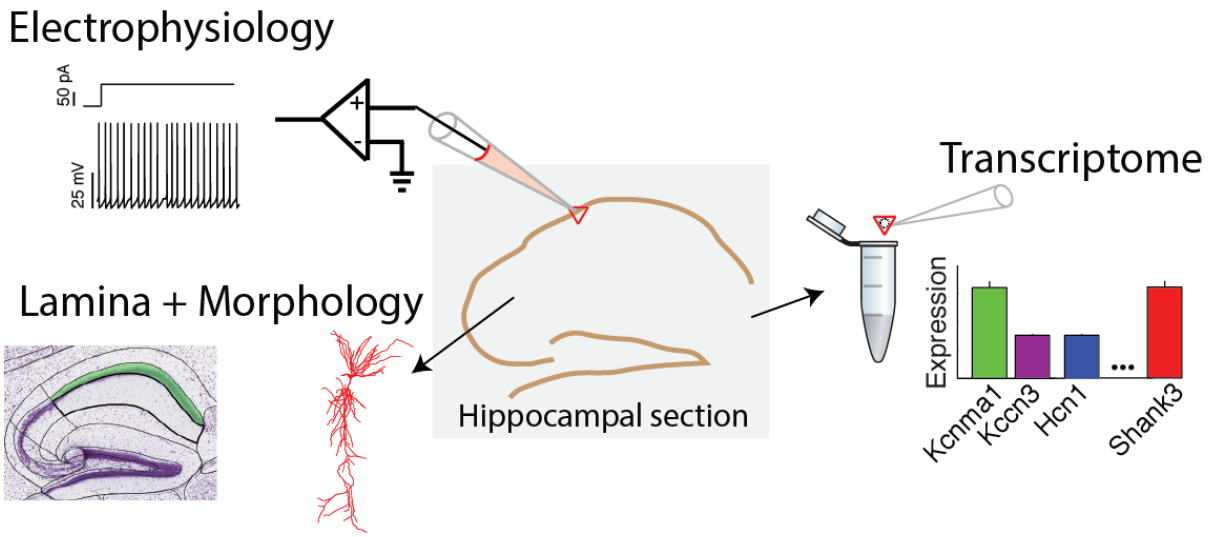
Abstract: Patch-seq, enabling simultaneous measurement of transcriptomic, electrophysiological, and morphological features, has recently emerged as a powerful tool for neuronal characterization. Here, we present a re-analysis of 4 patch-seq datasets (3 from mouse acute brain slices and 1 from human cultured neurons) and present methods for quality controling and cross-analyzing these data.

Across each of the datasets we re-analyzed, we found widespread evidence for multi-cell contamination. We suggest that this off-cell type contamination is due to the passage of the patch-pipette through the processes of other cells before and after collection of cellular mRNA. We present a straightforward marker gene-based approach for identifying this contamination, based on atlases of dissociated-cell single-cell RNAseq from analogous cell types. Down-weighting lower quality single-cell transcriptomes in subsequent analyses allows us to control the confounding influence of off cell-type contamination.
Next, we correlated single-cell gene expression with electrophysiological features measured from the same cells. We specifically wanted to assess if the same genes contribute to electrophysiological heterogeneity across cell types: for example, in fast-spiking basket cells, is higher sodium channel expression correlated with more narrow action potential widths? and if so, is this also the case in non-fast-spiking interneurons? We further compared these within-cell type correlations to our previous analyses correlating gene expression with electorphysiology using data from pooled neuron types. We report a few suggestive examples of robust cross-dataset gene-ephys correlations, such as Scn1b and AP width, and Kcnab3 and AHP amplitude. Our work highlights the promise in using the patch-seq methodology to help reveal how combinatorial gene expression gives rise to cellular electrophysiological features. However, we note that relatively small sample sizes and high technical noise of the currently available patch-seq datasets limits the resolution of these analyses.



Disclosures: S. Tripathy: None. **C. Bomkamp:** None. **L. Toker:** None. **O. Mancarci:** None. **P. Pavlidis:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

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Program #/Poster #: 519.07/JJJ26

Topic: I.02. Systems Biology and Bioinformatics

Support: NSF grant NSF0744649
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Title: Combined singe-neuron methylome & trascriptome profiling from repeatedly identifiable neurons

Authors: *E. C. DABE[1], A. B. KOHN[2], A. RIVA[3], L. L. MOROZ[4]
[1]Univ. of Florida Whitney Lab., Saint Augustine, FL; [2]Universtiy of Florida Whitney Lab., Saint Augustine, FL; [3]Univ. of Flordia, Gainesville, FL; [4]The Whitney laboratory for Marine Biosci., Univ. of Florida, Saint Augustine, FL

Abstract: On the genomic level, neuronal identity is encoded by complex epigenetic mechanisms leading to coordinated expression of ~10,000 proteincoding genes per neuron. To assess these mechanisms, we performed the singlecell bisulfite sequencing (BSseq) from individual functionally identifiable neurons of *Aplysia californica. Aplysia* neurons are some of the largest somatic cells in the animal kingdom, allowing us to directly correlate both genome-wide methylation and gene expression from the very same identified neurons . We produced methylome profiles (n=3 per cell type) for 2 symmetrical serotonergic (5HT) interneurons (MCC) & 2 homologous cholinergic (ACh) motor neurons (R2 and LPl1), Sensory neuron clusters (VC,BuccalSN), & from non-neuronal tissues. Each BSseq library had an average of 18 million paired-end reads per run. On average, 10.4 million uniquely mapped as pairs & 2.2 million as single-end reads, which is ~12x the reads currently reported per single human neuron BSseq. PCA analyses show that globally neither CpG or CH gene body methylation (gbm) clustered neurons by their known functional or transmitter identity. In contrast to previous single-neuron methylomes studies in mammals, we did not find an inverse correlation between high CH gbm & transcription. We analyzed CpG & CH gbm for cell-type specific individual genes. *Sensorin*, a neuropeptide specific to SNs, showed a marked increase in mCH gbm in VC & BuccalSNs vs. outgroups. In ACh (*ChAT, VAchT*) & 5-HT (*TPH,VMAT, SERT*) neurotransmitter biosynthesis genes there is no total gbm to transcription correlation, but sub-regions show differential CH methylation across neurotransmitter phenotypes . It also suggests much more complex epigenomic regulation of neuronal phenotypes than anticipated.

Disclosures: E.C. Dabe: None. **A.B. Kohn:** None. **A. Riva:** None. **L.L. Moroz:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.08/JJJ27

Topic: I.02. Systems Biology and Bioinformatics

Support: The University of Connecticut, School of Medicine, Start-Up Funds (to E.F.T.).

Title: Novel subtypes of retinal ganglion cells identified by single cell RNA-seq analysis

Authors: B. A. RHEAUME[1], A. JEREEN[3], M. BOLISETTY[4], M. S. SAJID[3], Y. YANG[3], K. RENNA[3], L. SUN[4], P. ROBSON[4,2], *E. F. TRAKHTENBERG[3]
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Abstract: Retinal ganglion cell (RGC) is one of the broad classes of retinal cells that pre-process and pass to the brain visual information collected in the eye. Thirty subtypes of RGCs have been identified to date. Here, we have analyzed 6,225 purified by Thy1 immunopanning postnatal day 5 RGCs (with on average 5,000 genes per cell) separately from the right and left eyes by single cell RNA-seq, and classified them into 40 subtypes using clustering algorithms. The cells were similarly enriched for pan-RGC markers such as RBPMS, Tubb3, and Thy1. We have identified novel subtypes and markers, as well as the transcription factors predicted to cooperate in specifying RGC subtypes. Markers of 5 previously identified subtypes, Jam2, NPY, Pde1a, Trhr, and Gna14, were amongst the markers predicted to be unique to 5 out of the 40 RGC subtypes. We validated two novel RGC subtypes by fluorescent in situ hybridization (FISH) and immunostaining for markers we predicted to be uniquely enriched in these subtypes (subtype marker-positive RGCs were quantified as fraction of all RBPMS-positive RGCs). We also identified the right eye enriched subtype, which we validated by immunostaining in situ, using another novel marker predicted to be unique for this RGC subtype. In total, out of the 40 predicted subtypes, 5 were validated by markers in previous studies and 3 more we validated here using novel markers. A number of other established RGC markers were enriched in more than one subtype, suggesting that they label larger subpopulations of RGCs, that are further subdivided into subtypes based on the molecular differences in their transcriptomes. For example, Cartpt, Cdh6, and Col25a1 markers of the ON-OFF direction-selective RGCs were enriched in one group of subtypes, whereas Opn4, Eomes, and Igf1 markers of the intrinsically photosensitive RGCs were enriched in a different group of subtypes. These findings contribute to our understanding of the retinal component of the visual system through characterization of the molecular differences between RGC subtypes.

Disclosures: B.A. Rheaume: None. **A. Jereen:** None. **M. Bolisetty:** None. **M.S. Sajid:** None. **Y. Yang:** None. **K. Renna:** None. **L. Sun:** None. **P. Robson:** None. **E.F. Trakhtenberg:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

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Program #/Poster #: 519.09/JJJ28

Topic: I.02. Systems Biology and Bioinformatics

Title: Profiling claustral and layer 6 neocortical neurons using single-cell transcriptomics

Authors: *L. FODOULIAN[1,2], A. CARLETON[1], I. RODRIGUEZ[2]
[1]Dept. of Basic Neurosciences, [2]Dept. of Genet. and Evolution, Univ. of Geneva, Geneva, Switzerland

Abstract: The claustrum (CLA) is a thin sheet of subcortical grey matter located between the insular cortex and the putamen. It has dense reciprocal connections with a large number of neocortical regions, which suggests a role in attention, consciousness and saliency detection. However, its function and the underlying neuronal mechanisms remain elusive. This lack of evidence results from the scarcity of tools to specifically modulate CLA activity. In particular, gene-targeted mouse lines are lacking, due to the poorly defined genetic characteristics of CLA neurons. Here, we aimed at identifying the transcriptional identity of mouse CLA projection neurons. To ensure an unbiased sampling of CLA neurons, we injected a fluorophore-encoding transsynaptic adeno-associated virus in the primary motor cortex of the mouse. Anatomical validation of this tracing showed the transsynaptic labelling of CLA neurons. Subsequent to CLA dissection and cell dissociation, GFP^+ cells were FACS sorted and captured on a $C1^{TM}$ high-throughput (HT) integrated fluidic circuit (IFC) (Fluidigm). Following single-cell RNA-sequencing, an unsupervised graph-based clustering of 579 cells identified 4 main cellular populations. Differential gene expression analysis revealed that one of these clusters corresponds to CLA projection neurons, while the three remaining were formed of cortical layer 6 (L6) pyramidal neurons, oligodendrocytes and striatal medium spiny neurons. CLA neurons were differentiated from L6 pyramidal neurons by a wide range of specific markers. Consistent with previous reports, typical CLA markers were also identified by our analysis. However, some of those genes, considered as canonical markers of the CLA, such as *Nr4a2* and *Gnb4*, also appeared to be expressed by a substantial proportion of L6 neurons. In conclusion, we identified a series of genes discriminating claustral from cortical neurons, which represents a first step in the molecular dissection of the claustral circuitry.

Disclosures: L. Fodoulian: None. **A. Carleton:** None. **I. Rodriguez:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

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Program #/Poster #: 519.10/JJJ29

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant R24MH114788
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Hearing Restoration Project of the Hearing Health Foundation
Contract from the CHDI Foundation

Title: Neuroscience multi-omic (NeMO) archive and analytics: BRAIN Initiative resources for neurogenomic data access, analysis, and visualization

Authors: *S. A. AMENT[1], S. ADKINS[2], J. CRABTREE[3], V. FELIX[3], M. GIGLIO[4], H. HUOT CREASY[3], J. KANCHERLA[6], C. MCCRACKEN[3], J. ORVIS[3], C. COLANTUONI[7], H. CORRADA BRAVO[6], R. HERTZANO[5], A. MAHURKAR[3], O. R. WHITE[3]
[1]Dept. of Neurosci. and Inst. for Genome Sci., [2]Inst. for Genome Sci., Univ. of Maryland Baltimore, Baltimore, MD; [3]Inst. for Genome Sci., [4]Inst. for Genome Sci. and Dept. of Med., [5]Dept of Otorhinolaryngology-Head & Neck Surgery and Anat. of Neurobio. and Inst. Genome Sci., Univ. of Maryland Sch. of Med., Baltimore, MD; [6]Dept. of Computer Sci., Univ. of Maryland, College Park, MD; [7]Dept. of Neurol., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: The national Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative promotes the development and application of technologies to describe the temporal and spatial dynamics of cell types and neural circuits in the brain. The wealth, depth and quality of multi-omic data generated through funding from the BRAIN initiative is unprecedented. It ranges from bulk and single cell RNA-seq and epigenomic data throughout the developing and adult brain, as well as multi-modal datasets that integrate these genomic data with the brain's spatial organization, neuronal morphology, and neurophysiology. To promote smooth interactions across a large research consortium, we are developing the Neuroscience Multi-Omic Archive (NeMO Archive; www.nemoarchive.org), a data repository that is specifically focused on the storage and dissemination of omic data from the BRAIN Initiative and related brain research projects. The information incorporating into the NeMO Archive will, in part, enable understanding of cell types in the mammalian brain and of cell states associated with disease. In parallel, we are developing a suite of web-accessible tools to analyze and visualize these and other neurogenomic data (NeMO Analytics). NeMO Analytics is based on two existing webtools for visualization of omic data - the gene Expression Analysis Resource (UMgEAR.org) and EpiViz (epiviz.github.io) with further integration of advanced analytics for

single-cell genomics, network analysis (www.trena.org), and integration across datasets (https://rdrr.io/github/genesofeve/ProjectR/). Our goal is to enable users to answer diverse questions of relevance to brain research, ranging from simple queries on the expression of individual genes to complex multi-omic workflows. It will also provide the basic knowledge to guide the development and execution of predictive and machine learning algorithms in the future.

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Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

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Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.11/JJJ30

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH 5U01MH105985
NIH 5R21MH112161
NIH U19MH114831
NIH 1R21HG009274

Title: Single-cell epigenomic profiling uncovers regulatory diversity of brain cell types and diseases

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Abstract: The epigenome is an ensemble of chemical modifications of DNA and chromatin. Genome-wide mapping of epigenomic signatures is one of the most effective approaches for identifying gene regulatory elements such as enhancers. Our recent study demonstrated robust classification of brain cell types using single-cell DNA methylation profiles. Single-cell epigenomic approaches enable unbiased mapping of the regulatory landscape for virtually all brain cell populations. With support from NIMH and NINDS as part of the BRAIN Initiative

Cell Census Network (BICCN), we are analyzing cell type and gene regulation diversity of the entire mouse brain with fine spatial resolution. Single-cell DNA methylome profiles are being produced from 116 dissected brain regions. To date we have generated over 46,000 single-cell methylomes from over 23 brain regions. We uncovered pervasive DNA methylation differences between excitatory neurons located in distinct cortical regions, whereas inhibitory neurons show less regional specification in the cortex.
We are further applying our single-cell DNA methylation assay to study the cell type diversity of human frontal cortex. DNA methylation signatures allow robust classification of both neuronal and glial cell sub-types, and prediction of regulatory sequences for human cortical cell populations. We identified enrichment of genetic variants associated with brain diseases such as schizophrenia in subtypes of excitatory and glial cells. Our single-cell epigenomic strategy provides opportunities to determine cell-type specific contributions of non-coding sequences in brain diseases.

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Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.12/JJJ31

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant MH114831

Title: Linking cortical projection cell types to epigenetic profiles

Authors: *Z. ZHANG[1], J. ZHOU[1,6], Y. PANG[2], A. RIVKIN[1], P. ASSAKURA MIYAZAKI[2], M. RASHID[2], A. BARTLETT[1], J. SANDOVAL[1], J. R. NERY[1], M. JACOBS[2], E. WILLIAMS[3], J. B. SMITH[3], C.-T. LEE[4], D. LE[1,7], R. CASTANON[1], K.-F. LEE[4], X. JIN[3], E. A. MUKAMEL[8], M. BEHRENS[5], J. R. ECKER[1,9], E. M. CALLAWAY[2]
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Abstract: Anatomy is a central and often defining feature for classification of neuronal cell types. While recent advances in single cell genomics have led to several high-resolution molecular characterizations of cell type diversity in the brain, neuronal cell types are often

studied out of the context of their anatomical properties. Our study aims to link molecular properties of cell types to neuronal connectivity by combining retrograde tracing with single cell DNA methylome sequencing. As part of the NIH Brain Initiative Cell Census Network (BICCN) effort, we are profiling epigenetic signatures of long-distance projecting neurons throughout the mouse brain. Our initial studies focus on cortical neurons from primary motor cortex (MOp), primary somatosensory cortex (SSp), anterior cingulate cortex (ACA), agranular insular cortex (AI), primary auditory cortex (AUDp), retrosplenial cortex (RSP), posterior parietal cortex (PTLp), and primary visual cortex (VISp) that project to various subcortical targets including striatum (STR), superior colliculus (SC), thalamus (TH), and pons (P), as well as other cortical areas. To ensure high-resolution and high-quality DNA methylation profiling of the projecting neurons, we generate single nuclei methylome profiles for at least 250 neurons (post-QC) of each cortico-subcortical projection. With these data, we are, for the first time, able to examine the molecular properties of these distinct groups of projection neurons. Our preliminary results show that the laminar location, cortical region, and projection target all contribute to the unique epigenetic signatures of individual neurons. In addition, we are identifying potential regulatory sequences such as enhancers that could be tested to specifically target and label each projection neuron type, enabling the targeted study and manipulation of projection neurons of interest. Supported by NIH grant MH114831.

Disclosures: Z. Zhang: None. **J. Zhou:** None. **Y. Pang:** None. **A. Rivkin:** None. **P. Assakura Miyazaki:** None. **M. Rashid:** None. **A. Bartlett:** None. **J. Sandoval:** None. **J.R. Nery:** None. **M. Jacobs:** None. **E. Williams:** None. **J.B. Smith:** None. **C. Lee:** None. **D. Le:** None. **R. Castanon:** None. **K. Lee:** None. **X. Jin:** None. **E.A. Mukamel:** None. **M. Behrens:** None. **J.R. Ecker:** None. **E.M. Callaway:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.13/JJJ32

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant MH114831

Title: Single nuclei chromatin accessibility analysis reveals epigenetic heterogeneity of mouse brain regions

Authors: *S. PREISSL[1], R. FANG[2], X. WANG[1], X. HOU[1], J. HAN[1], J. LUCERO[3], S. KUAN[2], J. CHIOU[4], D. U. GORKIN[1], K. GAULTON[4], M. BEHRENS[3], E. A. MUKAMEL[5], J. R. ECKER[6], B. REN[1,2]
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Abstract: Transcriptional regulatory regions in the genome including promoters and distal acting enhancers play fundamental roles for development and disease. These genomic regions can be identified by the presence of open chromatin as measured by ATAC-seq (Assay for transposase-accessible chromatin using sequencing). However, heterogeneity of primary tissues poses a significant challenge in mapping the precise chromatin landscape in specific cell types. Therefore, we optimized a combinatorial barcoding-assisted single-cell assay for transposase-accessible chromatin for use on flash-frozen primary tissue samples (single nuclei ATAC-seq, snATAC-seq). We applied the methodology to deconvolute the cellular composition of the mouse forebrain, defined cell-type-specific transcriptional regulatory sequences and inferred potential master transcriptional regulators. In addition, we identified cell-type specific enrichment of gene sequence variants associated with human disease in genome-wide association studies (GWAS). For example, regulatory elements accessible in the microglia population were highly enriched for Alzheimer's disease associated risk variants. Further process optimization including liquid handling robotics enables us now to robustly generate libraries for more than 5,000 single nuclei chromatin accessibility profiles in a single experiment. We use this approach to map the epigenetic heterogeneity in distinct regions dissected from the adult mouse brain. Initial analysis of more than 20,000 nuclei isolated from the primary motor cortex revealed more than 30 cell populations corresponding to all major neuronal and non-neuronal cell types. I will present the most recent insights from our analysis. This work is supported by NIH Grant MH114831.

Disclosures: S. Preissl: None. **R. Fang:** None. **X. Wang:** None. **X. Hou:** None. **J. Han:** None. **J. Lucero:** None. **S. Kuan:** None. **J. Chiou:** None. **D.U. Gorkin:** None. **K. Gaulton:** None. **M. Behrens:** None. **E.A. Mukamel:** None. **J.R. Ecker:** None. **B. Ren:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.14/JJJ33

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant MH114831

Title: Integrative analysis of mouse motor cortical cell type epigenomes using single nucleus DNA methylation and open chromatin (ATAC-Seq) data

Authors: *K. KOLODZIEJ[1], F. XIE[2], W. I. DOYLE[3], R. FANG[4], R. CASTANON[7], A. RIVKIN[7], J. NERY[7], S. PREISSL[5], C. LUO[8], M. BEHRENS[9], B. REN[10], J. R. ECKER[11], E. A.

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Abstract: The mammalian brain is comprised of a complex network of unique cell types. Powerful techniques for measuring mRNA abundance in single cells and nuclei have enabled unbiased surveys of brain cell types in mouse (Zeisel et al. 2015; Tasic et al. 2016; Tasic et al. 2017) and human (Lake et al. 2016). High throughput sequencing of DNA from single nuclei has also been applied to measure DNA methylation and regions of open chromatin. However, these data types have not yet been integrated to provide a unified, multimodal classification of brain cell types. Although mRNA expression provides highly informative signature of cell types, it can be affected by transient state changes as well as by neural activity. The regulatory information provided by epigenomic data identifies cell type specific gene regulatory elements such as enhancers. Integrating transcriptional and epigenetic data can provide a comprehensive framework for determining the molecular-genetic landscape of individual cell types.
We generated thousands of single neuron DNA methylomes from adult mouse motor cortex using single nucleus methylcytosine sequencing (snmC-Seq) as part of the BRAIN Initiative Cell Census Network (BICCN). In parallel, we used single nucleus assay for transposase-accessible chromatin (snATAC-Seq) to detect regions of open chromatin We identify putative gene regulatory elements (GREs) in these data sets using differentially methylated regions (DMRs) as well as peaks of snATAC-Seq read density that indicate accessible chromatin regions. We focus on GREs located far from gene promoters (>2 kb), many of which have a unique cell type specific profile. We find that GREs that are active in a specific cell type have low methylation and high snATAC-Seq read density. This correspondence allows us to identify cell types in the two datasets using the negative correlation between signals from cells of the same type. For example, we find a strong correlation between non-CG DNA methylation and snATAC read density for cells of the same type (Spearman r = -0.65 for PV cells). By contrast, the correlation between non-CG methylation in PV cells and snATAC read density in VIP cells is significantly lower (r = -0.35). By integrating data modalities we can produce a comprehensive picture of the epigenetic landscape of specific cell types in the mouse brain.

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Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.15/JJJ34

Topic: I.02. Systems Biology and Bioinformatics

Support: R21 MH112161

Title: Single neuron epigenomes and transcriptomes from human cortex have greater inter-individual variability for excitatory compared with inhibitory neurons

Authors: *F. XIE[1], C. LUO[3], J. NERY[4], R. CASTANON[4], J. LUCERO[4], D. MASH[5], M. BEHRENS[6], E. A. MUKAMEL[2], J. R. ECKER[7]
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Abstract: Single-cell sequencing technology enables an objective molecular taxonomy of human cortical neurons. Although the broad classes and fine distinctions among brain cell types are likely to be strongly conserved across individuals, genetic variation in the human population as well as differences in individual experience may lead to inter-individual differences in gene expression and epigenetic regulation of brain cells. The diversity of transcriptomic and epigenomic regulation of brain cell types across individuals is not well understood.
We performed single nuclei DNA methycytosine sequencing on 6,435 cells from frontal cortex samples from 3 adult males. We identified cell types by jointly clustering cells from all datasets using DNA methylation at CG and non-CG sites (mCG and mCH) in 100 kilobase bins across genome. This analysis identified more than 20 highly distinct putative cell types, including at least 10 excitatory and 8 inhibitory neuron types, as well glial cells.
By comparing mCH across 3 individuals, we found that excitatory neurons have a greater degree of variability between individuals within the same cell type than inhibitory neurons. Excitatory neurons clustered mainly by layer-specific cell type, but also had differences in methylation that correlated with biosample of origin. By contrast, inhibitory neurons from different biosamples clustered together. The top 40 genes with most variable DNA methylation (mCH) across biosamples have higher variability in excitatory neurons than in inhibitory cell types. A classifier based on linear discriminant analysis could predict the biosample of origin for each cell based on DNA methylation in gene bodies. The classifier performs better for excitatory cells (area under the receiver operating characteristic, AUROC = 0.90-0.98, range across cell types) than for inhibitory cells (AUROC = 0.68-0.78). To examine inter-individual differences at the transcriptional level, we analyzed single nuclei RNA sequencing data from 15,928 cells from cortex of 8 individuals (Allen Brain Institute). These data indicate that, like DNA methylation,

transcription in excitatory cells is more diverse across individuals than in inhibitory cells. Inter-individual variation could be due to genetic differences, such as single nucleotide polymorphisms. Alternatively, differences in development and environment between individuals could have greater impact on some cell types compared with others. Understanding the origin of conserved and variable molecular signatures of brain cell types across individuals is important for the functional interpretation of these cell type signatures.

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Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.16/JJJ35

Topic: I.02. Systems Biology and Bioinformatics

Support: U19MH114830

Title: Multimodal profiling of primary motor cortex neurons using patch-seq

Authors: *M. BERNABUCCI[1], F. SCALA[1], C. R. CADWELL[1], J. CASTRO[1], L. HARTMANIS[2], D. KOBAK[4], Y. BERNAERTS[4], D. RAMSKÖLD[2], Z. YAO[5], O. PENN[6], S. LATURNUS[4], K. R. TOLIAS[1], B. TASIC[7], P. BERENS[4], X. JIANG[1], R. SANDBERG[3], H. ZENG[6], A. S. TOLIAS[1]
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Abstract: The brain exhibits a considerable assortment of neurons that diverge in terms of morphology, electrophysiological proprieties, and gene expression. While other techniques can explore single-cell variability across one or two of these dimensions, we recently developed Patch-seq, which combines whole-cell patch-clamp recording with single-cell RNA- sequencing and immunohistochemistry, to comprehensively profile the transcriptomic, morphological and biophysical features of single neurons in brain slices.
Here, we present a detailed description of our recent modifications to the Patch-seq protocol, as well as the preliminary analysis of primary motor cortex (MOp) as part of the Brain Initiative Cell Census Network (BICCN) project.
Utilizing Patch-seq on brain slices of adult wild-type and several Cre line mice (PV+, SST+, VIP+, and HTR3a+/Vip-), along with algorithms to perform automatic electrophysiological and morphological analysis, we profiled pyramidal and γ-aminobutyric acid-releasing (GABAergic) neurons from MOp layers 2/3 and 5.

We mapped transcription profiles of cells obtained by Patch-seq to cells obtained from dissociated tissue using fluorescence-activated cell sorting (FACS), revealing a clear correspondence among gene expression profiles.
The generation of a comprehensive cell type atlas, based on genome expression data, electrophysiological, and morphological features, could significantly contribute to the study of central nervous system structure and function; as well as neuropsychiatric disorders by identifying the specific cell types that express disease-associated genes.

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Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

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Program #/Poster #: 519.17/JJJ36

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH U19 MH114830
NIH R01 MH103108
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NIH DP1 EY023176
NIH DP1 OD008301
Swedish Research Council
NIH F30 MH095440

Title: Multimodal profiling of excitatory neurons using Patch-seq reveals diversity of cell types within individual clonal units

Authors: *C. R. CADWELL[1], F. SCALA[2,3], Z. YAO[4], P. G. FAHEY[2,3], D. KOBAK[5], S. LI[2,3], B. TASIC[4], H. ZENG[4], P. BERENS[5], R. SANDBERG[6], X. JIANG[2,3], A. S. TOLIAS[2,3,7]
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Abstract: Neurons exhibit a rich diversity of morphological phenotypes, electrophysiological properties and gene expression patterns, and understanding how this tremendous cellular diversity is generated during the course of normal development remains poorly understood. We recently developed Patch-seq, a technique that combines whole-cell patch clamp recording,

immunohistochemistry and single-cell RNA-sequencing (scRNA-seq) to comprehensively profile single neurons from mouse brain slices. By streamlining this technique and making additional modifications to the patching mechanics and recording procedure, reagents and recipes, procedures for immunohistochemistry and other protocol steps, we are able to obtain high-quality morphological, electrophysiological and transcriptomic data from single neurons with increasing rates of success and throughput. We applied Patch-seq to explore the multidimensional phenotypic variability among excitatory neurons with a shared developmental lineage and show that clonally related cells within the same clone recapitulate the diversity of neocortical cell types. Our findings support the idea that clonal units may serve as developmental building blocks of the neocortical circuit.

Disclosures: C.R. Cadwell: None. **F. Scala:** None. **Z. Yao:** None. **P.G. Fahey:** None. **D. Kobak:** None. **S. Li:** None. **B. Tasic:** None. **H. Zeng:** None. **P. Berens:** None. **R. Sandberg:** None. **X. Jiang:** None. **A.S. Tolias:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.18/DP14/JJJ37

Topic: I.02. Systems Biology and Bioinformatics

Support: NIMH Grant 1U19MH114830-01

Title: Building high-resolution mouse brain atlas of transcription cell types - strategies and discoveries

Authors: *Z. YAO, L. T. GRAYBUCK, T. NGUYEN, K. A. SMITH, N. DEE, D. BERTAGNOLLI, J. GOLDY, O. FONG, O. PENN, S. M. SUNKIN, B. TASIC, H. ZENG
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Abstract: Building high-quality atlas of cell types in the mouse brain is a critical step towards understanding the complicated mammalian nervous system. As part of the BRAIN Initiative Cell Census Network (BICCN), we will create a most comprehensive to this date, single-cell transcriptomic cell type atlas from all brain regions of adult male and female mice, using highly standardized methods to achieve consistency and comparability across different brain regions. In order to determine the optimal profiling strategy, BICCN launched a Mouse Mini-Atlas project to test and compare multiple single-cell RNA-sequencing platforms on mouse primary motor cortex. We have generated data using several scRNA-seq methods including SmartSeq V4 whole cells, SmartSeq V4 nulcei, 10X whole cells, 10X nuclei, and SplitSeq. The number of cells or nuclei profiled are from 6K to 130K. Preliminary results suggest that the number of genes detected by these methods vary significantly, and consequently, so does the number of

clusters for each dataset produced by the same clustering pipeline. While all the datasets provide very similar major type separation, the cell type resolution for finer splits as well as cell type compositions are different. Further comprehensive evaluation that accounts for sequencing depth, number of cells, cost per cell and cell type resolution will be informative for determining optimal strategies to profile the entire mouse brain.
Towards building whole brain atlas, we have currently analyzed 54602 cells collected thus far by SmartSeq V4 from 16 cortical and subcortical regions and identified 259 clusters. We observe cell type/cluster dependent regional specificities as well as gradients across regions. Overall, these large-scale transcriptomic datasets are revealing organizational rules of molecularly defined cell types across a range of brain areas.

Disclosures: Z. Yao: None. **L.T. Graybuck:** None. **T. Nguyen:** None. **K.A. Smith:** None. **N. Dee:** None. **D. Bertagnolli:** None. **J. Goldy:** None. **O. Fong:** None. **O. Penn:** None. **S.M. Sunkin:** None. **B. Tasic:** None. **H. Zeng:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.19/JJJ38

Topic: I.02. Systems Biology and Bioinformatics

Support: Chan Zuckerberg Initiative Grant 2017-174399
Wellcome Trust grant 108726

Title: Towards a cell type classification and spatial census of transcriptomic cell types in mouse and human cortex

Authors: *J. A. MILLER[1], B. TASIC[1], T. E. BAKKEN[1], Z. YAO[1], O. PENN[1], E. D. VAISHNAV[2], B. D. AEVERMANN[4], A. REGEV[3,5], R. H. SCHEUERMANN[4], P. V. KHARCHENKO[6], K. D. HARRIS[7], H. ZENG[1], E. LEIN[1]
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Abstract: Modern high-throughput methods for single cell or single nucleus RNA-seq allow a comprehensive interrogation of cellular diversity in dissected samples, but these methods do not provide the spatial organization of those cell types in tissue. Highly multiplexed spatial transcriptomics methods provide a means to directly map molecularly-defined cell types back to the originating tissues by analyzing sets of genes that discriminate among those types. However, these various methods have not yet been systematically applied to highly complex cellular tissues such as neocortex. The Chan-Zuckerberg Initiative (CZI)-funded SpaceTx consortium

seeks to (1) evaluate and compare the performance of different methods and (2) to build consensus maps of cortical cell type distributions in human and mouse neocortex based on combined analysis of single cell, single nucleus, and spatially-resolved transcriptomics. Essential elements of this strategy are the rigorous definition of transcriptomic types and the optimal selection of gene panels to discriminate among them.
Here we address these two key challenges for the mouse and human neocortex. We sought to compare and then combine clustering results on two reference data sets published on the Allen Cell Types Database (http://celltypes.brain-map.org/): single cell RNA-seq from >20,000 cells in mouse primary visual cortex and anterior lateral motor cortex, and single nucleus RNA-seq from >15,000 cells in human middle temporal gyrus. We first applied multiple computational methods to generate clustering results, and then derived consensus clusters in both date sets as the target for spatial transcriptomics methods. The consensus clustering found remarkably good agreement in broader cell classes and highly distinct types, and we intentionally over-partitioned heterogeneous cell types to capture more subtle features like gradient changes in expression in broader clusters.
We next addressed the challenge of optimizing gene panel selection for each spatial transcriptomics method, which is non-trivial given differing limitations on the lengths, expression level, and total number of genes that can be concurrently assayed. We describe here a multi-pronged approach including use of prior knowledge, generation of new tools for gene discovery, application of multiple computational strategies, and extensive cross-group collaboration to select gene panels for each experimental protocol. The results provide a set of generalized tools for reference cell type classification and marker gene panels generation that should be useful for creating spatial cell type censuses or study of specific cell types in complex tissues.

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Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.20/JJJ39

Topic: I.02. Systems Biology and Bioinformatics

Title: Single-cell multimodal correspondence typing through patch clamp electrophysiology, two-photon optogenetics, and multiplexed FISH in thick tissue

Authors: *R. NICOVICH, B. LONG, M. TAORMINA, T. NGUYEN, E. THOMSEN, B. LEVI, C. A. BAKER, T. A. HAGE, A. BOSMA-MOODY, B. TASIC, J. CLOSE, E. LEIN, H.

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Abstract: Spatial relationships between distinct types of cells are fundamental to the function of the brain and other complex organs. To define relationships between transcriptomically defined cell types and cellular morphology, electrophysiological properties, and connectivity, we have developed a pipeline that examines brain tissue in a sequential manner for various cellular characteristics. For defining molecular cell types in the tissue, we are using multiplexed fluorescence RNA *in situ* hybridization (mFISH), and are mapping the mFISH-derived single cell profiles to our benchmark dataset derived by single cell RNA-sequencing.
As a use case, we defined the transcriptomic types of cells previously targeted by optogenetic stimulation at cellular resolution in slice physiology experiments. We use light-sheet microscopy to interrogate intact 350-micron-thick physiology slices to identify cell morphology, anatomical location, connectivity, and transcriptomic identity on a cell-by-cell basis. Connecting the results of the patch clamp and optogenetic experiments to the those from mFISH and potentially morphology yields correspondences between these different modalities.
This pipeline is aimed at robust and repeatable interrogation of mouse and human brain tissue. Scaling these methods to the necessary throughput involved many challenges we have overcome with solutions that should be widely applicable in the field. We will share our approaches to these challenges as well as alternatives that allow us to assign molecular types to single cells previously interrogated for their intrinsic physiology, anatomy, and connectivity.

Disclosures: R. Nicovich: None. **B. Long:** None. **M. Taormina:** None. **T. Nguyen:** None. **E. Thomsen:** None. **B. Levi:** None. **C.A. Baker:** None. **T.A. Hage:** None. **A. Bosma-Moody:** None. **B. Tasic:** None. **J. Close:** None. **E. Lein:** None. **H. Zeng:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.21/JJJ40

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant 1U19MH114830-01
Chan Zuckerberg Initiative 2017-174399
NIH Grant 1U01MH114812-01

Title: Exploring neuronal cell types in mouse and human brain using multiplex fluorescence *in situ* hybridization

Authors: *B. R. LONG[1], J. L. CLOSE[2], B. TASIC[3], B. P. LEVI[1], E. J. GARREN[1], Z. MALTZER[1], T. NGUYEN[1], E. THOMSEN[1], T. BAKKEN[1], J. A. MILLER[1], P. R. NICOVICH[1],

E. LEIN[2], H. ZENG[4]
[2]Human Cell Types, [3]Cell and Circuit Genet., [4]Structured Sci., [1]Allen Inst. for Brain Sci., Seattle, WA

Abstract: The molecular identity of the building blocks of the brain have recently been elucidated in using large-scale transcriptomic methods on single cells and single nuclei. Definition of transcriptomic identities of neuronal cell types is an important milestone, but single-cell transcriptomic methods have very limited spatial resolution and lack the spatially-unbiased anatomical context needed to accurately quantify abundance of the many cell types in the brain. This limitation has motivated a growing number of spatial transcriptomic methods that seek to measure mRNA expression in single cells in intact tissue. Here we present our results in developing a multiplex fluorescence in situ hybridization (FISH) pipeline capable of mapping neuronal cell types in mouse and human brain. We routinely apply multiround single molecule (smFISH) and hybridization chain reaction (HCR) FISH labeling methods to thin tissue sections, including multiround image collection, registration, mRNA localization, cell segmentation and cell type identification across hundreds of image tiles and many square millimeters of mouse and human brain tissue. We will present recent results on cell type identification in human middle temporal gyrus, computational removal of lipofuscin autofluorescence in human brain tissue and scalable image analysis for large datasets.

Disclosures: B.R. Long: None. **J.L. Close:** None. **B. Tasic:** None. **B.P. Levi:** None. **E.J. Garren:** None. **Z. Maltzer:** None. **T. Nguyen:** None. **E. Thomsen:** None. **T. Bakken:** None. **J.A. Miller:** None. **P.R. Nicovich:** None. **E. Lein:** None. **H. Zeng:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.22/JJJ41

Topic: I.02. Systems Biology and Bioinformatics

Support: CZI Grant 2017-144399
NIH Grant 1U01MH114812-01

Title: Mapping human neuronal subtypes with spatial transcriptomics

Authors: *J. L. CLOSE[1], E. THOMSEN[1], Z. MALTZER[1], T. NGUYEN[2], B. R. LONG[2], E. GARREN[2], R. D. HODGE[2], J. A. MILLER[2], T. BAKKEN[2], E. LEIN[1], H. ZENG[3], B. P. LEVI[2], R. NICOVICH[2], B. TASIC[4]
[1]Human Cell Types, [3]Structured Sci., [4]Cell and Circuit Genet., [2]Allen Inst. for Brain Sci., Seattle, WA

Abstract: Single-nucleus transcriptomics data derived from human medial temporal gyrus (MTG) indicates that there are at least 69 neuronal cell types in the human cortex. To place select cell classes and types in spatial context and determine the proportion of each cell type in a given area of human cortical tissue, we applied multiplexed fluorescent in situ hybridization techniques to human brain slices. Both amplified (hairpin chain reaction) and unamplified (sequential smFISH) methods of detection were used to allow us to visualize genes within a wide window of expression level and gene length. To analyze our spatial transcriptomics data, we utilized image quantification and analysis tools developed in collaboration with the Chan Zuckerberg Initiative's SpaceTx consortium. Our data suggest that the proportion and layer location of certain GABAergic and Glutamatergic neuronal classes and types differs between mouse and human. This could have significant implications for circuit architecture and information processing.

Disclosures: J.L. Close: None. **E. Thomsen:** None. **Z. Maltzer:** None. **T. Nguyen:** None. **B.R. Long:** None. **E. Garren:** None. **R.D. Hodge:** None. **J.A. Miller:** None. **T. Bakken:** None. **E. Lein:** None. **H. Zeng:** None. **B.P. Levi:** None. **R. Nicovich:** None. **B. Tasic:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.23/JJJ42

Topic: I.02. Systems Biology and Bioinformatics

Support: CZI Grant Number: 2017-174399

Title: *Fish: Developing a computational pipeline for spatial transcriptomics in the brain

Authors: *E. LEIN[1], B. R. LONG[2], D. GANGULI[3], A. CARR[3], T. TUNG[3], J. FREEMAN[3]
[1]Human Cell Types, [2]Allen Inst. for Brain Sci., Seattle, WA; [3]Chan Zuckerberg Initiative, San Francisco, CA

Abstract: ABSTRACT: Spatial transcriptomic methods such as multiplex fluorescence in situ hybridization (FISH) and in situ sequencing have the potential to provide detailed transcriptional profiling of thousands of single cells in tissue. As part of the SpaceTx effort to compare these methods we are developing *FISH (pronounced "starfish"), a computational pipeline to produce standardized outputs from input images originating from a wide range of spatial transcriptomic methods. This open source pipeline will be designed to scale from running on a personal computer with locally stored data to to using cloud-based compute and storage resources. The pipeline allows users to build an analysis recipe for their data from various computational modules for image filtering, mRNA spot localization, cell segmentation and decoding of barcoded mRNA identities. By standardizing intermediate data formats and final output, the

*FISH pipeline will facilitate direct comparison of critical parameters across methods, including mRNA detection sensitivity and dynamic range, total mRNA counts per cell and number of genes measured in each experiment. After mapping to previously-defined transcriptomic cell types, SpaceTx output will generate single cell transcriptomic profiles and spatial maps of cell types as well as detailed maps of gene expression in mouse and human brain tissue.

Disclosures: B.R. Long: None. **D. Ganguli:** None. **A. Carr:** None. **T. Tung:** None. **J. Freeman:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.24/JJJ43

Topic: I.02. Systems Biology and Bioinformatics

Title: Establishing correspondence between morphology, electrophysiology, synaptic connectivity and gene expression in specific cell types in local human cortical networks

Authors: *M. KIM[1], E. THOMSEN[1], B. R. LONG[2], R. NICOVICH[2], C. LEE[3], S. A. SORENSEN[2], N. W. GOUWENS[2], J. BERG[2], B. E. KALMBACH[1], R. HODGE[2], J. L. CLOSE[1], J. A. MILLER[2], T. BAKKEN[2], J. T. TING[1], B. P. LEVI[2], L. CAMPAGNOLA[2], C. KOCH[2], T. JARSKY[2], G. J. MURPHY[2], E. LEIN[1]
[1]Human Cell Types, [3]Modeling Analysis and Theory, [2]Allen Inst. for Brain Sci., Seattle, WA

Abstract: A major goal for understanding human cortical function is to understand the cellular makeup of the cortical microcircuit and the connectivity among those circuit elements. Recent advances in single cell transcriptomics now allow a molecular classification of cell types, but the relationship between gene expression and other cellular phenotypes including their electrophysiology, anatomy, and local synaptic connectivity remain largely uncharacterized. To approach this problem, we are probing the synaptic connectivity between human cortical cell types in neurosurgical resections of human middle temporal cortex and defining cell types through a combination of electrophysiology, cellular morphology, synaptic physiology and gene expression, by combining multipatch slice physiology with single molecular fluorescent in situ hybridization (FISH). In addition to intrinsic membrane properties and cellular morphology, cell types can be defined by their synaptic connectivity rates to other neurons, and properties of short-term synaptic dynamics when they are connected. In order to identify both synapse-specific cell types and transcriptional cell types in the same neurons, we combined methods to do multiple patch-clamp recordings and post-hoc FISH using the method of multiplexed hybridization chain reaction (HCR) in thick brain slice tissue. After simultaneous patch-clamp recordings in multiple neurons, the electrophysiological cell type in each neuron is identified and characterized by current stimulus sets. Then, we analyze synaptic connectivity by brief

sequential current injections in patched neurons. As a post-hoc process, we recover clustered neuronal morphologies by streptavidin antibody staining with biocytin diffused through patch pipettes during electrophysiological recordings. Finally, after this procedure, we visualize spatial gene expression discriminating different cell types in cortical slices at the single cell level including clustered patched neurons with FISH with the amplified HCR. We describe here progress on developing and using these tools to be able to define human cortical cell types/classes in individual neurons simultaneously at different levels in cortical columnar network.

Disclosures: M. Kim: None. **E. Thomsen:** None. **B.R. Long:** None. **R. Nicovich:** None. **C. Lee:** None. **S.A. Sorensen:** None. **N.W. Gouwens:** None. **J. Berg:** None. **B.E. Kalmbach:** None. **R. Hodge:** None. **J.L. Close:** None. **J.A. Miller:** None. **T. Bakken:** None. **J.T. Ting:** None. **B.P. Levi:** None. **L. Campagnola:** None. **C. Koch:** None. **T. Jarsky:** None. **G.J. Murphy:** None. **E. Lein:** None.

Poster

519. Systems Biology and Bioinformatics: Genomics, Proteomics, and Systems Biology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 519.25/JJJ44

Topic: I.02. Systems Biology and Bioinformatics

Support: Allen Institute for Brain Science
NIMH Grant 1U01MH114812-01

Title: A 3-D digital human brain common coordinate framework for positional mapping of single cell data

Authors: *S.-L. DING, J. J. ROYALL, P. LESNAR, B. A. C. FACER, Y. LI, M. NAEEMI, D. FENG, S. M. SUNKIN, H. ZENG, L. NG, J. A. HARRIS, E. S. LEIN
Allen Inst. for Brain Sci., Seattle, WA

Abstract: Human brain mapping at multiple spatial scales and across data modalities has become a routine approach for understanding brain structure, function, lesion and treatment in the neuroimaging community. These approaches have been facilitated by the availability of population average atlases such as the MNI_ICBM152 template and tools such as Freesurfer. In contrast, histological and cellular analyses of human brain typically utilize traditional plate-based atlases of individual brains as reference atlases. With the increase in higher resolution anatomical and cellular analysis approaches such as those of the BRAIN Initiative Cell Census Network (BICCN), there is a need for a whole brain 3D annotated common coordinate framework (CCF) to map single cell data and allow spatial and cross-modal analyses. This cellular resolution presents significant challenges for accurate representation in probabilistic atlases, but a

meaningful coarse mapping to probabilistic templates will allow meaningful analyses and correlation between single cell and neuroimaging data, especially if that template space has a 3D annotation of all brain regions. To better meet these needs and provide a human brain CCF, we present here a 3-D digital Human Brain CCF annotated on the MNI_ICBM152 template. Cortical annotations were based on sulcal patterns of the MNI152 template while subcortical structures were based on a combined analysis of intrinsic template features and histology-based parcellation resources of the human brain (i.e. Allen Human Brain Reference Atlas; see Ding et al. J Comp Neurol, 524: 3127-3481, 2016) using ITK-SNAP. In this CCF, we delineated and segmented approximately 53 cortical gyri/regions using the ontology created for Allen Human Brain Reference Atlas including subdivisions of the previously defined large fusiform gyrus into perirhinal gyrus (anterior part) and real fusiform gyrus (posterior part). For subcortical regions, a total of 45 parent and/or large structures were identified and segmented in basal forebrain, basal ganglia, amygdaloid complex, thalamus, hypothalamus, cerebellum, and brainstem. Finally, 15 representative white matter fiber bundles and the ventricular structures were also annotated for landmark reference. In summary, the Human Brain CCF presented here represents the first manual 3-D segmentation of whole human brain structures on the commonly used MNI_ICBM152 template and will provide a useful tool for documentation, visualization, analysis and comparison of large-scale mapping data across different laboratories.

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Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 520.01/JJJ45

Topic: I.04. Physiological Methods

Support: NIH MH101634
NIH MH113924
Cystinosis Research Foundation
Schmitt Foundation

Title: Sex differences in behavioral training

Authors: *E. WARNER[1,2,3], K. PADMANABHAN[1,2,3,4]
[1]Neurosci., [2]Neurosci. Grad. Program, [3]The Ernest J. Del Monte Inst. for Neurosci., [4]Ctr. for Visual Sci., Univ. of Rochester, Rochester, NY

Abstract: Behaviors can reflect the internal state of an animal. One such behavior, active locomotion, or running, is easily assessed, correlates with an array of brain states, and impacts neural activity, including in primary sensory regions. In mice, voluntary wheel running is used often in tandem with a head-fixing protocol to keep the brain stable for electrophysiological or imaging experiments. To habituate animals to this paradigm, progressive periods of training are used, ensuring that subsequent experiments are not confounded by the novelty of being head restrained in an unfamiliar environment. While the training period is generally thought of as a precursor to an actual experimental manipulation or assessment, how animals behave during this phase can impact how they respond in the future. Thus, to assess behavior during training, we recorded running for 15 minutes during a 1-hour training session over 7 consecutive days in head-restrained mice (males and females) on a circular one-dimensional running wheel. First, we found an increase in both the probability of running and velocity for all animals over the seven days of training. Second, when we examined the running behaviors of males and females, we found significant sex differences between the two groups. Although there was no significant change in the probability of running or velocity of running between males and females, we found sex differences in the direction of running on early days of training. In this paradigm, animals can run forward or reverse, with forward running reflecting a more natural behavior. On day 2 of training, near 90% of female mice (N=8/9) were running forward while only 44% of the male mice were running forward (N=4/9). By day 3, 100% of the female mice ran forward ($P<0.0001$, Wilcoxon Rank Sum, N=9 males, N=9 females). By contrast, only following 5 days of training did all the male mice run forward. Finally, once the animals learned to run in the forward direction, there was no reversion to the reverse direction in following days. These results demonstrate that animals habituate differently during experiments, and that one source of variation is the sex of the animal. Consequently, paradigms that use both males and females in experimental design should monitor differences during training, as these differences may impact subsequent behavioral manipulations, including how those manipulations reflect neural circuit function.

Disclosures: E. Warner: None. **K. Padmanabhan:** None.

Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 520.02/JJJ46

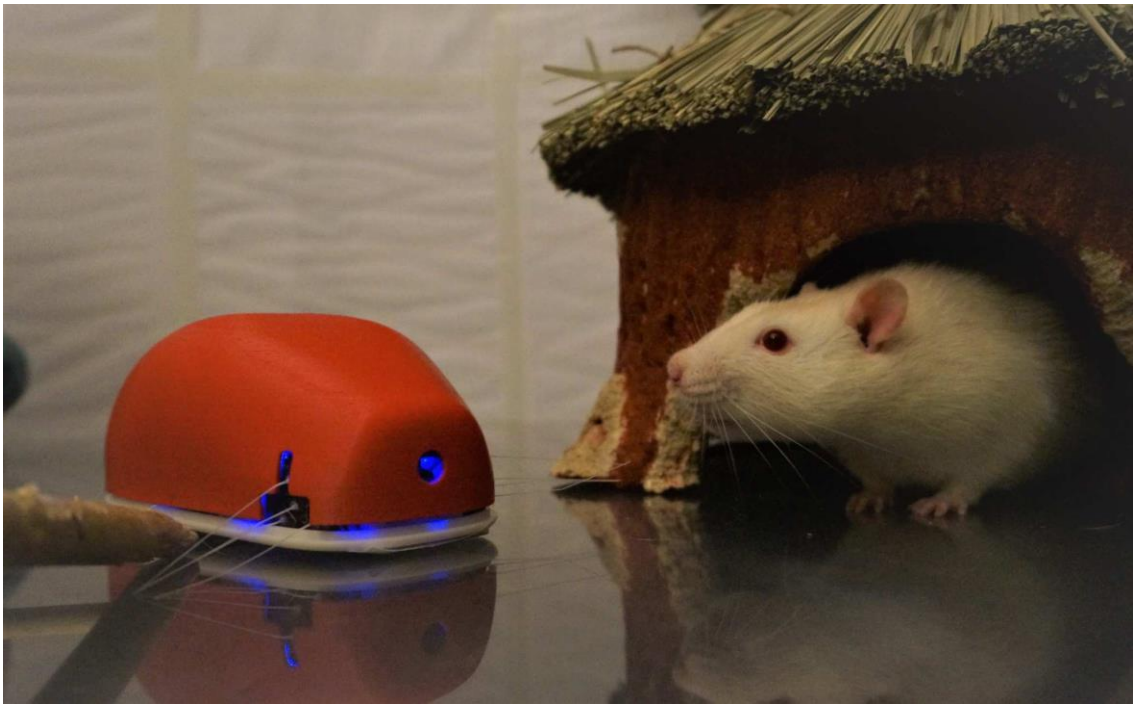
Topic: I.04. Physiological Methods

Support: NIH
TDLC

Title: PiRat: An autonomous rat-sized robot as a social companion for studying social behavior in rats using real-time tracking

Authors: S. HEATH[1], C. A. RAMIREZ-BRINEZ[1], J. ARNOLD[1], O. OLSSON[1], J. TAUFATOFUA[1], P. POUNDS[1], *J. WILES[1], E. LEONARDIS[2], E. GYGI[2], E. LEIJA[2], L. QUINN[2], A. A. CHIBA[2]
[1]The Univ. of Queensland, Brisbane, Australia; [2]UCSD, La Jolla, CA

Abstract: Rats are highly social creatures, so measuring the neural and behavioural responses from rats during social interactions is important to studying and understanding the rodent brain. However, the study of rat dyads presents a number of challenges, including preventing injury to a rat or damage to instrumentation from the other rat, and identifying and isolating responses to different social behaviours. Robot-rat studies provide an alternative to dyadic interactions where the use of the robot helps to address these challenges: the robot can be controlled to prevent injury or damage, and individual social behaviours can be added or removed to isolate responses. In the current research, we designed and evaluated a robot framework for performing robot-rat interaction studies, consisting of a new, rat-sized robot platform, the PiRat, an overhead real-time tracking system that uses a depth sensor, and a behaviour manager that allows different behaviours or models to be implemented and run on the PiRat.
Our framework was pilot tested by individually running the robot rat with several different rats (male Sprague-Dawleys and Brown Norways). The rats were first run through a habituation phase, and then with PiRat performing different types of behaviour, including an avoiding behaviour, and an approaching behaviour. The PiRat and real rats were autonomously tracked in the majority of trials, with system-support for real time human-in-the-loop tracking adjustments when required. The quality of the interactions were evaluated using: the mean distance between rat and robot, number of meetings, and sum of velocity towards PiRat. The habituation ranked better in all metrics than either the avoid or approach behaviours. This study presents the first demonstration of a closed-loop robot-rat framework and lays the foundation for further autonomous robot-rat interactions, where different behaviours can be implemented using the positions of the rat and iRat as inputs.



Disclosures: S. Heath: None. **C.A. Ramirez-Brinez:** None. **J. Arnold:** None. **O. Olsson:** None. **J. Taufatofua:** None. **P. Pounds:** None. **J. Wiles:** None. **E. Leonardis:** None. **E. Gygi:** None. **E. Leija:** None. **L. Quinn:** None. **A.A. Chiba:** None.

Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 520.03/JJJ47

Topic: I.04. Physiological Methods

Support: NIMH 1R01MH110514-01
BRAIN EAGER NSF SMA 1451221

Title: Real-time tools for the classification of social behavior and correlated brain activity in rodents

Authors: *M. AGUILAR-RIVERA[1], E. GYGI[2], A. THAI[2], J. MATSUMOTO[3], H. NISHIJO[3], T. P. COLEMAN[1], L. K. QUINN[2], A. A. CHIBA[2]
[1]Bioengineering, [2]Cognitive Sci., UCSD, La Jolla, CA; [3]Univ. of Toyama, Toyama-Shi, Japan

Abstract: Behavioral coding based on video data is a time-consuming task involving more than one highly trained human classifier. This load increases when multiple rodents are involved,

particularly when engaging in social interactions. Within the field of social neuroscience, there is a growing interest in studying prosociality from a behavioral to an electrophysiological perspective. In this regard, the interoceptive system composed of the amygdala, insular cortex, and the autonomic system, is of particular interest in the study of prosocial behaviors and emotions. It is known that the amygdala is involved in the control of facial expression and face processing. In addition, there is evidence showing facial expression control by the insula, as well as a correlation between its activity and facial and behavioral expression of physical discomfort. Providing frame-by-frame behavioral coding with sufficient temporal resolution and precise synchronization to examine the physiological and electrophysiological correlates of such behaviors is arduous at best. We, therefore, present a real-time behavioral sorter based on videos and inertial measurement units (IMUs) for the classification of social behaviors, affect, and distress, which can be coupled with electrophysiological recordings. Automatic classification of behavior and detailed facial expression are obtained through 3D video of interacting rodents and through the use of high-resolution (4K) cameras. The 3D video system receives input from IMUs (gyroscope, accelerometer, and magnetometer) mounted on the rats' electrophysiological implant increasing its temporal resolution. The IMUs also enable the system to continuously track and provide behavioral classification when rodents are in naturalistic environments where they may be obscured from the camera. The 3D system generates a train of TTL pulses that allow precise synchronization of the system with the 4K cameras, IMUs, and the electrophysiological and physiological recording devices. Together, this technology provides the affordances necessary to build an integrated view of social dynamics and physiology in real time, the first steps towards examining the correlates of prosocial behavior.

Disclosures: M. Aguilar-Rivera: None. **E. Gygi:** None. **A. Thai:** None. **J. Matsumoto:** None. **H. Nishijo:** None. **T.P. Coleman:** None. **L.K. Quinn:** None. **A.A. Chiba:** None.

Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 520.04/JJJ48

Topic: I.04. Physiological Methods

Support: CIHR Grant FDN-143210
Huntington Society of Canada

Title: Assessing forelimb motor learning and kinematics within the mouse home-cage: An open-source system for the study of rodent models of disease

Authors: *C. L. WOODARD, J. D. BOYD, T. H. MURPHY, L. A. RAYMOND
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Abstract: Behavioural testing of genetically modified mice is an important step in determining the validity of these animals as models of human disease and assessing the effects of potential therapeutics. To improve both the throughput and reproducibility of this testing, there has been an increase in the use of automated systems that assess behavioural phenotypes of mice within their own home-cage. These allow for the 24-hour testing and monitoring of group-housed mice, who can be individually tracked through subcutaneously implanted RFID chips. However, current commercially available systems are expensive and limited in their ability to test certain behaviours relevant to the study of neurological disorders, such as motor skill learning and fine motor control. To address this, we have developed an open-source system to assess forelimb motor learning, reversal learning and kinematic measures of motor control within the mouse home-cage. Animals learn to pull a metal lever to a defined range over several weeks of continuous testing, and high-resolution lever position analysis as well as video recording allows for automated assessment of learning and behaviour. In previous work with an earlier version of this system, we found several motor learning and control deficits in the YAC128 model of Huntington disease (HD) at an early stage of disease progression. Current work has focused on refining the testing methodology and hardware of the system, and the development of new software applications. We continue to assess both the YAC128 and Q175FDN models of HD for motor, cognitive and circadian phenotypes, and to characterize progression over time. This platform should prove useful for preclinical drug trials toward improved treatments in HD and other neurodegenerative disorders.

Disclosures: J.D. Boyd: None. **T.H. Murphy:** None. **L.A. Raymond:** None.

Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 520.05/JJJ49

Topic: I.04. Physiological Methods

Title: A simple method of analyzing spatial learning, prosocial behavior, and empathy in mice utilizing the Barnes maze and damsel-in-distress paradigm

Authors: *E. B. CLABOUGH[1], J. INGERSOLL[1], M. MOODY[1], R. HOLLAND[1], J. WINSLOW[1], W. KUEGLER[1], C. MURRAH JR.[1], B. DUGAN[1], N. REYNOLDS[1], N. LLOYD[1], M. HAMMOCK[1], K. HOULE[2]
[1]Dept. of Biol., Hampden-Sydney Col., Hampden Sydney, VA; [2]Col. of Med. at the Med. Univ. of South Carolina, Charleston, SC

Abstract: The Barnes maze is a reliable measure of spatial learning and memory that does not require food restriction or exposure to extremely stressful stimuli. The Barnes maze can also be used to assess other mouse behaviors, such as general motivation to escape from the maze

platform and exploratory behavior. We explore the use of an aversive ultrasonic noise to enhance motivation to enter the target hole. This behavioral test can be adapted in several ways to assess acquisition and retention of memory in the context of a genetic mutation or environmental variable, as well as provide information about the search strategy employed by the mice. Representative results use the Barnes maze to detect a memory deficit in adult mice following a single developmental ethanol exposure event. The newly described Damsel-in-Distress paradigm exposes a mouse to a female mouse trapped in a chamber in the open center field of an arena. The Damsel-in-Distress paradigm provides an opportunity for the mouse to socially respond to the trapped female and allows for both prosocial behavior and empathy (in the form of investigation and digging near the trapped conspecific). It can also be used to assess rodent locomotor activity and behavior in a novel arena. Both the Barnes maze and the Damsel-in-Distress protocols require minimal financial investment and most aspects of the tests can be constructed from common lab supplies. These flexible and accessible tools can also be used to detect behavioral changes over the course of development.

Disclosures: E.B. Clabough: None. **J. Ingersoll:** None. **M. Moody:** None. **R. Holland:** None. **J. Winslow:** None. **W. Kuegler:** None. **C. Murrah Jr.:** None. **B. Dugan:** None. **N. Reynolds:** None. **N. Lloyd:** None. **M. Hammock:** None. **K. Houle:** None.

Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 520.06/JJJ50

Topic: I.04. Physiological Methods

Support: R01MH059803

Title: Auditory discrimination learning in a rodent model of human targeted cognitive training

Authors: *B. Z. ROBERTS[1], N. R. SWERDLOW[2], R. F. SHARP[1], J. W. YOUNG[1]
[1]Dept Psychiatry, UCSD, La Jolla, CA; [2]UCSD Sch. of Medicine, Dept of Psychiatry, La Jolla, CA

Abstract: Introduction: After 50 hours of Targeted Cognitive Training (TCT) schizophrenia patients show large gains in neurocognition. However, durable changes may require extended training, functional gains are modest, and individual responses are variable. We describe a novel paradigm for studying mechanisms of learning in TCT, in advance of testing interventions to enhance its clinical impact.
Methods: Male Long Evans rats (n=15) were trained to respond for reward in 3 distinct auditory discrimination tasks (ADT). Auditory stimuli were either a 500 ms pure tone of high (7 kHz) or low frequency (4 kHz) (ADT#1); a 200 ms sound sweep ranging from low to high frequency

("upsweep") or high to low frequency ("downsweep") (ADT#2); or a 500 ms upsweep or downsweep (ADT#3). The primary outcome variable was accuracy in choosing the lit aperture associated with the stimulus.
Results: Learning was reflected in a main effect of session on accuracy ($F_{(16,160)}$=3.467, $p<0.05$). A session x group interaction ($F_{(32,160)}$=1.522, $p<0.05$) revealed that the 500 ms sweeps group (ADT#3) learned faster than the other two groups. By training day 6 of 17, rats in ADT#3 exhibited greater accuracy vs. day 1. Performance superior to day 1 was never achieved in ADT#1, and required 13 days in ADT#2.
Conclusions: Long Evans rats: 1) can discriminate auditory frequency upsweeps vs. downsweeps; 2) learn faster from sweeps than pure tones; and 3) learn faster from long (500 ms) vs. short (200 ms) sweep duration. Studies will now assess the impact of pharmacologic agents on this model of TCT learning.
Funding Sources: R01MH059803 (NRS)

Disclosures: B.Z. Roberts: None. **N.R. Swerdlow:** None. **R.F. Sharp:** None. **J.W. Young:** None.

Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 520.07/JJJ51

Topic: I.04. Physiological Methods

Title: Highly multiplexed concerted monitoring of deep-brain hypothalamic neuronal dynamics, gene expression, and behavior reveals cell type ensembles setting behavioral state

Authors: *S. XU, H. YANG, F. E. HENRY, V. MENON, A. LEMIRE, S. M. STERNSON
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Abstract: Brain function depends on a complex interplay of gene expression, neuronal dynamics, and behavior. Deep-brain areas are important for setting behavioral states and they are comprised of multiple molecularly defined neuron populations that are thought to influence distinct behaviors, however little is known about neuronal dynamics in these structures. Moreover, single cell transcriptomics comprehensively predicts neuronal identity, but it requires considerable effort and expense to examine the dynamics of each of these specific neuron populations using existing tools, such as Cre-lox technologies. To address these opportunities and technical challenges, we developed a new functional imaging platform that can simultaneously investigate neuronal dynamics of multiple molecularly defined cell types in a deep-brain structure. GCaMP was pan-neuronally expressed in a deep-brain region. Neuronal calcium activity was recorded through a GRIN lens by two photon volumetric imaging in awake behaving animals under multiple behavioral states. After in vivo imaging, the brain was

sectioned and molecular identity was assigned to the previously imaged cells by 12-plex fluorescence in situ hybridization. Using this new imaging platform, we simultaneously recorded neuronal ensemble dynamics of multiple molecularly cell types in the paraventricular hypothalamus (PVH), which plays a major role in controlling behavioral states associated with animal survival. This platform links traditional system neuroscience ensemble activity measurements with detailed molecular identity of individual neurons and behavior within a single experiment, thus it bridges the gap from gene expression to neural dynamics and behavior.

Disclosures: S. Xu: None. **H. Yang:** None. **F.E. Henry:** None. **V. Menon:** None. **A. Lemire:** None. **S.M. Sternson:** None.

Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

Location: SDCC Halls B-H

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Program #/Poster #: 520.08/JJJ52

Topic: I.04. Physiological Methods

Support: FAER MRTG-BS
NIH R01 GM107117
NIH K08 GM123317

Title: *In vivo* adduction of photolabel anesthetic in mouse rostral pons profoundly extends drug behavioral effects

Authors: *A. R. MCKINSTRY-WU[1], A. WASILCZUK[1], W. P. DAILEY[2], M. B. KELZ[3]
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Abstract: Introduction:Many drugs that act to modify complex behaviors, including antidepressants, sedative-hypnotics, and antipsychotics, produce their effects through multiple molecular mechanisms on interconnected neuronal populations. The resulting behavioral phenotype may not be entirely separable from the cumulative effects on a relevant circuit. To study such circuit-level effects, we use a photolabel-derivative of the common hypnotic agent propofol, m-azipropofol (aziPm), systemically with near UV light directed to a small region of the rostral pons centered about the locus coeruleus (LC) to covalently bind drug in vivo, testing whether behavioral-level effects can be prolonged when drug is trapped in a tightly circumscribed region.
Methods:C57/B6 male mice (n=30) implanted with EEG, EMG, and bilateral cannulae stereotaxically directed at the rostral pons (the LC.) During EEG/EMG recording, intravenous 100 mg/kg aziPm given over 5 minutes + or - 375 nm fiber-optic-delivered laser light. A sticker was placed on the mouse's nose and time to remove noted. Cannulae localized postmortem.Mice

with cannula were given IV 1 mg/kg [^{3}H]-aziPm with 375 nm light via cannula. Mice were perfused 1 hour after exposure, and 50 um thick brain sections placed on a phosphor imaging plate for 1 week before images were developed.Slice electrophysiology performed as described previously (Moore 2012). Neurons of the LC were patched in current clamp, and after characterization, baseline established and 10 uM aziPm given with and without 375 nm light.Analyses performed using custom code in Matlab 2016a and with Prism 7.0.
Results:Mice with cannula targeting the rostral pons (centered on the LC) that received UV and aziPm had time to behavioral recovery compared to mice with cannula >300 um off-target or those given drug alone increased by a factor of 10 ($p<0.01$.) Spectral estimates of frontal EEG show extended increases in delta and decreases in gamma and theta power in drug+UV, suggesting prolonged hypnosis, while EMG tone did not differ between groups and heart rate and respiratory rates were not different after drug bolus. Radiolabeled aziPm binding confirmed with a similar exposure, drug photoadduction occurs within a ~300 um sphere. Slice recordings of LC neurons showed a profound prolonged decrease in firing after being given aziPm and UV light vs drug alone ($p<0.001$.)
Conclusion:m-Azipropofol, when photoadducted in the rostral pons in the region of the LC, profoundly extends the hypnotic state. Recordings show some neuronal populations within the relevant area are silenced.
Ref: Moore, J. T. et al. Curr. Biol. 22, 2008-16 (2012).

Disclosures: **A.R. McKinstry-Wu:** A. Employment/Salary (full or part-time):; University of Pennsylvania. **A. Wasilczuk:** None. **W.P. Dailey:** None. **M.B. Kelz:** None.

Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

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Topic: I.04. Physiological Methods

Support: NIH Grant R01 MH111875

Title: Micro-TMS technology for ultra-focal brain stimulation

Authors: *R. LAHER[1,2], D. Z. PRESS[1], C. E. MCILDUFF[1], S. B. RUTKOVE[1], G. BONMASSAR[2], A. PASCUAL-LEONE[1]
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Abstract: Transcranial Magnetic Stimulation (TMS) is a non-invasive brain stimulation technique widely utilized in both research and clinical settings. However, the relatively large size of the conventional 70 mm figure-of-eight coil limits spatial resolution and prevents

simultaneous network stimulation at multiple sites. With a goal of increasing stimulation focality, we have engineered a 13 mm Microcoil (μTMS) with a focality of 1-5mm as compared to the conventional 10-30 mm. The system utilizes two stereo, high powered audio amplifiers connected at the input to a pulse generator and at the output to an oscilloscope for monitoring. Miniaturization was achieved via a Flex design consisting of four copper traces, each a width of 711μm, selected to create a 2Ω resistance on 1oz of copper. The amount of amperage needed for the μTMS to induce a magnetic field of similar intensity to Magstim in tissue was determined using modeling and the Biot-Savart law. Aerogel, a material with extraordinary thermal insulation properties, was used for insulation between the skin and the coil. We plan to test the efficacy, safety, and focality of μTMS in peripheral nerves in the upper extremity that are commonly assessed with nerve conduction studies. First, an electrical stimulator will be used to perform standard motor and sensory nerve conduction studies of the median and ulnar nerves. The procedure will then be repeated using the standard figure-of-eight coil as the stimulator to demonstrate activation of evoked potentials by conventional TMS methods. Finally, the process will be repeated using μTMS. A focality map of sensory and motor responses relative to the stimulated peripheral nerve will be generated. This proof-of-concept investigation could provide support for the use of a new μTMS coil capable of stimulating the central nervous system at multiple nodes with greater focality than is available today.

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Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

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Topic: I.04. Physiological Methods

Support: DARPA/ElectRx

Title: On demand control of hormone release from adrenal gland using magnetothermal stimulation

Authors: *D. ROSENFELD[1], A. SENKO[1], J. MOON[1], D. GREGUREC[1], A. S. WIDGE[3], P. ANIKEEVA[2]
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Abstract: The adrenal glands play a central role in the regulation of stress responses in patients suffering from psychiatric and behavioral disorders. The glands are responsible for secretion of hormones such as cortisol and (nor)epinephrine, known also as the “fight or flight” hormones. Abnormal production of adrenal hormones has been linked to altered stress responses in mental disorders, including major depressive disorder and post-traumatic stress disorder affecting about 10% of the US population. The adrenal gland is therefore a high-value target for peripheral neuromodulation and control of hormones. Magnetic nanoparticles (MNPs) dissipate heat upon exposure to alternating magnetic fields (AMFs), which then can trigger thermally-sensitive ion channels in electro-active cells. Local heating from MNPs can be converted into an electrochemical gradient across the cell membranes, leading to depolarization in response to the externally applied AMF. The use of MNPs eliminates the need for invasive and tissue-damaging electrodes. Moreover, AMF has higher penetration depth (>10cm) compared to other fields and therefore is more suitable for deep tissue stimulation. It has been shown that heat sensitive ion channels, such as TRPV1, exist in various tissues, including the adrenal glands. Here, hysteretic heating of MNP in the presence of AMF was used to trigger hormone release from adrenal glands. The size, concentration, saturation magnetization, and specific loss power of the MNPs were examined and tailored to the applied AMF. We established a mixed primary adrenal cell culture from adult rat. Adrenal cells were shown to respond robustly to magnetothermal stimulation using calcium imaging. The effects of magnetothermal adrenal stimulation were then assessed in live rats. We developed a surgical procedure to directly inject MNPs to the adrenal gland. One week post-surgery AMF was applied using a custom apparatus. We found that both corticosterone, produced in zona fasciculata of adrenal cortex, and (nor)epinephrine, produced in chromaffin cells of adrenal medulla, can be released on demand with second precision in response to AMF. These results indicate the utility of magnetothermal approach for control and regulation of peripheral organ function.

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Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 520.11/JJJ55

Topic: I.04. Physiological Methods

Title: Non-invasive whole body imaging using magnetography

Authors: R. R. LLINÁS[1], M. USTININ[2], S. D. RYKUNOV[2], *K. D. WALTON[1], G. M. RABELLO[1], J. GARCIA[1], A. I. BOYKO[2], V. V. SYCHEV[2]

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Abstract: A novel spectroscopic paradigm has been developed that allows the magnetic field emissions generated by the electrical activity in the human body to be imaged in real time. The growing significance of imaging modalities in biology is evident by the almost exponential increase of their use in research, from the molecular to the ecological level. The method of analysis described here allows totally non-invasive imaging of muscular activity (heart, somatic musculature) and the imaging of real-time pathway conduction and the localization of activity in peripheral nerve, spinal cord, brain stem, deep mesencephalic structures, and thalamo-cortical activity. Such imaging can be obtained without additional methodological steps such as the use of contrast media. An unexpected finding in this study was the ability to image activity associated with muscle pain. Thus, this method offers a non-invasive biomarker for muscular pain, and significantly of the very prevalent neck and back pain, which now relies mainly on the patient's report of signs and symptoms.

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Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

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Topic: I.04. Physiological Methods

Support: EU Horizon 2020 grant agreement

Title: Brain MRI at ultra-low field: New multifunction instrument

Authors: *K. C. ZEVENHOVEN, A. J. MÄKINEN, I. LEHTO, M. HAVU, R. J. ILMONIEMI Aalto Univ., Helsinki, Finland

Abstract: While conventional MRI has evolved towards increasingly high magnetic fields of several teslas, another approach has emerged, where the signal is detected in an ultra-low field (ULF) on the order of Earth's field. Despite many similarities, ULF-MRI differs from high-field MRI in several interesting ways. Using such low fields, the pulsed magnetic fields can be applied silently and with an open-geometry coil system. The detected kHz-range signal can be modeled from theory with high accuracy. The unique possibilities of ULF-MRI also include the combination of MRI and magnetoencephalography (MEG), the measurement of the weak magnetic fields generated by the electrical activity of the brain. ULF-MRI and associated methods such as current-density imaging (CDI) can significantly improve the localization of

brain activity.
To make ULF-MRI ready for commercial devices for research and clinical applications, we have put significant effort in improving the image quality. Furthermore, the spatial calibration of the system provides vital information for localizing brain activity and submillimeter registration for MEG-MRI. Our aim is to, one by one, solve the problems that limit the possibilities of ULF-MRI. The long-term goal is to bring imaging of electrophysiology to the next level.
Superconducting quantum-interference devices (SQUIDs) configured as pulse-tolerant magnetic-field sensors for ULF-MRI can also be used for MEG. Compared to our first hybrid prototype, our current-generation system uses more robust techniques and a new software platform. With dedicated ultra-low-noise amplifiers, it is possible to switch off even B0 during an imaging sequence. This enables encoding three-dimensional information for current-density imaging (CDI) using novel techniques. We also describe Dynamical Coupling for Additional dimensioNs (DynaCAN), a method using specifically designed pulse waveforms to couple to complex dynamics that have memory of their past. In ULF MRI, DynaCAN-based techniques are useful for solving various problems.
We demonstrate the state of the art of ULF-MRI technology and evaluate the techniques that have led to the dramatic improvements compared to the previous-generation prototypes.

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Poster

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Title: Effects of iTBS on dorsolateral prefrontal cortex, posterior parietal cortex, and primary motor cortex in older healthy adults: A TMS-EEG study

Authors: *A. JANNATI, P. J. FRIED, A. MENARDI, A. PASCUAL-LEONE, M. M. SHAFI
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Abstract: Background. Transcranial magnetic stimulation (TMS) techniques such as intermittent theta-burst stimulation (iTBS) enable the modulation of cortical and cortico-motor reactivity in humans. Concurrent TMS and electroencephalography (EEG) allow for the recording of TMS-evoked EEG potentials (TEPs). While the effects of iTBS over the primary motor cortex (M1) have been investigated in previous studies, the effects of iTBS on the reactivity of other brain regions, including dorsolateral prefrontal cortex (DLFPC) and inferior parietal lobule (IPL), remain poorly understood.
Methods. We examined the correlation between early TEPs from single TMS pulses before and after iTBS to the left DLPFC, the left M1, and the left IPL in 3 sessions in 14 older adults (age range: 50-80). Neuronavigated TMS was performed using the MRI-guided Nexstim eXimia system and a figure-of-eight biphasic coil. MEPs were recorded from the right first dorsal interosseous muscle. Single TMS pulses before and after iTBS were delivered at 120% of individual resting motor threshold. EEG was recorded with a 60-channel TMS-compatible EEG device. A passive-cooled figure-of-eight coil attached to a MagPro X100 stimulator was used to deliver iTBS (total of 600 pulses) at 80% of individual active motor threshold. Before and after iTBS, 3 blocks of 30 single TMS pulses were administered. Cortical reactivity was reassessed at 5, 10, and 20 minutes post-iTBS in each visit. For pre- and post-iTBS conditions, peak-to-trough amplitudes of N15-P30 TEPs (averaged over all post-iTBS trials) were determined. Average TEP amplitudes were calculated at all channels and separately at the region of interest (ROI). ROIs were defined bilaterally for M1 (FC3, FC1, FCZ, FC2, and FC4), DLPFC (F5, F1, FZ, F2, and F6), and IPL (CP5, CP3, CP1, CPZ, CP2, and CP4). Changes in the N15-P30 TEP amplitude were calculated as log(post-iTBS/pre-iTBS) in each ROI for each subject.
Results. Changes in M1 TEPs showed a moderate (and marginally significant) negative association with changes in DLPFC TEPs (r=-.56, p=.058) and a moderate (but non-significant) positive association with changes in IPL TEPs (r=.48, p=.13). Changes in IPL and DLPFC TEPs (r=0.34, p=0.30) were not significantly correlated with each other.
Conclusions. Overall, the impact of iTBS on TEPs was only modestly correlated across brain regions within individual subjects, suggesting that inferences about the effects of TMS neuromodulatory protocols on cortical reactivity across brain regions cannot be based solely on effects in primary motor cortex. The negative correlation between DLPFC and M1 TEPs might reflect the inhibitory motor control of the prefrontal cortex.

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Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

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Title: Continuous theta-burst stimulation (cTBS) measures of corticalplasticity in adults with autismspectrum disorder andneurotypical adults

Authors: A. JANNATI[1], *M. A. RYAN[2], G. BLOCK[2], L. M. OBERMAN[3], A. ROTENBERG[4], A. PASCUAL-LEONE[5,6]
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Abstract: We tested the utility of cortical plasticity measures by transcranial magnetic stimulation (TMS) delivered in a continuous theta-burst stimulation (cTBS) pattern as a physiologic biomarker in adults with autism spectrum disorder (ASD). Twelve high-functioning adults with ASD (11 males, age mean ± SD, 36.3 ± 12.0), and 23 neurotypical (NT) adults (22 males, age mean ± SD, 36.4 ± 14.3) underwent neuronavigated cTBS of the left primary motor cortex (M1). Stimulation was delivered by a figure-of-eight hand-held TMS coil. Each stimulation train consisted of 50 Hz bursts of three biphasic pulses repeated at 5 Hz for 40 seconds (for a total of 600 pulses), at an intensity of 80% of the individual active motor threshold

(AMT). Cortico-motor reactivity was assessed before and after cTBS by applying single biphasic TMS pulses to M1 at 120% of the individual resting motor threshold. Peak-to-peak amplitudes of motor evoked potentials (MEPs) were recorded from the right first dorsal interosseous muscle. Log-transformed, baseline-corrected MEP amplitudes (LnMEPs) were calculated at 5-, 10-, or 15-minute intervals between 5 and 60 minutes post-cTBS (*T5*-*T60*). Saliva samples were assessed for the Val66Met single-nucleotide polymorphism in the brain-derived neurotrophic factor (*BDNF*) gene. Logistic regression analyses found that, after controlling for AMT, cTBS aftereffects at T30 and T60 together significantly predicted whether a participant belonged to the ASD or the NT group: the model had 83.3% sensitivity and 85.7% specificity among *BDNF* Val66Val participants (n=20), whereas it had 100% sensitivity and 100% specificity among *BDNF* Val66Met participants (n=15). These results support the utility of cTBS as a physiologic biomarker for adults with ASD and emphasize the importance of considering *BDNF* genotypes in the analysis of the neurophysiologic results.

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Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

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Title: Towards a neurophysiological reactivity monitor (NERMO) to assess coma severity in stroke patients

Authors: *C. A. SERBAN[1,2,3], A. BARBORICA[1,2,3], C.-A. PISTOL[1,2], A. ROCEANU[4], I. MINDRUTA[4], J. CIUREA[5], A.-M. ZAGREAN[6], L. ZAGREAN[6], M. MOLDOVAN[7,6,2]
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Abstract: Background Our previous research (Nita et al. 2016) showed that during deep unconsciousness with burst-suppression EEG, the decrease in EEG suppression probability during photic stimulation, referred to as burst-suppression reactivity, correlates with coma

severity as measured by the Glasgow Coma Scale (GCS). **Hypothesis** We hypothesize that a binary reactivity measure can be used to assess post-stroke coma severity in patients with continuous EEG. **Objective** To develop and validate a novel analysis technique, the default EEG reactivity (DERI). **Methods** We recorded multi-channel EEG from comatose patients with strokes of different localizations and etiologies. A group of healthy volunteers served as controls. From each subject we recorded at least 6 EEG trials lasting 3 minute each. Each trial comprised of a 1-minute stimulation (STIM) epoch preceded by a 1-minute baseline (PRE). During STIM, repeated stimuli were delivered with a frequency of 1 Hz either as binocular flashes or electrical stimuli to the median nerve at wrist. To distinguish changes in arousal we recorded heart rate variability (HRV). To further identify changes in awareness we conducted an additional series of measurements using auditory subject's own name (SON) stimuli. The STIM epoch consisted of repeated SONs generated by a native language voice synthesizer. The SON trials were alternated with trials where the SON was played in reverse (rSON). For each trial we calculated the default EEG reactivity index (DERI) by segmenting the EEG into consecutive classes with similar topographic frequency distribution and then identifying the default class with the largest decrease in occurrence probability from PRE to STIM. DERI was quantified from the binary default class as the relative decrease in probability (PRE-STIM)/PRE. Given the relatively short recording duration, HRV was quantified by the standard deviation of normal-to-normal intervals (SDNN). An awareness index was defined as mean DERI(SON) - mean DERI(rSON). **Results** We found that a mean DERI lower than 40% could discriminate comatose patients from controls irrespective of stimulation modality. The reduction in DERI appeared independent of arousal measures derived from SDNN. The AI was 24.1 % in controls and only -0.3 % in unconscious patients. **Discussion** Our data suggest that DERI (patent pending) and its derivate measures such as AI in conjunction with autonomic nervous system reactivity measures provide a valid neurophysiological measure of coma severity. We therefore feel encouraged to develop a hardware neurophysiological EEG reactivity monitor (NERMO) to facilitate long term DERI tracking to assess coma severity.

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Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

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Program #/Poster #: 520.16/JJJ60

Topic: I.04. Physiological Methods

Support: Grants-in-Aid for Science Research on Innovative Areas "Brain Information Dynamics" (18H05114)

Title: Simultaneous monitoring of intact respiratory signals and membrane potentials of CA1 pyramidal neurons in mice

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Abstract: Respiratory function is essential for survival. Besides, information processing related to respiration in the brain is also crucial. However, it has been controversial whether hippocampal neuronal activity is correlated with respiration. To fully understand the relationship between them, it is necessary to monitor intact and accurate respiratory signals. Conventionally, a thermal / CO_2 sensor is put into the nasal cavity to measure respiratory rhythm, but it obstructs nasal airway and affects respiratory rate itself. Thus, this method does not provide intact respiratory information. To work on this issue, we devised a method to monitor intact respiratory rhythms, which does not obstruct nasal airway. Based on the idea that respiration is likely to drift thoracic impedance, we implanted an electrode into pectoral muscles of anesthetized mice, thereby recorded electrocardiograms (ECGs). Then, we derived low frequency components from ECGs using the fast Fourier transform (FFT), and demonstrated that the low frequency oscillations corresponded to the respiratory rhythms. We confirmed that the low frequency was identical to the frequency of the side abdominal movement and the local field potentials (LFPs) of the olfactory bulb, which were regarded as respiratory indicators. In addition, even when the respiration was manipulated by the injection of respiratory stimulant (acetazolamide) or depressant (diazepam), we confirmed that all the three bio-signals shifted in parallel. Furthermore, even in awake (but immobile) mice, the respiratory signals were isolated from ECGs. Finally, we simultaneously performed ECG recordings and *in vivo* whole-cell patch-clamp recordings from hippocampal CA1 neurons of anesthetized mice. Interestingly, on the membrane potential level, some (but not all) CA1 neurons oscillated intermittently coherent with respiratory rhythm. In conclusion, we provided a simple and less-invasive technique to obtain the respiratory signals, which is co-applicable to various physiological and pharmacological experiments. This respiration-deriving algorithm is so simple that it can feed back the respiratory information to animals in real-time, which will disclose the causal relationship between the neural system and respiration.

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Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

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Topic: I.04. Physiological Methods

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KMA

Title: Development of three-dimensional (3D) cell culture models of the human brain

Authors: *U. ENGLUND JOHANSSON[1], M. CASTRO ZALIS[2], A. BRUZELIUS[2], S. JOHANSSON[2], F. JOHANSSON[3]
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Abstract: Studying the human brain require sophisticated models to reconstitute the complex architecture and functions of brain cells. *In vitro* models are essential for precise measurements in controlled conditions. However, existing models are limited in their capacity to replicate the three-dimensional (3D) environment, complex interactions between brain cells and physiology. Therefore, we here study novel 3D human neural cell culture systems, using engineered bioscaffolds and validation against corresponding 2D cell cultures and later relevant animal models for advancing brain research. We fabricated polycaprolactone (PCL) fibrous substrates using electrospinning, consisting of either randomly-- and aligned oriented fibers (thickness: 6 μm, fiber diameter: 550--700 nm). Human neural progenitor cells (HNPC), were cultured for 10- to 20 days on 3D scaffolds or 2D (flat) glass surfaces. Immuno- and biochemical assays and microarrays were used to study gene expression profiles, viability, neurogenic potential and morphometry. PCL scaffolds were found very permissive for survival and attachment of the HNPC. Morphological formation was strongly influenced by culture substrates, with significantly more multipolar morphologies found at random fibers and flat controls. In addition, focal adhesion points formed varied between 2D and 3D substrates, as well as nuclear shape. Preliminary data reveals a significant increase in neuronal differentiation, and decrease in neural stem cells on 3D scaffolds compared to flat surfaces. On-going analysis demonstrates a trend towards different gene expression profiles after culture at 2D and 3D surfaces respectively. Our results demonstrate that the topography indeed matters for the cell fate of cultured human neural progenitor cells, i.e. 3D artificial scaffolds shows great promise for the development of novel and more in-vivo like models of the human brain. Such 3D biomimetic cell culture models of the human brain may indeed serve as an important i*n vitro* screening tool in future drug discovery.

Disclosures: U. Englund Johansson: None. **M. Castro Zalis:** None. **A. Bruzelius:** None. **S. Johansson:** None. **F. Johansson:** None.

Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 520.18/JJJ62

Topic: I.04. Physiological Methods

Support: NIH Grant NINDS R33 NS088358

Title: 3D cultures from rat and human IPSC derived neurons exhibit epileptic seizure-like activity

Authors: *M. HASAN[1], S. GHIASVAND[2], Y. BERDICHEVSKY[1,2]
[1]Dept. of Electrical and Computer Engin., [2]Dept. of Bioengineering, Lehigh Univ., Bethlehem, PA

Abstract: Most of the current in vitro epilepsy models use brain slices, which limits these models' experimental throughput.. Here, we present a simple yet novel and high-yield method to create Polydimethylsiloxane (PDMS) confined scaffold-free 3D neuronal cultures from dissociated rat cortex that show spontaneous culture-wide synchronized seizure-like activity without the application of any convulsant agent. These 3D cultures are far more amenable to high-throughput studies than slices. Genetically encoded Ca^{2+} indicator R-GECO1(1) and Micro-electrode array was used to optically and electrically observe the neuronal activity from these cultures. Spontaneous bursts were significantly longer than those observed in 2D dissociated neuronal cultures, but similar to epileptiform activity in hippocampal slices. Application of Tetrodotoxin and Kynurenic acid abolished all burst activity, indicating the key role of neuronal firing and glutamatergic network behind seizure-like activity. Application of anti-epileptic drug (AED) Phenytoin resulted in concentration-dependent modulation of total activity duration. 3D cultures from human induced pluripotent stem cell (hIPSC) derived neurons also exhibited similar seizure-like activity. This method can potentially provide a new and better way for high-throughput anti-epileptic drug (AED) screening. A patient-specific drug development system also becomes feasible with the integration of hIPSC with this technique.

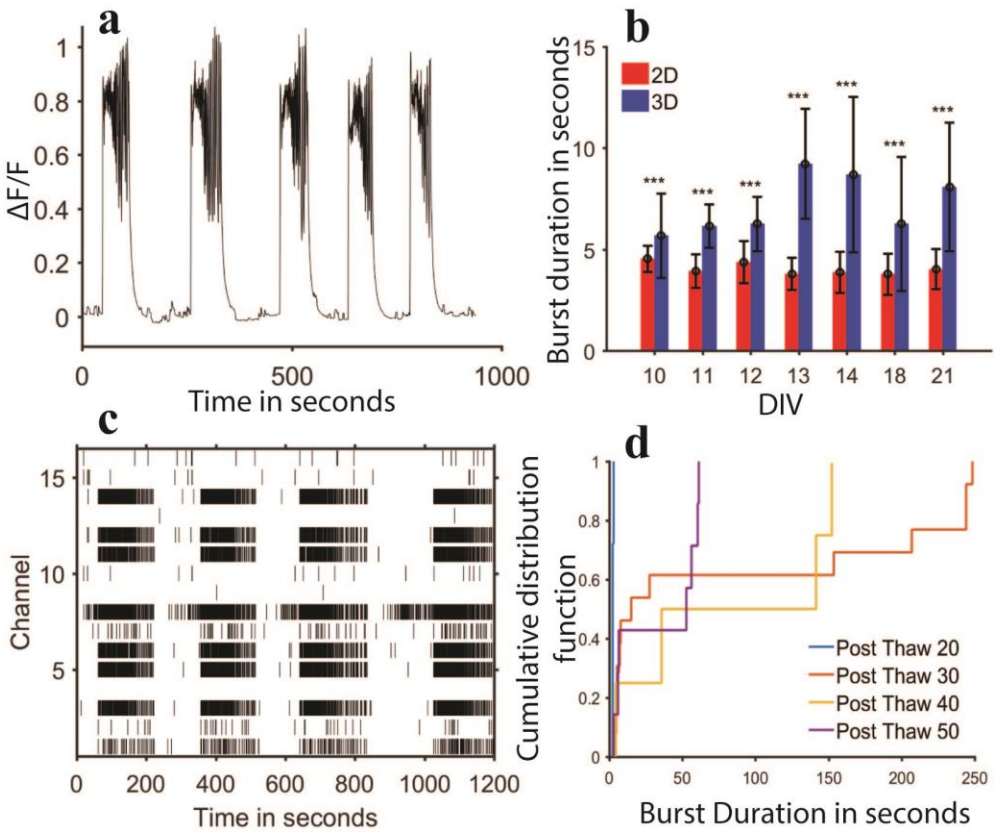

Figure 1: a) Fluorescence changes and c) raster plot of 16 channel MEA recorded extracellular field potential of rat 3D culture on DIV 14, b) Mean with standard deviation of burst duration of rat 2D and 3D cultures on different DIVs. (n=15, 19, 16, 16, 19, 140, 55 and n=21, 28, 18, 19, 39, 116, 32 for 3D and 2D cultures respectively, ***= P<=0.001 for t-test)) d) CDF of burst duration across different post-thaw days for 3D cultures created with hIPSC derived neurons.
(1) Yongxin Zhao et al., An Expanded Palette of Genetically Encoded Ca2+ Indicators, Year 2011, Vol. 333, pp. 1888-1891

Disclosures: M. Hasan: None. **S. Ghiasvand:** None. **Y. Berdichevsky:** None.

Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 520.19/JJJ63

Topic: I.04. Physiological Methods

Title: Highly homogeneous and highly functional 3-dimensional human cortical spheroids applied to high throughput and high content screening platform in drug discovery

Authors: *C. CARROMEU, S. DEA, S. BIESMANS, S. MORA-CASTILLA, S. ROMERO, A. SALEH, F. ZANELLA
Stemonix, San Diego, CA

Abstract: The human cerebral cortex is organized in a complex 3-dimensional (3D) structure comprising different neural cell types. The coordinated work of these different cell types is key for brain function and homeostasis. Recently, much work has been focused on obtaining 3D brain organoids in an attempt to better recapitulate the brain development/function *in vitro*. However, current protocols may lead to variable organoid size and function, making the use of these powerful tools impractical in an investigative toxicology setting. Here we describe the development of a highly homogenous human induced Pluripotent Stem Cell (hiPSC)-derived cortical spheroid screening platform in 384 well format, composed of neurons and astrocytes. Immunofluorescence analysis confirmed the cortical identity of the cells. Viability assays carried out with compounds with known mechanism of action indicated scalability and feasibility of the assays, with results comparable to a standard 2D model employing the same culture composition. High trhoughput calcium flux analysis performed in a Fluorometric Imaging Plate Reader (FLIPR) highlighted that the spheroids present quantifiable, robust and uniform spontaneous calcium oscillations. The calcium signal was modified with excitatory and inhibitory modulators coherently and in a highly reproducible fashion. High speed confocal imaging confirmed homogenous calcium oscillations at the cellular level, whereas multielectrode array (MEA) analysis demonstrated robust synchronous neurophysiological activity at the network level. Altogether, the developed 3D cortical spheroid platform can be easily implemented as a reliable high throughput screening platform to investigate complex cortical phenotypes *in vitro*, as a reliable high-throughput screening platform for toxicology studies, disease modeling and drug testing.

Disclosures: C. Carromeu: None. **S. Dea:** None. **S. Biesmans:** None. **S. Mora-Castilla:** None. **S. Romero:** None. **A. Saleh:** None. **F. Zanella:** None.

Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 520.20/JJJ64

Topic: I.04. Physiological Methods

Support: NIH/NIEHS RES024644B

Title: Three-dimensional cultures of ipsc-derived human motor neurons and tracheal smooth muscle cells in high-throughput format using magnetic 3D bioprinting

Authors: *G. R. SOUZA[1], W. HAISLER[2], B. LARSON[3], M. L. HENDRICKSON[4]
[1]Greiner Bio-One North America, Houston, TX; [2]Greiner Bio-One, Monroe, NC; [3]BioTek, Winooski, VT; [4]BrainXell, Inc., Madison, WI

Abstract: Three-dimensional (3D) neuronal cultures present an opportunity to more accurately model the nervous system and allow for more applicable pharmacology, toxicity, and developmental studies. Magnetic 3D cell culture enables these cultures to be combined with somatic target cells to create functional units that can be manipulated in vitro. Toward this goal, we were able to successfully magnetize and create 3D cultures with iPSC-derived human motor neurons (MNs) from BrainXell using the standard protocol for suspension cells combined with the neuron protocol. We also generated co-cultures with tracheal smooth muscle cells (SMCs) using equal numbers of cells of each type and equal amounts of each media. Cells magnetically levitated in a 24 well plate displayed a normal morphology. MN cultures magnetically bioprinted into rings and spheroids in a 384-well plate did not show significantly significant mobility but did become cohesive structures. Bioprinted co-cultures with SMCs did show considerable movement in the first 24 hours and retained their cohesive shape in the following days. The numbers of MNs and SMCs and their ratio were optimized in 384-well format for both ring and spheroid patterns. Our results demonstrate the feasibility of this approach to produce three-dimensional neuronal and neuronal-smooth muscle systems with more physiologically relevant structures.

Disclosures: G.R. Souza: A. Employment/Salary (full or part-time):; full. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock, stock option, royalty. **W. Haisler:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stock option. **B. Larson:** None. **M.L. Hendrickson:** None.

Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 520.21/JJJ65

Topic: I.04. Physiological Methods

Support: CIRM Bridges 2.0 EDUC2-08391

Title: Application of atmospheric pressure and hypoxia during culture promotes neural induction of iPSCs and subsequent differentiation into motor and CNS-type neurons

Authors: Z. PAPPALARDO[1], *B. A. ADAMS[2]
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Abstract: Induced pluripotent stem cells (iPSCs) can be used for autologous regenerative medicine to treat a multitude of health conditions, including spinal cord injuries and neuropathology-associated genetic disease. iPSCs can successfully differentiate to neural progenitor cells (NPCs), a multipotent stem cell population that can give rise to all lineages of adult neuronal cells. However, a confounding limitation of differentiated neurons from iPSC-derived NPCs is that they are not genetically and functionally equivalent to adult neurons in vivo, thus rendering them sub-optimal for studying pharmaceutical or environmental responses in the dish. Recent studies highlight the significance of micro-environmental factors such as hypoxia and mechanical force / pressure on stem cell maintenance and directed-differentiation to specific cell lineages, yet none have evaluated the combined contribution of these factors towards differentiation of iPSCs to NPCs or on the differentiation of NPCs into adult neurons. Here we demonstrate the biological impact of oxygen and atmospheric pressure on differentiation of human iPSCs to NPCs as well as on differentiation of both motor and central nervous system-type neurons using the AVATAR™ cell control system. For this study, we demonstrate that combinatorial oxygen and pressure are significant drivers of neural ectoderm differentiation from multiple human iPSC lines. We compared either 5% versus 15% oxygen and increased pressure (+2 PSI) versus atmospheric pressure during culture of human iPSCs and show an induction of neural ectoderm by PAX6 and NESTIN staining specifically in cultures exposed to higher atmospheric pressure. We further show that low oxygen and increased pressure promotes the differentiation and survival of central nervous system-type neurons and motor neurons as determined by the enhanced and pro-longed expression of mature neuronal markers using immunofluorescence microscopy. Our findings suggest that physiologically relevant oxygen and pressure are important drivers of neural differentiation from human iPSCs, and that these micro-environmental factors have the potential to induce maturation of neurons such that they are better suited for translational studies in vitro and in the clinic.

Disclosures: Z. Pappalardo: None. **B.A. Adams:** None.

Poster

520. New Behavioral, In Vivo, and In Vitro Physiological Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 520.22/JJJ66

Topic: I.04. Physiological Methods

Support: IBS grant IBS-R015-D1

Title: Conductive self-assembling peptide-based hydrogel for highly effective neural interface

Authors: *J. NAM[1], H. LIM[5,2], M. SUH[5,3,6,7], Y. KIM[1,5,3,7,4]
[1]SKKU Advance Inst. of Nanotechnology (SAINT), [2]Dept. of Biol. Sci., [3]Dept. of Biomed. Engin., [4]Dept. of Chem., Sungkyunkwan Univ., Suwon, Korea, Republic of; [5]Ctr. for Neurosci. Imaging Research, IBS, Suwon, Korea, Republic of; [6]Dept. of Hlth. Sci. and Technol., Samsung Advanced Inst. for Hlth. Sci. & Technology, Sungkyunkwan Univ., Seoul, Korea, Republic of; [7]Biomed. Inst. for Convergence at SKKU (BICS), Suwon, Korea, Republic of

Abstract: The biomechanical dissimilarity between rigid electrodes and soft neural tissues is a recurring problem in recording neural activity from the live brain, yet the development of stable neural interface that enables a complete biointegration remains a challenge. Self-assembling peptide has great advantages in developing a new biomaterial because along with its inherent biocompatibility, chemical and physical properties in macroscopic level can be controlled by sequence modulation. However, unwanted proteolytic degradation of α-peptide based material imposes challenges on chronic utilization. Here, we presented a conductive, biocompatible, and biostable neural interface with a peptidomimetic foldamer-based biopolymer hydrogel which forms a complex with carbon nanotubes (CNTs). To endow conductivity into β-peptide based hydrogel with controlled features of excellent structural and proteolytic stability, hierarchical assembly of β-peptide was designed to self-assemble into nanofiber that associate with carbon nanotubes (CNTs). Transmittance electron microscopy images revealed the end-to-end assembling of β-peptide nanofibers and tight wrapping of the nanofibers around CNTs. The intercortical and epidural neural signal recorded with the conductive hydrogel were founded to be augmented, especially in high frequency range, due to increased contact area and tight coupling with neural tissues. The soft hydrogel-based neural interface suggests many possibilities for developing advanced neural implants with secured signal reliability.

Disclosures: J. Nam: None. **H. Lim:** None. **M. Suh:** None. **Y. Kim:** None.

Poster

521. Computation, Modeling, and Simulation: Network Models: Experimentation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 521.01/JJJ67

Topic: I.06. Computation, Modeling, and Simulation

Support: BBSRC grant BB/L002353/1
BBSRC grant BB/L000814/1
BBSRC grant BB/L00111X/1

Title: A computational model of sensory pathway integration and motor decision making in the xenopus tadpole

Authors: *A. FERRARIO[1], R. BORISYUK[1], S. KOUTSIKOU[2], W. LI[3], R. MERRISON-HORT[1], A. ROBERTS[4], S. SOFFE[4]
[1]Plymouth Univ., Plymouth, United Kingdom; [2]Medway Sch. of Pharm., Univ. of Kent, Chatham Maritime, United Kingdom; [3]Univ. of St Andrews, St Andrews, United Kingdom; [4]Univ. of Bristol, Bristol, United Kingdom

Abstract: What are the neuronal mechanisms underlying decision making? A general approach to studying this problem is to postulate that the information from different noisy sensory signals is integrated and temporarily stored to guide decisions (Gold & Shadlen, 2007, Annual review of neuroscience, 30). For motor decisions, this integration process can lead to long and variable delays between sensory activation and the first motor response. Where does this accumulation occur? Using computational modelling, we explore how multiple sensory signals activation lead to the decision to swim in hatchling Xenopus tadpoles. This animal provides a good system to study decision making because the repertoire of sensory signals is small, and many biological details are known. Recordings from brainstem reticulospinal neurons driving swimming show they receive slow, variable synaptic excitation which would allow integration of sensory inputs and explain the long, variable delays to swimming. There are at least four different sensory pathways whose stimulation can lead to starting or stopping. Swimming can be reliably started by trunk skin stimulation (TS), head touch (HT) or by activation of photoreceptors in the pineal eye by light dimming (LD). It can be reliably stopped by head skin pressure (HP). In each of these pathways distinct neuronal populations process the sensory signal which can start/stop locomotion. Previously we developed a model of the TS sensory pathway and a central pattern generator network which mimics swimming initiation following skin touch. Led by new experimental findings, we improve this model by adding new neuron populations which relay the sensory signals initiating swimming. Additionally, we include new populations for the other sensory pathways. We use the Hodgkin-Huxley formalism to describe neuronal and synaptic properties, based on previous experimental and computational data. Our model represents a biologically realistic reconstruction of the known tadpole's swimming neuronal network and it can reproduce the initiation, stopping and maintenance of the animal's swimming behavior. In agreement with experiments, the model suggests two distinct mechanisms for decision-making: (1) the TS and LD pathways generate slow and variable summation of excitation to threshold, and provide a simple mechanism of working memory. (2) The HP and HT pathways can provide much faster and less variable decisions, more comparable to reflex response times. Our computational model provides a framework for exploring multi-sensory integration and simple motor decision making, to generate new ideas and hypotheses for experimental testing.

Disclosures: A. Ferrario: None. **R. Borisyuk:** None. **S. Koutsikou:** None. **W. li:** None. **R. Merrison-Hort:** None. **A. Roberts:** None. **S. Soffe:** None.

Poster

521. Computation, Modeling, and Simulation: Network Models: Experimentation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 521.02/JJJ68

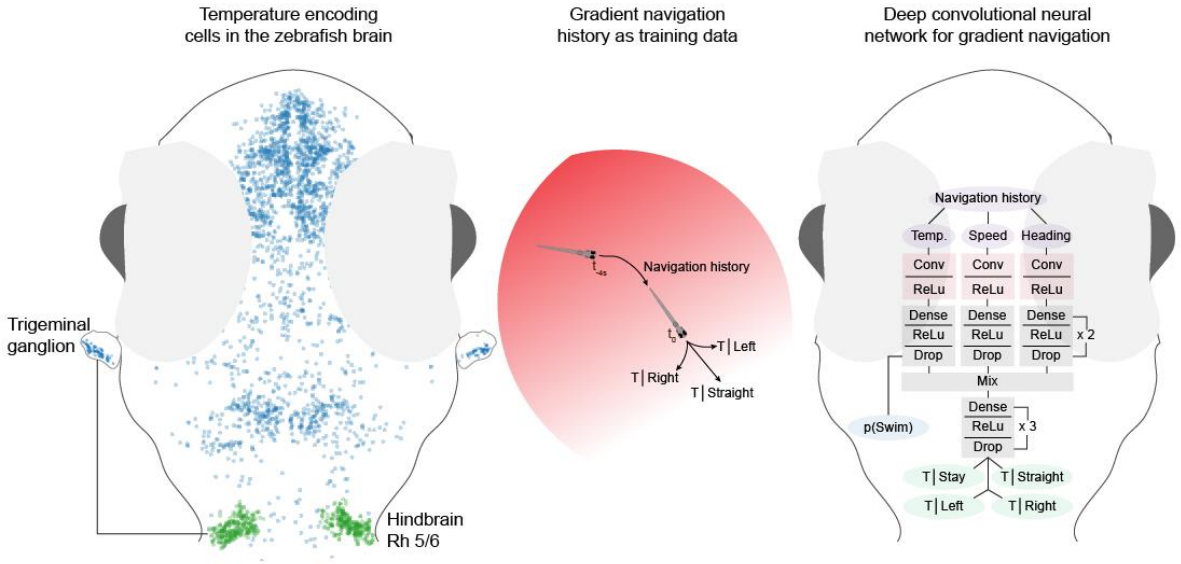
Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant 1U19NS104653
NIH Grant 1DP1HD094764

Title: Convergent evolution of artificial and biological neural networks performing heat gradient navigation

Authors: *M. HAESEMEYER[1], A. SCHIER[1,2], F. ENGERT[1]
[1]Harvard Univ. Biolabs, Harvard Univ., Cambridge, MA; [2]Univ. of Basel, Biozentrum, Basel, Switzerland

Abstract: Brains represent the external world in form of concerted neuronal activity. While the neural encoding of stimuli could be arbitrary, it is expected that stimuli are represented in a way that facilitates important tasks such as categorization or the generation of adaptive behaviors. This view is well supported by neuroscience studies that uncovered preferential representations of stimulus features important for behavior generation. However, in animals it is very difficult to ascertain a causal relationship between goals and behavioral repertoire on the one hand and neural stimulus representation on the other. Here, we train deep convolutional neural networks that are constrained to predict the consequences of behavioral actions within a heat gradient using either a zebrafish or *C. elegans* behavioral repertoire. This allowed us to test whether these constraints alone lead to a neural representation of temperature observed in the animals themselves. Indeed, we find striking similarities between representation of temperature in the artificial networks and true neural representations. Interestingly, in spite of the same underlying network structure, representations differ when constrained by zebrafish versus *C. elegans* behavioral output. The networks furthermore allow to generate regressors for and identify previously missed response types in the zebrafish brain. At the same time, ablating cell types corresponding to real zebrafish neurons severely impacts gradient navigation performance of the networks while they are robust to deletions of other types. Importantly, retraining networks after ablations was only successful if they were allowed to recover fish-like neuron types. These results strongly suggest that neural stimulus representations can be seen as an optimal consequence of behavioral goals and motor repertoires.



Disclosures: M. Haesemeyer: None. **A. Schier:** None. **F. Engert:** None.

Poster

521. Computation, Modeling, and Simulation: Network Models: Experimentation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 521.03/JJJ69

Topic: I.06. Computation, Modeling, and Simulation

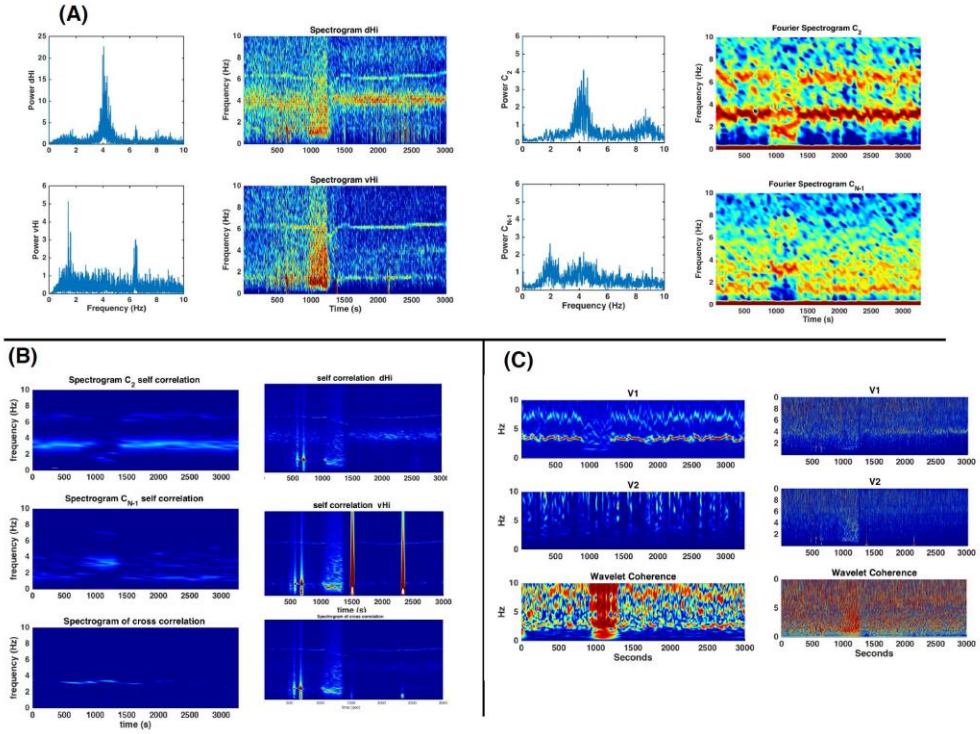
Support: CONACYT CB-238744
CONACYT CB-283279
DGAPA-UNAM-PAPIIT IN216214

Title: Analysis and modeling of low frequency local field oscillations in a hippocampus circuit under osmotic stimuli

Authors: *H. BARRIO[1], A. MOLINA[1], V. S. HERNANDEZ[1], T. GOVEZENSKY[2], R. A. BARRIO[3], L. ZHANG[1]
[1]Physiology, Fac. of Med., [2]Inst. de Investigaciones Biomedicas, [3]Inst. of Physics, Univ. Nacional Autonoma de Mexico, Ciudad de Mexico, Mexico

Abstract: Time series analysis is known to be a useful tool in the study of the dynamics and characteristics of complex systems, such as neural interactions. This study explores the behavior of different analytical methods for measurements made inside of two regions of interest of the

hippocampus, dorsal and ventral CA2 regions, of adult male Wistar rats. A 2% body weight volume of a 900 mM NaCl (hyperosmotic) solution, was intraperitoneally injected to perturbate the hypothalamus activity and measurements were obtained using electrodes inserted in the hippocampus to observe the local field potential (LFP). The resulting data was analyzed using Fourier Transformations and Wavelet Analysis. In all the methods it was observed that there was a modification in the delta (0.1 - 4.0 Hz) and an increase theta (4.0 -8.0 Hz) oscillations after the solution injection into the rat. A comparison between the signals was then done to determine the quality of the data and correlation methods were used to determine if there was any coherence between the signals due to the perturbation, under the hypothesis that the strength of the functional connections between the vasopressinergic hypothalamic magnocellular neurons and their target in the hippocampus is affected by the hyperosmotic solution. Results showed an increased coherence for these regions which would suggest that increased activity in the hypothalamus provides neuromodulatory input to the hippocampus, as well as enhancing functional coupling between the theta oscillations. Based on the hypothesis of these connections, a model is then developed to emulate the behavior of the signals observed. On the figure provided for this abstract we can see an example of the experimental and theoretical results obtained in this work: Shows comparison of (A) Analysis of the Fourier transform, (B) the correlation analysis and (C) the Wavelet analysis. The results of the theoretical model and those of the experiment show a similar behavior which reinforce the hypothesis of the connections between the hypothalamus and the hippocampus proposed in this study.



Disclosures: H. Barrio: None. **A. Molina:** None. **V.S. Hernandez:** None. **T. Govezensky:** None. **R.A. Barrio:** None. **L. Zhang:** None.

Poster

521. Computation, Modeling, and Simulation: Network Models: Experimentation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

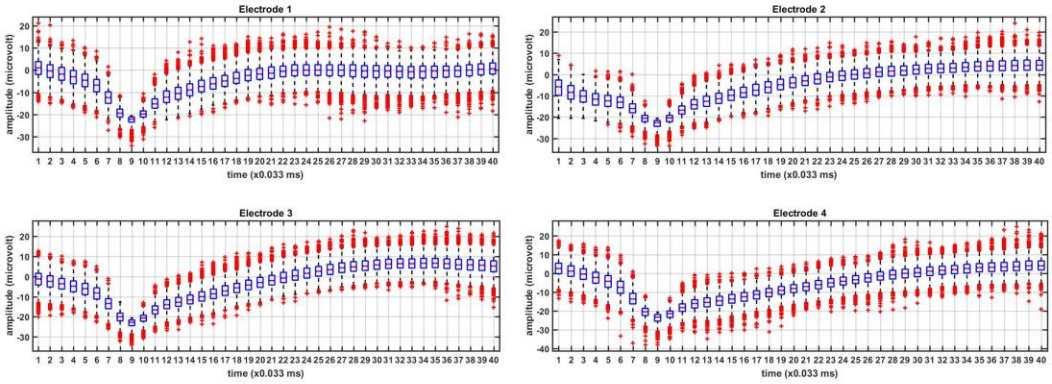
Program #/Poster #: 521.04/JJJ70

Topic: I.06. Computation, Modeling, and Simulation

Title: Development of bidirectional 'mini-Brain' computer interface (mBCI) to modulate functional neural circuits - stimulation and recording from a cerebral organoid

Authors: M. BHATTACHAR[1], *A. DUTTA[3], D. FREEDMAN[2], E. K. STACHOWIAK[4], M. K. STACHOWIAK[5]
[1]Biomed. Engin., [2]Anatom. Sci., Univ. at Buffalo SUNY, Buffalo, NY; [3]Biomed. Engin., Univ. At Buffalo SUNY, Buffalo, NY; [4]SUNY, Buffalo, Buffalo, NY; [5]State Univ. New York Buffalo, Buffalo, NY

Abstract: INTRODUCTION Electrophysiology can be a powerful technique in deciphering functional microcircuits based on the evoked responses. In this exploratory work, we developed a bidirectional stimulation and recording system using tetrodes and Intan RHD2132 amplifier board for cerebral organoids. We hypothesized that evoked responses generated by multi-neuronal activation in the vicinity of the stimulating electrode would reveal the maturity of the neuronal circuit. METHODS Cerebral organoids were generated using a modified protocol published earlier [1]. We stimulated a 48-day old cerebral organoid using a platinum/iridium wire (dia: 25 µm) and recorded using a polyimide-coated nickel-chrome tetrode wire (dia: 50µm). We conducted spike detection and computational analysis of the tetrode data using custom code in Matlab. RESULTS Spontaneous neuronal activity was not detected in the 48-day old cerebral organoid, however, multi-neuronal activity could be evoked with electrical stimulation. Computational analysis of the evoked responses (see Figure: boxplot of the spikes) revealed correlated tetrode data. We found that our mBCI setup is capable of stimulation, multi-unit recording and online spike sorting. DISCUSSION We showed that continuous online monitoring of the tetrode data is feasible to detect evoked multi-neuronal activity, however, correlated data indicated weak connections and lack of circuit maturation. To detect spontaneous activity, longer cultured organoids are being examined and electrophysiology data compared with two-photon calcium imaging based on prior work in adult fly brain [2]. Furthermore, spontaneous activity triggered stimulation is possible with our mBCI to guide "Hebbian" learning and microcircuit maturation which will be a useful tool for the electrophysiology-based research in cerebral organoids. REFERENCES [1] E. K. Stachowiak et. al. Translational Psychiatry, 7(6) (2017). [2] J. D. Seelig et al. Nat Methods, 7(7):535-540 (2010).



Disclosures: M. Bhattachar: None. **A. Dutta:** None. **D. Freedman:** None. **E.K. Stachowiak:** None. **M.K. Stachowiak:** None.

Poster

521. Computation, Modeling, and Simulation: Network Models: Experimentation

Location: SDCC Halls B-H

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Program #/Poster #: 521.05/LLL1

Topic: I.06. Computation, Modeling, and Simulation

Support: grant agreement no. 604102 (HBP)
grant agreement no. 720270 (HBP SGA1)

Title: Acetylcholine regulates redistribution of synaptic efficacy in neocortical microcircuitry

Authors: *C. COLANGELO[1], A. KHUBIEH[2], H. MARKRAM[3], S. RAMASWAMY[4]
[1]EPFL Blue Brain Project, Geneva, Switzerland; [2]EPFL, Lausanne, Switzerland; [3]EPFL, Blue Brain Project, Lausanne, Switzerland; [4]EPFL - Blue Brain Project, Geneva, Switzerland

Abstract: Acetylcholine is one of the most widely characterized neuromodulatory systems involved in the regulation of cortical activity. Cholinergic release from the basal forebrain controls neocortical network activity and shapes behavioral states such as learning and memory. However, a precise understanding of how acetylcholine regulates local synaptic transmission that reconfigures global brain states remains poorly understood. To fill this knowledge gap, we analyzed whole-cell patch-clamp recordings from connected pairs of neocortical neurons to investigate how acetylcholine release modulates synaptic transmission. We found that bath-application of 10 µM carbachol differentially redistributes the available synaptic efficacy and the short-term dynamics of excitatory and inhibitory connections. We propose that redistribution of synaptic efficacy by acetylcholine is a potential means to alter content, rather than the gain of information transfer of synaptic connections between specific cell-types in the neocortex.

Disclosures: C. Colangelo: None. **A. Khubieh:** None. **H. Markram:** None. **S. Ramaswamy:** None.

Poster

521. Computation, Modeling, and Simulation: Network Models: Experimentation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 521.06/LLL2

Topic: I.06. Computation, Modeling, and Simulation

Support: This work was supported by funding from the ETH Domain for the Blue Brain Project. The Blue Brain Project's IBM BlueGene/Q system, BlueBrain IV, was funded by the ETH Board and hosted at the Swiss National Supercomputing Center (CSCS).

Title: Recurrent neocortical circuitry supports spike-time reliability amidst cellular noise and chaos

Authors: *M. NOLTE, M. W. REIMANN, J. G. KING, H. MARKRAM, E. B. MULLER
Blue Brain Project, EPFL, Geneva, Switzerland

Abstract: Electrical activity of neocortical neurons *in vivo* is highly variable. The reliability of spike times in response to sensory stimuli is constrained by the amount of variability that arises directly from noise sources within local cortical circuitry, as opposed to encoding unobserved external signals. High internally generated variability would imply that the precise time of a spike cannot matter for coding, as is often suggested. However, the internally generated variability has been impossible to measure *in vitro* or *in vivo*. Here, we estimated this variability during spontaneous and evoked activity using the Blue Brain Project's digital reconstruction of neocortical microcircuitry. The reconstruction contains biological noise sources, such as synaptic noise and ion-channel noise, and detailed synaptic connectivity. We found that the variable neurotransmitter release due to synaptic noise is amplified by recurrent connectivity to cause highly variable, chaotic *spontaneous* activity. However, we found that relatively weak thalamocortical stimuli can *evoke* reliable packets of activity with millisecond spike-timing precision amidst the noise and chaos. These reliable events require the recurrent neocortical connectivity and are not a mere result of feed-forward thalamocortical input. We conclude that cortical circuitry supports millisecond-precision spike-time reliability amid highly variable, chaotic network activity. This resolves a vast body of conflicting previous studies.

Disclosures: M. Nolte: None. **M.W. Reimann:** None. **J.G. King:** None. **H. Markram:** None. **E.B. Muller:** None.

Poster

521. Computation, Modeling, and Simulation: Network Models: Experimentation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 521.07/LLL3

Topic: I.06. Computation, Modeling, and Simulation

Support: The ETH Domain for the Blue Brain Project (BBP)
The Human Brain Project through the European Union Seventh Framework Program (FP7/2007-2013) under grant agreement no. 604102 (HBP)
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The Cajal Blue Brain Project (MINECO)
The BlueBrain IV BlueGene/Q system is financed by ETH Board Funding to the Blue Brain Project as a National Research Infrastructure and hosted at the Swiss National Supercomputing Center (CSCS)
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This research used resources of the Argonne Leadership Computing Facility, which is a DOE Office of Science User Facility supported under Contract DE-AC02-06CH11357

Title: Stability of synaptic weights in a biophysical model of plasticity in the neocortical microcircuit without explicit homeostatic mechanisms

Authors: *M. W. REIMANN[1], G. CHINDEMI[2], E. B. MULLER[3], H. MARKRAM[4]
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Abstract: Spike-timing dependent synaptic plasticity has been characterized on a pairwise level in vitro. However, many of the identified forms of plasticity are inherently unstable in recurrent networks. For example, for hebbian-style plasticity the strengthening of a connection increases the likelihood that it will be strengthened further, leading to runaway potentiation. Homeostatic mechanisms have been proposed to stabilize the system, but physiological evidence for them remains indirect and inconclusive. For a morphologically detailed model of a cortical microcircuit in conjunction with a biologically constrained, calcium-based model of plasticity we characterized the stability of plastic connectivity in a population of neurons in the absence of an explicitly homeostatic mechanism. We explored the evolution of the strengths of 24 million recurrent glutamatergic synapses and their stability under in-vivo-like conditions with simulated external input. We found that while individual synapse weights evolved significantly, there was a remarkable degree of stability in terms of average synaptic strength both on the single cell and

population level. We then further characterized how the observed shift of synaptic strength between individual synapses affected the response properties of neurons, such as their average firing rates or their selectivity for individual stimuli and observed an increase in both for neurons in cortical layer 5.

Disclosures: M.W. Reimann: None. **G. Chindemi:** None. **E.B. Muller:** None. **H. Markram:** None.

Poster

521. Computation, Modeling, and Simulation: Network Models: Experimentation

Location: SDCC Halls B-H

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Program #/Poster #: 521.08/LLL4

Topic: I.06. Computation, Modeling, and Simulation

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The BlueBrain IV BlueGene/Q system is financed by ETH Board Funding to the Blue Brain Project as a National Research Infrastructure and hosted at the Swiss National Supercomputing Center (CSCS)
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This research used resources of the Argonne Leadership Computing Facility, which is a DOE Office of Science User Facility supported under Contract DE-AC02-06CH11357

Title: Improved memory efficient software workflow for data driven model building and simulation

Authors: *J. G. KING[1], P. S. KUMBHAR[1], J. FOURIAUX[1], G. CHINDEMI[1], F. PEREIRA[1], M. L. HINES[2], F. DELALONDRE[1], F. SCHUERMANN[1], H. MARKRAM[1]
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Abstract: The Blue Brain Project (BBP) is a data driven platform for developing biologically detailed neuronal models. We have worked on advancing software tools to enable *in silico* scientists to build tissue models of different brain regions and execute simulations on a variety of computational hardware. Our circuit building toolchain now uses Spark technology to handle

large-scale analysis necessary to process touches between neuronal branches in order to create the final set of functional, parameterized synapses. On the simulation side, close collaboration with the developers of simulation software NEURON has led to further development of CoreNEURON. CoreNEURON started as a stand alone application to extract the core capabilities of NEURON in order to facilitate code changes necessary to leverage better memory layout and new computing technologies. Early users had to apply a two-stage process to first initialize a model with NEURON before proceeding to evaluation with CoreNEURON. Recently, this has been simplified for users such that NEURON model constructing capabilities and CoreNERUON optimized execution can be built into a single executable. Members of BBP have started to integrate CoreNEURON into their workflows on various hardware platforms such as BlueGene/Q, Intel Skylake and KNL, and GPUs. This has especially been necessary for work with Structural Plasticity done as part of Argonne INCITE grant. This use case has substantially increased the size and feature set of the simulated model and thus higher memory and computational demands. Using CoreNEURON, the same hardware can support models 6-7 times larger. These improvements are accessible as well to users of smaller systems to better utilize limited resources.

Disclosures: J.G. King: None. **P.S. Kumbhar:** None. **J. Fouriaux:** None. **G. Chindemi:** None. **F. Pereira:** None. **M.L. Hines:** None. **F. Delalondre:** None. **F. Schuermann:** None. **H. Markram:** None.

Poster

521. Computation, Modeling, and Simulation: Network Models: Experimentation

Location: SDCC Halls B-H

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Topic: I.06. Computation, Modeling, and Simulation

Support: This work was supported by the EPFL Blue Brain Project Fund and the ETH Board Funding to the Blue Brain Project.

Title: Computational synthesis of cortical dendrites from their branching topology

Authors: *L. KANARI[1], A. CHALIMOURDA[1], G. ATENEKENG[1], J. W. GRAHAM[2], J. SHILLCOCK[1], K. HESS[3], H. MARKRAM[1]
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Abstract: The dynamical properties of neuronal networks depend on the branching of their neuronal morphologies, which is involved in both the functionality and the connectivity of neurons. Thus, it is essential for the accurate reconstruction and simulation of detailed brain networks to reproduce the anatomical properties of neurons. The digital reconstruction of a

physiologically realistic network, such as the Blue Brain Project (Markram et al. 2015), requires a large number of detailed neuronal morphologies that are difficult to acquire experimentally. Therefore, the digital generation of neurons that respect the branching properties of the biological cells is required.
The principles that control the final shape of dendritic and axonal arbors are still largely unknown. For this reason, there is a plethora of synthesis methods for the artificial generation of neuronal morphologies that range from biologically detailed methods (Ascoli et al. 2001, Koene et al. 2009) to minimally-constrained ones, which are based on fundamental mathematical principles (Cuntz et al. 2010). Each of these techniques contributes to our comprehension of neuronal growth, but no algorithm has managed to reproduce a large variety of neuronal shapes without manual selection of the appropriate input parameters.
A topological method that quantitatively captures the branching shapes of neurons, (Kanari et al, 2017) has previously been used to establish an objective classification scheme for cortical pyramidal cells. Here we use this topological descriptor, in combination with a small set of morphometrics, to synthesize dendritic morphologies. Each morphology is validated against a set of biological ones, based on a set of morphological features that have not been directly used as input. This topologically driven synthesis algorithm generates realistic morphologies for a large number of distinct dendritic cortical cell types as it implicitly captures correlations between the features inherent in a neuronal shape without manual identification of these inter-dependencies. Because the topologically-driven synthesis scheme is generalizable to a large number of different dendritic shapes it can be used to create the large number of morphological shapes needed for digital reconstructions of large-scale physiologically realistic networks.

Disclosures: L. Kanari: None. **A. Chalimourda:** None. **G. Atenekeng:** None. **J.W. Graham:** None. **J. Shillcock:** None. **K. Hess:** None. **H. Markram:** None.

Poster

521. Computation, Modeling, and Simulation: Network Models: Experimentation

Location: SDCC Halls B-H

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Program #/Poster #: 521.10/LLL6

Topic: I.06. Computation, Modeling, and Simulation

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An award of computer time was provided by the Innovative and Novel Computational Impact on Theory and Experiment (INCITE) program
This research used resources of the Argonne Leadership Computing Facility, which is a DOE Office of Science User Facility supported under Contract DE-AC02-06CH11357

Title: Biophysical modeling and simulation of synaptic plasticity in a large-scale reconstruction of neocortical microcircuitry

Authors: *G. CHINDEMI[1], V. DELATTRE[3], A. DEVRESSE[1], M. DORON[4], J. G. KING[1], P. S. KUMBHAR[1], M. NOLTE[1], R. PERIN[3], S. RAMASWAMY[1], M. W. REIMANN[1], C. RÖSSERT[1], W. VAN GEIT[1], F. DELALONDRE[1], M. GRAUPNER[5], K. HESS[6], H. MARKRAM[1], F. SCHÜRMANN[2], I. SEGEV[4], E. B. MULLER[1]
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Abstract: Structural and functional synaptic plasticity are constantly remodeling neural circuits, shaping them in response to stimuli coming from the external world and to the internal dynamics. This capability is thought to be the foundation of learning and memory in the brain. While plasticity mechanisms of few excitatory connection types have been extensively studied in vitro and in vivo, plasticity properties remain elusive for most of them. Furthermore, it is not clear how different plastic mechanisms, such as long-term potentiation (LTP) or synaptogenesis, would interact together on different time scales and how they could eventually enable learning and memory. In this work we presented a model of a plastic excitatory synapse, devised by integrating widely accepted theories and data on synaptic plasticity. In brief, synapses are located on spines; vesicle release is a stochastic process; functional changes are postsynaptic calcium dependent; N-methyl-D-aspartate receptors (NMDARs) and voltage-gated calcium channels (VGCCs) are the main source of postsynaptic calcium; synapse formation and elimination are stochastic process and the latter is assumed to depend on synaptic strength. The synapse model was parameterized using only a small set of experimental observations on synaptic plasticity, i.e. spike-timing dependent plasticity (STDP) in layer 5 thick-tufted pyramidal cell (TTPC) connections [Markram et al. 1997], and successfully validated against independent in vitro datasets from literature [Egger, Feldmeyer, and Sakmann 1999; Sjöström and Häusser 2006]. This approach allowed us to produce a first predictive map of connection type-specific plastic dynamics in the neocortex. We then analyzed the impact of synaptic plasticity on a large-scale reconstruction of neocortical microcircuitry. Our goal was to assess whether specific connectivity patterns emerge due to plasticity and, if so, how they influence network activity. We exposed a reconstruction of a neocortical network to a set of structured stimuli and monitored the evolution of excitatory synapses over one hour of biological time. Our preliminary results show

that synaptic plasticity can selectively alter the strength of specific connections, while preserving the overall firing activity.

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Poster

521. Computation, Modeling, and Simulation: Network Models: Experimentation

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 521.11/LLL7

Topic: I.06. Computation, Modeling, and Simulation

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The Cajal Blue Brain Project (MINECO)
The BlueBrain IV BlueGene/Q system is financed by ETH Board Funding to the Blue Brain Project as a National Research Infrastructure and hosted at the Swiss National Supercomputing Center (CSCS)

Title: Revealing the information content of voltage-sensitive dye imaging-derived spatiotemporal patterns in cortex

Authors: *T. H. NEWTON, S. EILEMANN, E. MULLER, M. NOLTE, M. REIMANN, J. VILLAFRANCA DÍAZ, H. MARKRAM
EPFL BBP, Geneva, Switzerland

Abstract: Voltage-sensitive dye imaging (VSDI) is a commonly used method for imaging mescosale activity patterns in the cortex of awake and anesthetized animals. However, given that VSDI reflects a highly aggregate mix of cellular and synaptic signals, its precise interpretation can be challenging. Here, we present a study of the information content of the spatiotemporal patterns revealed by VSDI using a biophysically detailed digital reconstruction of rodent neocortical microcircuitry (Markram et al., 2015) to model VSDI signals and isolate the sources of the various signals. In particular, we demonstrate that the principal contributions to the VSD signal are both activity-dependent and layer- and cell-type-specific. Furthermore, by stimulating our microcircuit at varying locations and at varying time lags with in vivo-like injections of

current, we derive a theoretical upper bound to the spatial and temporal resolving power of VSDI. Finally, by performing in silico VSDI recordings of multiple trials of spontaneous and evoked activity that differ only in terms of local intracortical synaptic noise, we calculate the magnitude and timescale of divergence for VSDI signals under ideal conditions. These data suggest fundamental constraints for the interpretation of VSDI signals as meaningful reflections of cortical activity.

Disclosures: T.H. Newton: None. **S. Eilemann:** None. **E. Muller:** None. **M. Nolte:** None. **M. Reimann:** None. **J. Villafranca Díaz:** None. **H. Markram:** None.

Poster

521. Computation, Modeling, and Simulation: Network Models: Experimentation

Location: SDCC Halls B-H

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Title: Estimating the readily releasable vesicle pool size at layer 5 pyramidal connections in the neocortex

Authors: *N. BARROS-ZULAICA, J. RAHMON, G. CHINDEMI, R. PERIN, H. MARKRAM, S. RAMASWAMY, E. MULLER
Cells and Circuits Team BBP, EPFL, Lausanne, Switzerland

Abstract: Previous studies based on the 'Quantal Model' for synaptic transmission suggested that neurotransmitter release is mediate by a single release site at individual synaptic contacts in the neocortex (Del Castillo, 1954; Silver RA, 2003 & Markram H, 1997). However, recent studies seem to contradict this hypothesis (Rudolph S, 2015) and indicate that multi-vesicular release (MVR) could better explain the synaptic response variability observed in vitro (Wang Y, 2006).
In this study we present a novel method to estimate the number of release sites per synapse, also known as the size of the readily-releasable pool (NRRP), from paired whole-cell recordings of layer 5 thick tufted pyramidal cell (L5-TTPC) connections in the somatosensory neocortex. Our approach extends the work of Loebel and colleges (Loebel A, 2009) to take advantage of a recently reported data-driven biophysical model of neocortical tissue (Markram H,et al. 2015). From a collection of 33 paired whole cell patch-clamp recordings of L5-TTPC in the P14 rat

somatosensory cortex, we extracted the synaptic parameters for the Tsodyks-Markram model of synapse dynamics (TM-model) and estimated the maximal synaptic conductance through matching experimental EPSPs values with equivalently sampled pairs simulated in the neocortical tissue model *in silico*. Finally, the size of the readily releasable pool, NRRP, was adjusted to obtain the best match between the coefficient of variation (CV) profile of the EPSPs for the in vitro data and in silico simulations. Using this approach, we estimated NRRP to be between 2 to 3 for connections between layer 5 thick tufted pyramidal cells. To constrain NRRP values for other connections in the microcircuit, we developed and validated a generalization approach using data on EPSP CVs from literature and matching to in silico experiments.
Our study shows that synaptic connections in the neocortex generally are mediated by MVR and provides a data-driven approach to constrain the MVR model parameters of the microcircuit. These findings have important implications for synaptic transmission, biophysical models of synaptic plasticity, and when considering synaptic noise sources for information processing in the neocortex.
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Poster

522. Computation, Modeling, and Simulation: Computational Tools: Neuroimaging

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 522.01/LLL9

Topic: I.06. Computation, Modeling, and Simulation

Support: TUBA GEBIP 2015
BAGEP 2017
EMBO IG 3028

Title: Spatially-informed voxelwise modeling (SPIN-VM) for naturalistic fMRI experiments

Authors: E. CELIK, *T. CUKUR
Bilkent Univ., Ankara, Turkey

Abstract: Voxelwise modeling (VM) has been shown to be powerful in the analysis of fMRI data acquired under naturalistic conditions (Cukur et al., Nat Neuro, 2013; Huth et al., Nature, 2016). VM accurately predicts single-voxel responses evoked by a rich set of stimulus features present in complex natural stimuli in various modalities such as vision (e.g., movies) or language (e.g., stories). A potential drawback of VM is that it disregards response correlations known to exist across neighboring voxels (Zarahn et al., Neuroimage, 1997). Here, we introduce spatially-informed voxelwise modeling (SPIN-VM) to leverage response correlations in spatial neighborhoods of voxels. To optimally utilize shared information, SPIN-VM employs a graph Laplacian matrix representing inter-voxel spatial distances and performs regularization across spatial neighborhoods in addition to stimulus features. Therefore, SPIN-VM can offer improved sensitivity in model estimation while still predicting single-voxel responses.
We demonstrated SPIN-VM in a natural vision experiment, where 3600 time samples of whole-brain BOLD responses were recorded while human subjects passively viewed natural movies. Two separate models were considered based on 1705 distinct object and action categories (category model; Huth et al., Neuron 2012), and 2139 spatiotemporal Gabor filters (motion-energy model; Nishimoto et al., Curr Biol, 2011). To comparatively examine the performance of VM and SPIN-VM, separate voxelwise models were trained using the full set (3600 samples), a half set (1800), and a quarter set (900) of the experimental data. Prediction scores were calculated as Pearson's correlation between measured and predicted BOLD responses. To quantify the local coherence of the resulting models, we calculated the standard deviation across model weights of voxels in a neighborhood of 3×3×3 voxels.
SPIN-VM yields significantly higher prediction scores across cortex compared to VM (p<0.05). Improvements up to 17% are observed in high-level visual areas such as FFA, EBA and LOC for the category model; and improvements up to 11% are observed in low-level retinotopic visual areas for the motion-energy model. We also find that SPIN-VM better captures local coherence of information representations across cortex. Compared to VM, SPIN-VM yields 13% higher local coherence for the category model, and 11% higher local coherence for the motion-energy model (p<0.05). These results suggest that, by leveraging spatially correlated information in BOLD responses, SPIN-VM enhances sensitivity in single-voxel estimates of functional selectivity.

Disclosures: E. Celik: None. **T. Cukur:** None.

Poster

522. Computation, Modeling, and Simulation: Computational Tools: Neuroimaging

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 522.02/LLL10

Topic: I.06. Computation, Modeling, and Simulation

Support: CIR

Title: Grey matter detection study using magnetic resonance imaging

Authors: *G. COVER[1], R. FARIVAR-MOHSENI[2]
[2]Ophthalmology, [1]McGill Univ., Montreal, QC, Canada

Abstract: Brain tissue loss, such as the gray matter (GM) thickness, is a potentially-reliable marker of injury and equally important, its reversal could serve as a powerful sign of recovery. GM thickness *in vivo* is detected using magnetic resonance imaging (MRI). MRI quality is tightly related to thermal noise, which is dependent on resolution and acquisition time. Recent developments have made it possible to acquire images that are substantially higher in resolution (i.e., 0.5mm isotropic), but such images suffer from high noise and require multiple acquisitions and averaging in order to yield suitable quality for analysis. Given that the only relevant information to GM thickness measurement is the boundary of white-gray-CSF, it may be possible to denoise high-resolution MRI. The objective of this work was exactly this: to improve the sensitivity of surface-based GM estimation from 0.5mm resolution MRI acquired over a clinically-normal time (~8min). We evaluated four denoising image filters: Optimized Nonlocal Means, Oracle-based, Adaptive Optimized Nonlocal Means, and Prefiltered Rotationally Invariant Nonlocal Means filter. The Adaptive Optimized Nonlocal Means filter exhibited the best segregation of white and GM based on an analysis of the voxel histograms. The GM thickness difference between the denoised image and a gold-standard (mean of 6 acquisitions with no denoising) were visualized as an overlay on the cortical surface (Fig. 1). Overall, GM thickness did not differ between the denoised image and the gold-standard, but there were regions were the denoised image yielded different GM thickness as compared to the gold-standard, suggesting further optimization is needed. As a bonus, the denoised images were preprocessed faster. This work showed that it is possible to reduce MRI acquisition time and maintain relevant image features for the GM thickness, plus the feasibility of 0.5mm isotropic anatomical imaging in clinically-relevant duration using software denoising to emphasize the crucial image features for extracting GM thickness estimates.

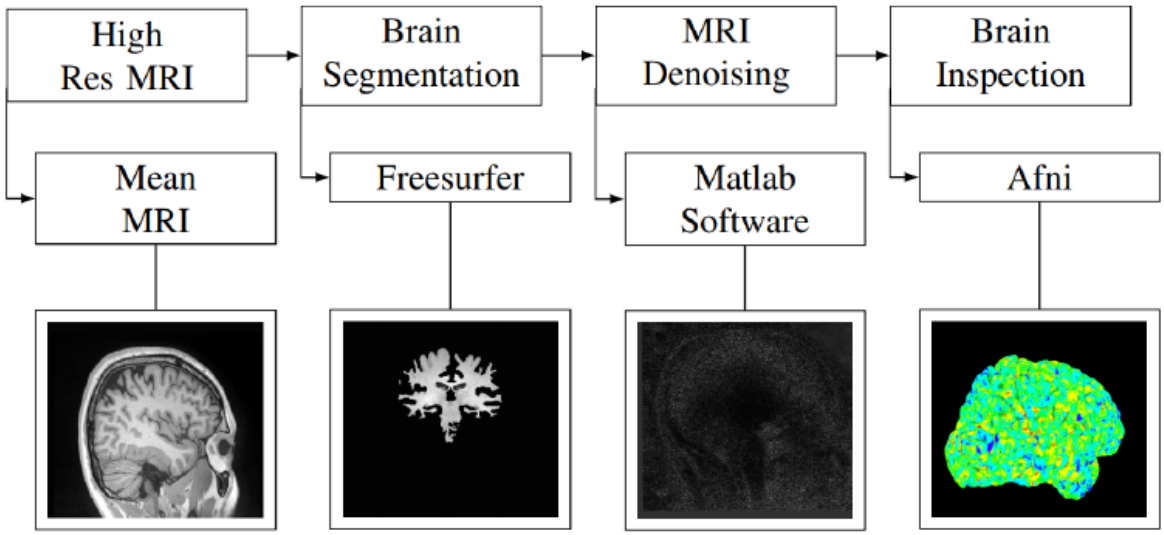

Figure 1: Pipeline of the grey matter detection study using magnetic resonance imaging.

Disclosures: G. Cover: None. **R. Farivar-Mohseni:** None.

Poster

522. Computation, Modeling, and Simulation: Computational Tools: Neuroimaging

Location: SDCC Halls B-H

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Program #/Poster #: 522.03/LLL11

Topic: I.06. Computation, Modeling, and Simulation

Support: NASA Grant NNX13AJ92G

Title: Intracranial positioning of brain changes following long-duration spaceflight with implications for longitudinal neuroimaging studies

Authors: *D. ASEMANI[1], M. A. ECKERT[2], T. R. BROWN[3], D. R. ROBERTS[4]
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Abstract: Objectives
When assessing longitudinal changes in brain structure, neuroimaging studies conventionally neglect changes in brain positioning within the cranium as processing algorithms begin with skull stripping. Neglecting this global change in brain structure can be a source of error in the estimation of atrophy/growth of brain regions over time. Here we evaluated longitudinal changes in brain structure in a novel population: International Space Station astronauts. We demonstrate that the assumption of a fixed brain position over time is incorrect.
Methodology
Following IRB approval from NASA and our local institution, we analyzed brain MRI scans of 12 NASA astronauts obtained prior to spaceflight and soon after return to Earth. We developed a novel image analysis pipeline that began with the skull-based alignment between pre- and post-flight MRI scans. We used the skull as a reference as the skull does not undergo bone loss during spaceflight[1]. Our algorithm used a multi-objective optimization approach by preferentially weighting the calvarium over the skull-base. Next, the pre-flight brain was affine transformed to the post-flight brain to obtain a 12 degrees of freedom matrix representing shift, rotation, stretch and skewing across three axes. This global transformation matrix from the pre- to post-flight brain was then mapped to a common 3D space (MNI152) for statistical analysis.
Results
Comparing the pre- to post-flight MRIs, there was an obvious change in brain positioning in reference to the skull. Following spaceflight, there was a significant upward brain shift (+0.6mm, $p = 0.03$) and stretching (+0.8%, $p = 0.002$) superiorly along with a transverse compression (-0.4%, $p = 0.002$). These findings were confirmed by independent radiological reading by neuroradiologists[2].
Conclusion

Long-term microgravity exposure results in a significant change in global brain position. Previously, we have shown similar changes in brain structure in subjects undergoing long-term bedrest[3]. We hypothesize brain position within the cranium may also be altered by factors such as aging and various pathologies. We suggest that longitudinal neuroimaging studies consider global as well as local changes in brain structure.

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3. Roberts DR, et al. Structural Brain Changes following Long-Term 6 degrees Head-Down Tilt Bed Rest. AJNR 2015;36:2048-54.

Disclosures: D. Asemani: None. **M.A. Eckert:** None. **T.R. Brown:** None. **D.R. Roberts:** None.

Poster

522. Computation, Modeling, and Simulation: Computational Tools: Neuroimaging

Location: SDCC Halls B-H

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Program #/Poster #: 522.04/LLL12

Topic: I.06. Computation, Modeling, and Simulation

Support: New Jersey Commission on Brain Injury Research (CBIR15MIG004)

Title: Regional fractal dimension analysis as qualitative and quantitative imaging markers in traumatic brain injury

Authors: L. ZHANG[1], G. R. WYLIE[2], *G. H. YUE[3]
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Abstract: Traumatic brain injury (TBI) is one of the leading causes of mortality and disability worldwide. Due to the heterogeneous nature of the disease, it is challenging to accurately characterize the injury and predict clinical outcome. The purpose of this study was to investigate the potential of regional fractal dimension (FD) assessment as imaging markers to aid for TBI diagnosis and recovery prognosis. A framework was developed to perform qualitative and quantitative analyses of the brain structure based on standard T1-weighted anatomical MRI. The system computes regional FD, a complexity index, of cortical and subcortical structures (113 regions of interest) segmented from MR images and performs correlation analysis between FD values and cognitive function scores. The regional FD values are mapped onto the 3D brain to show structural complexity patterns in TBI. Correlation maps are generated to show the

relationship between local structural complexity and cognitive function scores. T1-weighted MR images of 13 moderate to severe TBI patients (6 left-sided and 7 right-sided injuries) were analyzed using the system. Processing speed, a standard neuropyschological test sensitive to detect cognitive impairment in TBI, was used for correlation analysis. Significant positive and negative correlations were observed between processing speed and FD values of various cortical and subcortical structures. However, these correlations differed between patients with left and right hemisphere injuries. For example in patients with left-sided injuries in frontal, temporal and parietal lobes, positive correlations were found in the thalamus proper, anterior part of the right middle frontal gyrus, right superior temporal gyrus and left posterior cingulate gyrus. In contrast patients with injuries in right frontal, temporal and occipital lobes had positive correlations in the left cerebellar cortex, right lateral ventricle, right lateral occipital gyrus, and right middle temporal gyrus. These findings suggest that regional FD, as an imaging marker may potentially serve as an injury classifier to aid clinicians in performing TBI diagnosis and to predict cognitive outcome. Future work will focus on understanding if regional FD is a more sensitive index than global FD in TBI classification and/or if FD of a given region is related to a specific domain of cognitive function.

Disclosures: L. Zhang: None. **G.R. Wylie:** None. **G.H. Yue:** None.

Poster

522. Computation, Modeling, and Simulation: Computational Tools: Neuroimaging

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 522.05/LLL13

Topic: I.06. Computation, Modeling, and Simulation

Title: Searchlight analysis over functional rather than anatomical space reveals higher representational similarity with deep learning models

Authors: *S. KUMAR, C. ELLIS, T. O'CONNELL, Z. TANG, M. M. CHUN, N. B. TURK-BROWNE
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Abstract: Perceptual and cognitive representations are expressed in patterns of activity widely distributed throughout the brain. Despite being distributed, these representations can be localized in fMRI using a searchlight analysis. This involves passing a small, contiguous cube or sphere of voxels over the brain, extracting the pattern of activity from those voxels, performing some (typically multivariate) operation on the pattern, and assigning the result to the center voxel. This can reveal, for example, which local anatomical regions discriminate between stimuli or tasks. Although local information is expected from the gross functional organization of the brain, the assumption inherent to searchlight analyses that function is determined by anatomical proximity makes this approach blind to longer-range interactions that can contribute to whole-brain

analyses. Such interactions are widespread in the brain, including across sensory hierarchies, between homologous regions across hemispheres, and as a result of control or modulatory signals. Here we eliminate the anatomical constraint on searchlight analyses by remapping voxels from their original 3-D anatomical brain space into a 3-D functional space in which the proximity of voxels is determined by the similarity of their function. Specifically, we use shared response modeling (SRM) to find a lower-dimensional space of three orthogonal features in fMRI activity that are shared across participants while they view a common stimulus and then use the weights describing how voxels load onto these features as coordinates that place the voxels in functional space. To validate this method, we performed a representational similarity analysis on held-out data, comparing brain responses while participants watched an episode of Sherlock (Chen, et al., 2017) to the final layer of the deep learning vision model AlexNet while it "watched" the same movie frames. In 16/17 participants, the distribution of representational similarities across the brain was higher when brain activity patterns were obtained from searchlights passed over voxels arranged in functional compared to anatomical space. In other words, by removing the assumption that information is anatomically focal, we found that searchlights are consistently more correlated with model representations. These findings show that anatomically distant voxels carry information that may not exist in adjacent voxels. Using anatomical searchlights to localize multivariate effects seen at larger scale may thus miss important information.

Disclosures: S. Kumar: None. **C. Ellis:** None. **T. O'Connell:** None. **Z. Tang:** None. **M.M. Chun:** None. **N.B. Turk-Browne:** None.

Poster

522. Computation, Modeling, and Simulation: Computational Tools: Neuroimaging

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 522.06/LLL14

Topic: I.06. Computation, Modeling, and Simulation

Support: Intel Research Labs

Title: Brainiak education: User-friendly tutorials for advanced, computationally-intensive fmri analysis

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Abstract: Advanced brain imaging analysis methods, including multivariate pattern analysis (MVPA), functional connectivity, and functional alignment, have become powerful tools in

cognitive neuroscience over the past decade. There now exist multiple software packages that implement some of these techniques. Although these packages are useful for expert practitioners, novice users face a steep learning curve. These difficulties stem from: the need to learn a new programming language (e.g., Python); figuring out how to apply machine-learning methods to data-starved and high-dimensional fMRI studies; and inadequate documentation and training materials. Furthermore, most standard fMRI analysis packages (e.g., AFNI, FSL, SPM) focus primarily on preprocessing and univariate analyses, leaving a gap in how to integrate with advanced tools. BrainIAK (brainiak.org) is a new, open-source Python software package that seamlessly integrates several cutting-edge, computationally efficient techniques with other Python packages for file handling, visualization, and machine learning, picking up where standard packages leave off. As part of efforts to disseminate this package, we have developed user-friendly tutorials and exercises for learning BrainIAK and advanced fMRI in Python more generally. These materials cover cutting-edge techniques including: MVPA (Norman et al., 2006); representational similarity analysis (Kriegeskorte et al., 2008); background connectivity (Al-Aidroos et al., 2012); full correlation matrix analysis (Wang et al., 2015); inter-subject correlation (Hasson et al., 2004); inter-subject functional connectivity (Simony et al., 2016); shared response modeling (Chen et al., 2015); and real-time fMRI (deBettencourt et al., 2015). The learning materials were built using Jupyter notebooks and each notebook has an associated public dataset on which the code can be run. These notebooks were successfully deployed using GitHub Classroom for an advanced fMRI analysis class at Yale University. Students were able to perform analyses previously available only to experts in a simple, step-by-step manner by ssh tunneling into Jupyter on a high-performance compute cluster. We will be freely sharing these materials for public use, with the hope that they become part of a growing pool of open-source software and educational materials for large-scale, reproducible fMRI analysis.

Disclosures: M. Kumar: None. **C. Ellis:** None. **P.J. Ramadage:** None. **K.A. Norman:** None. **N.B. Turk-Browne:** None.

Poster

522. Computation, Modeling, and Simulation: Computational Tools: Neuroimaging

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 522.07/LLL15

Topic: I.06. Computation, Modeling, and Simulation

Support: James S. McDonnell Foundation: 2011 Scholar Award. Joern Diedrichsen (PI)

Title: Identifying functional boundaries in the human cerebellum

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Abstract: While in-vivo functional parcellations of the human cerebral cortex have advanced progressively in recent years (Glasser et al. 2016; Huth et al. 2016; Yeo et al. 2011), such detailed characterisation of cerebellar functional organisation is absent. We believe this is because previous fMRI studies have focused on a restricted number of task domains making it difficult to provide a comprehensive mapping of functional organisation on the same set of subjects. To address this problem, we developed a large task battery that allowed us to derive and evaluate a task-based functional parcellation of the human cerebellum on individual subjects. We developed a battery of 26 tasks, selected to engage a broad range of sensorimotor and cognitive processes and we scanned participants on this task battery over the course of four independent fMRI sessions (totaling 5.5 hours per subject). To derive a task-based parcellation, we used semi nonnegative matrix factorisation, which identified latent dimensions of the task-evoked activity patterns elicited by our multi-task dataset. This approach expressed the activation profile of each voxel across task conditions as a (non-negative) weighted sum of latent functional components. We then leveraged our diverse data set to develop a spatially unbiased criterion to evaluate the existence of functional boundaries in the human cerebellum. The spatial criterion that we have devised is predicated on the idea that if a boundary between two distinct regions is dividing two functionally heterogeneous regions, then two voxels that lie within the same region should be more functionally homogenous than two voxels that are separated by a boundary. Integral to the evaluation criterion was the requirement that the boundaries should generalise beyond the dataset upon which they were established. Our task battery was sufficiently large and diverse such that boundaries could be established on one dataset and then evaluated on an entirely novel set of tasks.
We found that the functional boundaries derived on our multi-task data set could predict functional boundaries on a novel set of tasks. However, a lobular parcellation, which is the current nomenclature for assigning functional activations in the cerebellum failed to identify functional boundaries. While parcellations derived on resting state data (Buckner et al. 2011; Cole et al. 2018) performed substantially better than a lobular parcellation, a task-based parcellation yielded the best results. Based on these findings, we advocate for a revision of the existing lobular nomenclature to incorporate functional subdivisions of the cerebellar cortex.

Disclosures: M. King: None. **R. Ivry:** None. **J. Diedrichsen:** None.

Poster

522. Computation, Modeling, and Simulation: Computational Tools: Neuroimaging

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 522.08/LLL16

Topic: I.07. Data Analysis and Statistics

Title: Harmonization of multi-site resting-state fMRI functional connectivity and network metrics

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Abstract: Background: Acquiring resting-state functional magnetic resonance imaging (fMRI) datasets on more than one MRI scanner and at multiple clinical sites can increase the overall sample size, which may improve statistical power and generalizability of the results. However, multi-site neuroimaging studies have reported considerable non-biological variability in fMRI measurements due to different scanner manufacturers and acquisition protocols. Ultimately, these extra, undesirable sources of variability may limit the statistical power to detect neurobiological and clinical associations of interest and may even result in erroneous findings. Until now, there has not been an approach to harmonization that entirely removes unwanted site or scanner effects in fMRI measurements.
Objective: We aimed to estimate the site effects on fMRI-based functional connectivity and network measures, and eliminate the identified site effects without affecting the true biological signal.
Methods: In this study, using a relatively large multi-site (4 sites) fMRI dataset consisting of 189 patients with major depressive disorder and 39 healthy controls, we investigated the impact of site effects on functional connectivity and network measures estimated by two widely used connectivity metrics (Pearson correlation and wavelet coherence) and three brain parcellations or atlases (anatomical: AAL; functional: Power and Gordon). To remove site effects, we applied ComBat, a harmonization technique that has previously been shown to eliminate site effects in multi-site diffusion tensor imaging (DTI) and cortical thickness studies.
Results: We found that ComBat successfully removed site effects identified in connectivity and network measures and increased the power to detect age associations when using optimal combinations of connectivity metrics and brain atlases. Moreover, the magnitude of site effects was influenced by the choice of connectivity metric and brain atlas. Particularly, we found that using wavelet coherence with the Power atlas resulted in the best power to detect anti-correlations between age and DMN functional connectivity as well as network efficiency measures following ComBat harmonization, suggesting the best preservation of underlying biological signal with this combination.
Conclusion: ComBat harmonization is a powerful technique for removing site effects in fMRI measurements, and simultaneously preserving biological variability. Our proposed ComBat harmonization approach for fMRI-derived connectivity measures facilitates reliable and efficient analysis of retrospective and prospective multi-site fMRI neuroimaging studies.

Disclosures: M. Yu: None. **K.A. Linn:** None. **P.A. Cook:** None. **M.L. Phillips:** None. **M. McInnis:** None. **M. Fava:** None. **M.H. Trivedi:** None. **M.M. Weissman:** None. **R.T. Shinohara:** None. **Y.I. Sheline:** None.

Poster

522. Computation, Modeling, and Simulation: Computational Tools: Neuroimaging

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 522.09/LLL17

Topic: I.07. Data Analysis and Statistics

Support: Society for Research in Child Development Victoria Levin Award "Early Calibration of Stress Systems: Defining Family Influences and Health Outcomes"

Title: Addressing the atlas concordance problem in fMRI

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Abstract: Reliable identification of brain regions involved in cognitive phenomena is essential for developing a coherent picture of the functional localization of cognition. A serious impediment to this is the misidentification of cognitive function due to the atlas concordance problem (also called the neuroanatomical nomenclature problem). This is summarized by the fact that the same anatomical coordinate may be labelled differently across atlases. We have developed a tool called Neurosift that leverages the Neurosynth fMRI database to assist in identifying common brain regions reported across studies agnostic to anatomical labelling. This provides an easy-to-use alternative to label-based searches. It also addresses a problem in which fine-grained functional specialization is obscured by attribution to the large anatomical ROIs frequently reported in the literature. This is particularly salient for emerging areas of neuroscience with an insufficient publication base to support systematic meta-analyses. We illustrate this in the emerging area of mothers' neural responsiveness to infant emotional cues. Using functional MRI, twenty-five mothers at 3 months postnatal were scanned while observing video presentations of their own or an unfamiliar infant in positive or negative emotional contexts. They also underwent either passive viewing or labelling of emotionally salient faces from the NimStim database to assess emotional regulation in a well-studied paradigm. Peak voxels extracted from exploratory analysis of these runs are surveyed across several commonly used atlases. While there is considerable overlap, consistent with the concordance problem, there is notable divergence, such as a peak in a preliminary contrast of Emotional Labelling > Passive Viewing identified as the post-central gyrus in the AAL and the central opercular cortex in the Harvard-Oxford atlases.
Using a pre-defined protocol of study selection, we illustrate diverging narratives when literature reviews are based on a search driven by different anatomical labels and a search using Neurosift

that identifies analyses reporting peak voxels within the smoothing kernel radius. We identify statistical limitations to this approach such as applicability only to studies using voxel-level correction, and discuss future expansion of this work, such as accommodation of cluster-based correction and potential methods to address the spatial conservativeness of this new type of literature search technology.

Disclosures: M. Finnegan: None. **S. Kern:** None. **D. Newberry:** None. **W. Heller:** None. **H. Laurent:** None.

Poster

522. Computation, Modeling, and Simulation: Computational Tools: Neuroimaging

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 522.10/LLL18

Topic: I.07. Data Analysis and Statistics

Support: eScience Institute
University of Washington Institute for Neuroengineering

Title: Combining citizen science and deep learning to amplify expertise in neuroimaging

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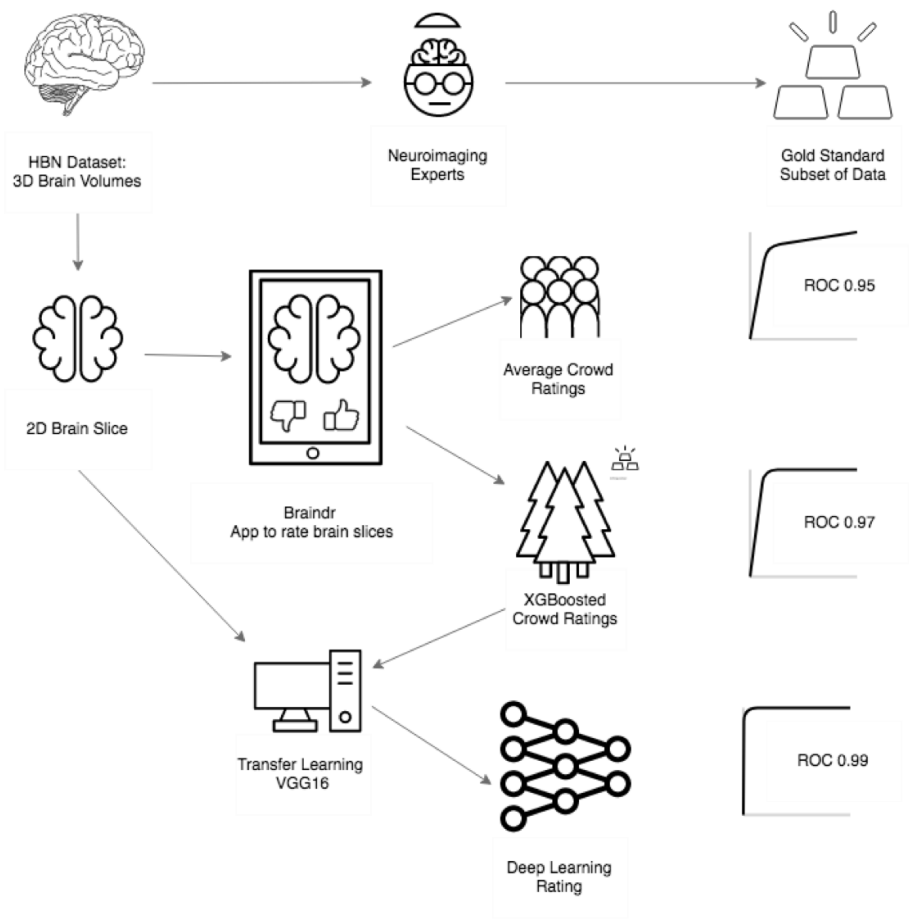
Abstract: Big data in neuroimaging holds the promise to answer important questions about the brain. However, many standard lab protocols that rely on experts examining each one of the samples is not feasible with large-scale datasets, because they are difficult to scale, and because automated approaches lack the accuracy of highly trained scientists. Our proposed solution is to 1) start with a small, expertly labelled dataset, 2) amplify labels through citizen science via web-based tools, and 3) train machine learning on amplified labels to emulate expert decision making. As a proof of concept, we developed a system to quality control over 700 T1-weighted images from the Healthy Brain Network dataset (Alexander, 2017). An initial expertly labelled dataset (of 200 images) was amplified by citizen scientists to the entire dataset (724) with over 80,000 ratings through a simple web interface called braindr (brain data review, https://braindr.us). A deep learning algorithm was trained to predict data quality with the aggregate citizen scientist labels in a subset of the data. In an ROC analysis on left out test data, the deep learning network performed as well as a state-of-the-art, specialized algorithm (MRIQC) for T1-weighted images (Esteban, 2017), each with an area under the curve of 0.99. Therefore, we assert that combining citizen science and deep learning can generalize and scale neuroimaging expert decision making; this is particularly important in the cases where specialized, automated tools do not already exist. Finally, as a specific practical application of the method, we explore how brain image quality

relates to the replicability of a well established relationship between brain volumes and age over development (Lebel, 2011).



Overview and results of our procedure: First, the HBN data set was rated by 4 neuroimaging experts to create a "gold standard" subset of data. Next, the 3D MRI scans were converted into 2D axial brain slices, which were loaded onto braindr (https://braindr.us), a web application to crowdsource the quality ratings. Area under the curve of the Receiver Operating Characteristic curve (AUC) was calculated for the average citizen scientist quality rating for each slice. Compared to an expert-labeled test set, this resulted in an AUC of 0.95. In an effort to remove unreliable raters, the ratings were aggregated by fitting a model (XGBoost) that weights each citizen scientist contribution to the slice score by how much that individual's scores match those of the experts. The resulting AUC was 0.97. Finally, the 2D brain slices together with the weighted citizen scientist ratings were used to train a neural network. In an ROC analysis on left out data, the AUC of these predictions was 0.99.

Disclosures: A. Keshavan: None. **J.D. Yeatman:** None. **A.S. Rokem:** None.

Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.01/LLL19

Topic: I.06. Computation, Modeling, and Simulation

Support: TUMS Grant 94-04-30-30878

Title: Use of high frequency rhythmic SSVEP visual stimuli patterns for better trade-off between fatigue rate and accuracy rate in normal subjects

Authors: A. KEIHANI[1], Z. SHIRZHIYAN[1], M. FARAHI[1], E. SHAMSI[1], A. MAHNAM[2], B. MAKKIABADI[1], A. JAFARI[1], *M. RAZA[3]
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Abstract: Steady state visual evoked potentials (SSVEP) are EEG responses generated due to periodic visual stimulation. These are commonly used to control brain computer interfaces (BCIs). LED screen can display high-frequency (26-90 Hz) visual stimuli that can reduce subjective fatigue while low (1-12 Hz) and medium (12-25 Hz) frequency visual stimuli lead to higher subjective fatigue. In this study we investigated the efficiency of the high frequency rhythmic visual stimuli patterns for using SSVEP-BCIs in normal subjects.
Twenty-two normal subjects (11 males and 11 females, aged 23-30 (25 ± 2.1) yrs) were enrolled in the study. Nine visual stimuli of 25, 30 and 35 Hz frequencies (three simple single high frequencies that used only one frequency in sequence e.g. S25-25-25, S30-30-30 and S35-35-35 and six rhythmic high frequency visual stimuli that used all three frequencies in different sequences e.g. R25-30-35, R25-35-30, R30-25-35, R30-35-25, R35-25-30 and R35-30-25) were presented on LED screen. Visual Analogue Scale (0-10) was used for the evaluation of fatigue rate. Fatigue and accuracy rates between simple single high frequency and rhythmic visual stimuli groups were compared.
Overall, rhythmic visual stimuli patterns showed reliable SSVEP responses and high accuracy rate (>90%), results showed lower within group fatigue rate for rhythmic group compared to simple single frequency group. VAS results showed maximum fatigue rate for S25-25-25 (4.95 ± 2.57) and minimum for S35-35-35 (2.95 ± 2.45) in simple stimuli group. Rhythmic group had

lower within group VAS variation (min=P25-30-35 [2.90 ± 2.45], max=P35-25-30 [4.81 ± 2.65]) as well as least individual pattern VAS (P25-30-35).
SSVEP were evoked robustly with high accuracy rate for rhythmic visual stimuli patterns. We conlcude that the lower within group fatigue rate in rhythmic high frequency visual stimuli group can increase user comfort and suggests further research for future application on SSVEP-BCI studies.
Keywords: Steady state visual evoked potential; brain computer interface; fatigue rate;

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Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.02/LLL20

Topic: I.06. Computation, Modeling, and Simulation

Title: Automated system for the placement of deep electrodes in small species with electroencephalographic monitoring system as a tool for learning neurosciences

Authors: *R. BELTRAN-RAMIREZ[1,2,3], R. MACIEL ARELLANO[1], V. LARIOS ROSILLO[1], R. ZEPEDA, Mr[1], J. ESPINOZA, Jr.[1], N. MUÑOZ FILIPPETTI[1], B. VILLANUEVA AVALOS[1], J. MARTÌNEZ MENDOZA[3], S. MONTOYA CALDERON[4], X. JIMENEZ ROMAN[2]
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Abstract: The study of neuroscience is complex from the point of view of the research since in most cases it is necessary to learn the neuroanatomy and neurophysiology of small species such as rats and mice for experimentation. However, there is a lack of technological tools that facilitate this learning as well as the research protocols in each case. It is necessary to innovate and implement new tools for assisted and practical learning of neurosciences.
By implementing tools for learning and developing the protocols of experimentation in the area of neuroscience, better results can be obtained, since the times and processes will be more efficient, counting with trained personnel in less time, as well as saving material in each case.
Experiment case.
An automated system for the development of deep electrodes in small species was developed with the intention of improving the precision at the moment of the acquisition of

electrophysiological signals. which is controlled by software in an intelligent device that allows the manipulation of the system in an efficient and easy way for the user. which was tested in a model of epilepsy by the supply of 4 Amino Pyridine in Wistar rats and using deep copper electrodes for electroencephalographic recording.

Material and methods

Wistar rats (200-250g) kept under the conditions of a bioterium, 12 hours light / dark, were used to later divide them into two groups, controls and experimental. The rats were anesthetized with isofluorane in O2 and placed in a stereotaxic frame with the incisor rod positioned at -3.3 mm. The rats were implanted with a guide cannula (internal diameter 0.5 mm) in the right entorhinal cortex (AP = -8mm, ML = 4.6mm and DV = 4mm) in order to place an injection needle in that region (DV = 5mm). A deep recording electrode placed in the mobile device was placed in the right hippocampus region (AP = -3.5mm and ML = 2.5mm, DV = 3), a surface electrode that functioned as a reference electrode (ahead of bregma).) and another electrode will be used as ground (below lambda). Subsequently, the mobile device was fixed on the skull of the animal with acrylic to finally allow the animals to recover for a period of 2 hours.

Disclosures: R. Beltran-Ramirez: None. **R. Maciel Arellano:** None. **V. Larios Rosillo:** None. **R. Zepeda:** None. **J. Espinoza:** None. **N. Muñoz Filippetti:** None. **B. Villanueva Avalos:** None. **J. Martìnez Mendoza:** None. **S. Montoya Calderon:** None. **X. Jimenez Roman:** None.

Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.03/LLL21

Topic: I.06. Computation, Modeling, and Simulation

Support: SUURPh/Norwegian Ministry of Education and Research
European Union Horizon 2020 Research and Innovation Programme Grant No. 720270

Title: Can the presence of neural probes be neglected in computational modeling of extracellular potentials?

Authors: *A. P. BUCCINO[1,4], M. KUCHTA[2], K. H. JÆGER[5], T. V. NESS[6], G. CAUWENBERGHS[4], K.-A. MARDAL[3], A. TVEITO[5]
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Abstract: In mechanistic modeling of neurons the conventional approach to simulation of neural recordings consists of two steps: first, transmembrane currents are computed using the Cable equation and second, their contribution is summed to compute the extracellular potential. This two-step approach, assumes an infinite and homogeneous extracellular space, without considering the presence of neural probes in the vicinity of neurons. In this work, our main purpose is to investigate how the presence of the neural probes affects the extracellular field. Our methods include a detailed modeling framework that allows an explicit representation of the neuron and the probe to evaluate the effect of the probes and thereby estimate the effect of ignoring them. We use meshes with simplified neurons and different types of probe and compare the extracellular action potentials with and without the probe in the extracellular space. We show that small probes (such as microwires/tetrodes) do not significantly affect the extracellular electric field and their presence can typically be ignored. However, larger probes (such as Multi-Electrode Arrays, MEAs) strongly affect the extracellular field by increasing the action potential amplitude up to a factor of 1.9. This amplitude modulation, however, depends on the neuron-probe alignment and on the probe orientation. The *probe effect* that we describe here should not be ignored in certain applications such as neural localization from extracellular action potentials and parametrization of neural models from extracellular recordings. In addition, including the presence of the probe in the modeling framework could improve the interpretation of extracellular recordings, by providing a more accurate estimation of the extracellular potential generated by neuronal models.

Disclosures: A.P. Buccino: None. **M. Kuchta:** None. **K.H. Jæger:** None. **T.V. Ness:** None. **G. Cauwenberghs:** None. **K. Mardal:** None. **A. Tveito:** None.

Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.04/LLL22

Topic: I.06. Computation, Modeling, and Simulation

Title: Optimization of seizure detection using machine learning

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Abstract: Epilepsy is a very common and devastating neurological disorder that affects 65 million people globally. Electroencephalography (EEG) recording is an essential tool in evaluating seizure activity, critical for epilepsy drug development and patient care. However, due to the random and low frequency of seizures, seizure evaluation requires continuous, long-term

EEG monitoring for weeks and months, producing huge volumes of data. This creates a formidable challenge for real-time tracking of seizures using wearable devices which have low computational power. Current algorithms for automating EEG seizure classification use computationally expensive methods to analyze minute features within small fragments of seizure events. However, despite this complexity, current algorithms still underperform, and laboratory technicians and clinical physicians alike still do not fully rely on these algorithms, opting to manually sift through thousands of hours of EEG data. Human visual analysis still drastically outperforms computer analysis. The proposed method in this study attempts to mimic the simplistic analysis of human vision for EEG seizure classification by focusing on broad, global trends in condensed EEG seizure data. EEG seizure clips were normalized and processed through a rolling mean function, producing smoothed EEG clips that represent the global shape of each clip. These signals were then directly inputted for machine training. This method achieved an accuracy rate of approximately 98.51%. Our approach provides a unique advantage in patient epilepsy management using wearables, where accuracy, computational cost, and speed are all critical to improving patient care.

Disclosures: Z. Huang: None. **Y. Ying:** None.

Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

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Program #/Poster #: 523.05/LLL23

Topic: I.06. Computation, Modeling, and Simulation

Support: NHMRC Project Grant APP1078464
ARC Australian Laureate Fellowship FL110100103
ARC Centre of Excellence in Integrative Brain Function CE140100007

Title: Time-varying approaches to recover the M/EEG recorded during tACS

Authors: *N. S. BLAND[1], J. B. MATTINGLEY[1,2], M. V. SALE[1,3]
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Abstract: Pairing techniques of rhythmic non-invasive brain stimulation with neuroimaging is scientifically valuable (e.g., to observe neural entrainment), but the recovery of this information *during* stimulation ("online") can be very challenging. For example, artefacts of transcranial alternating current stimulation (tACS)—where a low-intensity AC is delivered via scalp electrodes—contaminate spectral analyses of neural oscillations observable in the magneto- and electro-encephalogram (M/EEG). While there have been many attempts to salvage M/EEG data

recorded during tACS, most (if not all) methods have assumed linear (time-invariant) stimulation artefacts—an assumption that has been recently challenged. Rhythmic changes in body impedance (and position) by heartbeat and respiration can nonlinearly modulate the amplitude (Noury, Hipp, & Siegel, 2016) and phase (Noury and Siegel, 2017) of tACS artefacts, resulting in spectral symmetry around the frequency of tACS. We outline two time-varying template approaches that aim to capture these physiologically derived modulations, exploiting either the concurrent measurement of tACS voltage output, or heartbeat and respiration traces. Using both simulated and real data, we demonstrate these approaches dampen the spectral symmetry observed in artefactual M/EEG. Key advantages of these approaches are their computational efficiency and sensor-specificity (not requiring dense sensor arrays). Our analytic approach will be useful for those wishing to recover M/EEG from artefacts of tACS. We thank Nima Noury, Joerg Hipp, and Markus Siegel for providing data used in their previous works.

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Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.06/LLL24

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant R01MH100820

Title: Decomposing hippocampal-prefrontal functional interactions via bivariate phase amplitude coupling

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Abstract: Both hippocampus and prefrontal cortex (PFC) play important roles in memory. Anatomically, hippocampal CA1 region is known to project to PFC directly. More recent work reports polysynaptic projections from CA1 to PFC via the nucleus reuniens (RE) of the thalamus. How to determine the proportion of CA1-to-PFC neural transmission along these different pathways? We addressed this question by applying a recently proposed method of assessing directional interactions in LFP data called bivariate phase amplitude coupling (BPAC). In this method, broad-band high gamma activities are assumed to reflect population spiking, therefore the output activity of a neuronal ensemble, and the low frequency oscillations (e.g., theta) are assumed to reflect dendritic processing, therefore the input activity of a neuronal ensemble. For neuronal ensembles X and Y, significant X high gamma-Y theta coupling implies synaptic

transmission from X to Y (i.e., X->Y), and vice versa. Recording LFPs from CA1, PFC and RE in free-moving rats, and computing CA1 high gamma-PFC theta coupling (CA1->PFC), CA1 high gamma-RE theta coupling (CA1->RE) and RE high gamma-PFC theta coupling (RE->PFC) using BPAC, we found two results. First, CA1->PFC, CA1->RE, and RE->PFC were all significantly above 0 according to a permutation test. Second, a linear regression analysis with CA1->PFC as the dependent variable and CA1->RE and RE->PFC as independent variables yielded R^2=0.26. These findings suggest that in the present experiment, both CA1-PFC pathway and CA1-RE-PFC pathway are active, and theta-mediated synaptic transmission along the CA1-RE-PFC pathway explains 26% of the overall CA1->PFC theta activity transmission.

Disclosures: B. Nandi: None. **B. Kocsis:** None. **M. Ding:** None.

Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.07/LLL25

Topic: I.06. Computation, Modeling, and Simulation

Support: The Japan Spina Bifida and Hydrocephalus Research Foundation, 2017 Research Grant

Title: Computational fluid dynamics (CFD) simulation of cerebrospinal fluid in the ventricular system

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Abstract: <Introduction> Pediatric hydrocephalus is a challenging disease with high complication rate in the surgery, and development of new treatment is expected. It has been believed that human CSF flows from the choroid plexus to the arachnoid granulations. However, recent analysis has found many controversies in this classical theory, and better understanding of CSF dynamics is desired. Computational flow dynamics (CFD) analysis has been used in cardiovascular field for visualizing blood flow and its effects on the vessels, but little has done on CSF. We aim this study to visualize CSF flow and its effects on the ventricular walls by computer simulation with CFD analysis. **<Method>** The study was performed for the patients who were diagnosed with children with hydrocephalus and age-matched control. 1 mm slice, constructive interference steady state sequence (CISS) magnetic resonance images (MRI) were obtained by 1.5 tesla MRI. Image segmentation was achieved by medical imaging software, and then the 3D ventricular model was reconstructed. Volume data is meshed with 3 sublayers on the

wall boundary, and flow simulation was performed with CFD software (Ansys) (rigid wall, inlet velocity: 10 cm/second, bidirectional flow between inferior horns of the lateral ventricles and the foramen of Monro). Velocity, streamline, wall pressure and wall shear-stress (WSS) were calculated and visualized as 3D-color mapping. **<Results>**Site-specific pressure gradient was observed on both healthy and hydrocephalus ventricle walls, and larger gradient was found in the ventricles with significant dilatation. Surgical simulation of third ventriculostomy was performed on the imaging software, and decrease of wall pressure was confirmed. WSS mapping shows large site specificity in both healthy and pathological ventricles. CSF turbulence was visualized with streamlines. **<Discussion>** Simulation of CSF flow was successfully performed, and its clinical relevancy, at least partially, was confirmed. Computational simulations of biological phenomenon are done under limited condition in any cases, and the results have to be carefully interpreted. However, it also shows certain aspect that may not be able to observe. Addition of more factors will be considered for future studies to increase accuracy.

Disclosures: T. Wataya: None.

Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.08/LLL26

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH R01 MH106173

Title: The role of patient-specific volume conductor models in the simulation of local field potentials recorded from deep brain stimulation electrodes

Authors: N. MALING[1], B. HOWELL[2], T. J. STELWAGEN[2], H. S. MAYBERG[4], *C. C. MCINTYRE[3]
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Abstract: Emerging technological innovations in clinical deep brain stimulation (DBS) are enabling chronic recording of local field potentials (LFPs) from the implanted electrodes, with hopes that the signals could be useful as representative biomarkers of the patient-specific disease state. However, scientific details on the biophysical origin of these LFP signals remains elusive, and little is known about how the patient's unique brain anatomy and electrode placement impact the recording of such signals. To begin to address these questions, we developed a computational framework to theoretically analyze LFP recordings from clinical DBS electrodes that can be

customized to individual patients. To demonstrate our model system, we analyzed 6 subjects, suffering from treatment-resistant depression (TRD), who were implanted with the Medtronic Activa PC+S DBS system and had electrode contacts located in the subcallosal cingulate (SCC) region. For each subject, a patient-specific reconstruction of their head anatomy and DBS electrode implant location was generated using their clinical imaging data (MRI and CT). This patient-specific anatomical model was then used to define the parameters of a finite element volume conductor model, and to dictate the locations of thousands of multi-compartment cable model current sources relative to the implanted DBS electrode in an anatomically realistic way. We then used this model system to examine the impact of distributing subpopulations of highly synchronous neurons within the SCC region on the recorded LFP signal and compared those theoretical results to the experimentally measured LFPs. We found that incorporating patient-specific anatomical detail resulted in substantial changes to LFP signal compared to simplified models. Increasing the neuronal density near the electrode had a graded effect on LFP amplitude, while a more profound effect was generated by varying the synchrony of spatially discrete subpopulations of neurons.

Disclosures: **N. Maling:** A. Employment/Salary (full or part-time):; Boston Scientific Neuromodulation. **B. Howell:** None. **T.J. Stelwagen:** None. **H.S. Mayberg:** F. Consulting Fees (e.g., advisory boards); Abbott Neuromodulation. **C.C. McIntyre:** 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); Boston Scientific Neuromodulation, Kernel.

Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.09/LLL27

Topic: I.06. Computation, Modeling, and Simulation

Title: Methods for comparing models with eeg data using representational similarity analysis

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Abstract: Assessing the quality of a neural model requires a method for comparing model predictions to data. For example, a model can be evaluated based on its ability to predict neural responses (Yamins and Hong et al., 2014) or on the similarity of representations of the stimuli in the model and in the brain (Kriegeskorte et al., 2008). We focus on the latter—representational similarity analysis. Because there are several ways to compute representational similarity, we

want to understand which measure of similarity (distance metric) is best.
We use a state-of-the-art convolutional neural network (CNN) model that performs object categorization when trained on a large image set (Russakovsky et al., 2014). EEG responses from human participants passively viewing 72 images were used, where each image came from one of six object categories (Kaneshiro et al., 2015).
In order to compute representational similarity of stimuli in the CNN, we compute the activations from each stimulus in each layer. The similarity of stimulus representations is measured by the correlation between each pair of activations for each pair of stimuli. For the neural measurements, we focus on three distance metrics: correlation, classifier accuracy and absolute voltage difference between EEG signals from different images. We then compared the representational dissimilarity matrices (RDMs) from each of these distance metrics to the model RDMs across layers using Spearman's R.
Comparing RDMs computed across time from EEG data and from the model, the best correlation between the model and brain RDMs was found using classifier accuracy as the distance metric ($r=0.35$ compared to $r=0.32$ and $r=0.27$ for absolute difference and correlation respectively). Qualitatively, the RDM computed using classifier accuracy had a block diagonal structure corresponding to the categorical nature of the stimuli. On the other hand, this categorical structure was not as clear if correlation or absolute difference were used as the distance metrics. Finally, the correlation between the classifier RDM and the CNN RDM was a smooth inverted U-shape function of time for each layer. However, these time structures were strongly oscillatory, with period approximately 80 ms, when correlation or absolute difference RDMs were used. This periodicity suggests an underlying temporal structure possibly due to alpha rhythms in the EEG data. This complicates the interpretation of these forms of RDMs because the CNN model class does not have this type of dynamics.
Taken together, RDMs based on classifier accuracy are the preferred method for comparing representational similarity between models and EEG data.

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Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.10/LLL28

Topic: I.06. Computation, Modeling, and Simulation

Support: University at Buffalo

Title: Lobular electric field distribution during cerebellar transcranial direct current stimulation - Cognitive versus somatomotor sub-regions

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Abstract: INTRODUCTION We developed a computational pipeline to determine subject-specific lobular electric field (EF) distribution during cerebellar transcranial direct current stimulation (ctDCS). In this exploratory computational study, we investigated ctDCS-induced EF to understand its cognitive versus somatomotor effects. METHODS Head model was constructed from MR images of a healthy volunteer (female, age 31). Finite element analysis was conducted on the head model to find the ctDCS-induced EF. ctDCS was delivered via two 5cm×5cm electrodes at a direct current of 2mA based on two published 2-ch montages: anode over the right cerebellum 3 cm lateral to the inion, and 1) the cathode over the right buccinator muscle - Celnik montage [1], 2) the cathode on the contralateral supraorbital area - Manto montage [1]. Our pipeline isolated subject-specific cerebellar lobules using SUIT cerebellar atlas [2] and then computed average lobular EF distribution. We then optimized 8-ch high-definition (HD) ctDCS montage to target cognitive versus somatomotor sub-regions of the cerebellum. RESULTS Both 2-ch montages primarily affected the posterior and the inferior parts of the cerebellum (i.e., lobules VI-VIII) [1]. Multiple comparison post-hoc tests (see Figure) following ANOVA showed that Manto montage primarily targeted the somatomotor sub-regions (Lobules VIII, VII, IX) while Celnik montage targeted both motor (Lobules VIII, VII, IX) and cognitive (CrusI) sub-regions. Our software pipeline found novel 8ch HD-ctDCS montages for subject-specific focal targeting of cognitive versus somatomotor sub-regions. DISCUSSION To our knowledge, no previous study has optimized HD-ctDCS towards lobule-specific EF distribution [3].
REFERENCES [1] G. Grimaldi et al., Neuroscientist. 2016, 22(1): 83-97. [2] J. Diedrichsen, J. Neuroimage. 2006, 33(1): 127-138. [3] Z. R. H. Abadi and A. Dutta, 2017 8th International IEEE/EMBS Conference on Neural Engineering. 2017, 428-431.

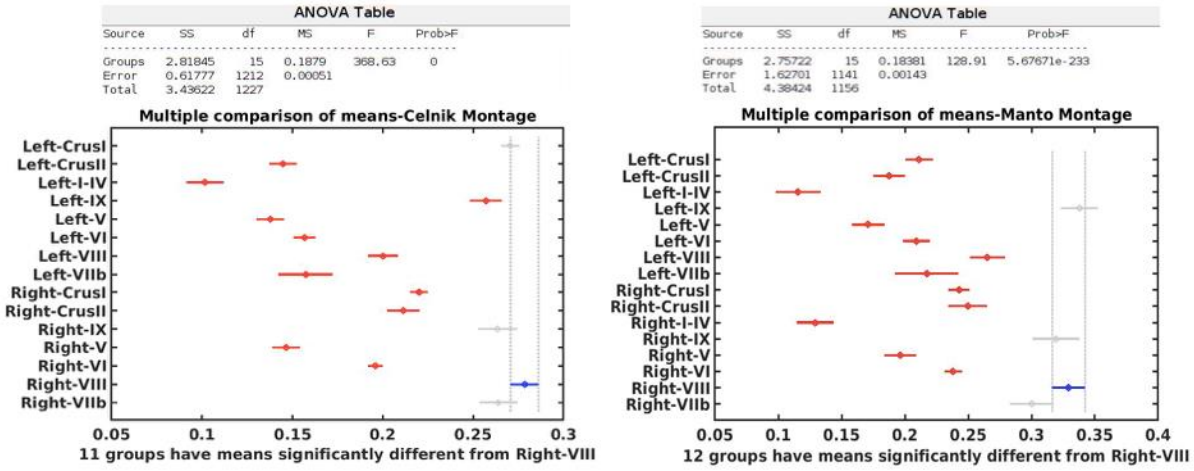

Figure 1: One-Way ANOVA Multiple Comparison results for Celnik Montage (top diagram) and Manto Montage (bottom diagram)

Disclosures: Z. Rezaee: None. **A. Dutta:** None.

Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.11/LLL29

Topic: I.06. Computation, Modeling, and Simulation

Title: Unsupervised learning techniques for electromyography classification

Authors: *E. LASHGARI, U. MAOZ
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Abstract: Improving the accuracy of synthesized human motion is an ongoing challenge in various disciplines such as neuroscience, physiology, biomechanics, brain-computer interface, and robotics. Electromyography (EMG) measures muscular contraction, as part of neuromuscular activation. Complex, non-linear, high-dimensional data sets—such as neuromuscular activity—are hard to study in their original form. Therefore, we often strive to find meaningful low-dimensional representations of the data that maintain important aspects of and relationships between parts of the original, high-dimensional data. Linear dimensionality reduction algorithms have proved to be of limited use because they ignore the structure of the manifold in which the data is embedded and cannot well handle nonlinearities in EMG signals. Here we used a nonlinear dimensionality-reduction technique named Manifold Learning to analyze and visualize EMG of 5 upper limb muscles in a dataset of 12 human subjects. Our results demonstrate the advantages of non-linear over linear techniques as preprocessing stages before classification.

Disclosures: U. MAoz: None.

Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.12/LLL30

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH/NIGMS 1P01-GM118629-01A1
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Department of Health Science and Technology (I.R.)
Picower Postdoctoral Fellowship (S.C.)

Title: Detecting bursts in electroencephalography and local field potential spectrograms using a hidden Markov model

Authors: *I. C. RICE[1], S. CHAKRAVARTY[2], P. KAHALI[2,5], J. DONOGHUE[1,2], M. MAHNKE[3], E. K. MILLER[2,3], O. JOHNSON-AKEJU[5], E. BROWN[1,2,3,5,4]
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Abstract: Electrophysiological activities in the brain are often analyzed via spectral estimation of neural recordings, e.g. electroencephalogram (EEG) and local field potentials (LFP). The multitaper (MT) spectrogram is a statistically principled tool to analyze cerebral activities, including distinctive patterns characterized by short-duration band-limited high-amplitude power (bursts). Such burst patterns are associated with various neurological states and can be potentially used as informative markers to track brain states during anesthesia-induced unconsciousness. A computational method to automatically detect such bursts will allow for efficient, unbiased processing of data prior to any statistical analysis. With this motivation, we have developed a computational scheme to automatically detect the bursts using a Hidden Markov Model (HMM). In the current work, we consider neural time-series data, which contains bursts of band-limited activity lasting for and repeating at an interval of a few seconds, where this cyclic pattern is sustained over an extended duration. We employ a HMM with Gaussian observations to detect various neural states, one of which is associated to the bursts. The observation sequence is the fraction of MT power estimate in a narrow frequency band, which contains the bursts of interest, relative to a wider band that includes the narrow band but excludes other frequencies with simultaneous high power activity. Both these user-specified bands are currently chosen such that bursts are characterized by visibly distinct increase in observation relative to neighboring epochs. This discrepancy in the relative power during the burst epoch is leveraged by the HMM to associate one of the hidden states with a burst. We demonstrate our scheme using scalp human EEG under ketamine-anesthesia and macaque LFP under propofol-anesthesia. In our current implementations we consider that the relative power sequence contains periods of low, medium, and high (burst state) power in the narrow band. Therefore, we fit the data with a three-state HMM and generate the most probable sequence of states given the observations, thus yielding the time-points of each burst epoch. The burst sequences generated by the algorithm are compared against manually segmented (by visual inspection) data on relevant time segments. The current version of the algorithm achieves burst detection sensitivity of 81% across two ketamine human EEG datasets and 93% - 99% across three macaque LFP datasets.

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Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.13/LLL31

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant 1U01GM104604

Title: Admittance method for estimating local field potentials generated in a multi-scale model of the hippocampus

Authors: *C. S. BINGHAM[1], J. PAKNAHAD[2], J.-M. C. BOUTEILLER[1], D. SONG[1], G. LAZZI[3], T. W. BERGER[1]
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Abstract: Significant progress has been made toward model-based prediction of hippocampal activation in response to extracellular electrical stimulation. While analytical methods provide a first order approximation suitable for model validation, efficient numerical methods are necessary to properly estimate fields arising from endogenous currents and to predict the influence that they have on nearby voltage-dependent mechanisms. Local field potential (LFP) estimation using a multi-scale model of the hippocampus may aid design of neural recording arrays by clarifying which features of tissue geometry or neuronal activity strongly contribute to the LFP. To achieve these goals, the authors have formulated an algorithm for bidirectional communication between an Admittance Method (AM) model volume conductor and a NEURON model hippocampal network. The approach is validated through the comparison of AM predicted evoked potentials with both analytically estimated and experimentally recorded signals. Closed-loop integration of the AM and NEURON models represents a step forward in the predictive power of multi-scale models of cortical tissue. These models may be used to deepen our understanding of hippocampal pathologies and the identification of efficacious treatment.

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Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

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Program #/Poster #: 523.14/LLL32

Topic: I.06. Computation, Modeling, and Simulation

Support: R01AG056015-01
R01AG054081-01A1
GM118269-01A1

Title: State space oscillator models for isolating neural frequencies

Authors: *A. M. BECK[1], E. P. STEPHEN[2], P. L. PURDON[3]
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Abstract: Rhythmic or oscillatory neuronal spiking is an important avenue for information processing within the brain. Populations of these spiking neurons give rise to oscillatory electrical signals that can be recorded in the electroencephalogram (EEG). These oscillatory signals play a role in cognition, attention, sensory processing, and states of altered arousal or consciousness. A traditional approach for quantifying these neural oscillations is to examine signal power or amplitude within frequency bands of interest, using spectral analysis or linear bandpass filtering. A significant problem with the traditional method is that the power in the frequency band of interest is not evaluated with respect to the shape of the complete power spectrum. Thus, power in any band will include broadband “1/f” power, whether or not an oscillation is present. We propose a state space method to identify oscillations in the time domain that describes each oscillation with a low-order autoregressive model. We estimate the autoregressive and noise parameters with an Expectation Maximization (EM) algorithm and identify the presence of oscillatory components, distinct from 1/f noise, using AIC. This method also makes it possible to characterize more precisely the shape or bandwidth of oscillations when they exist, and can distinguish low-frequency (e.g., slow) oscillations from low-frequency drifts. We demonstrate this method on univariate EEG data during resting state and under propofol-induced unconsciousness, where prominent oscillations have been previously characterized.

Disclosures: A.M. Beck: None. **E.P. Stephen:** None. **P.L. Purdon:** None.

Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.15/LLL33

Topic: I.06. Computation, Modeling, and Simulation

Support: Brain Initiative Grant

Title: Estimating and measuring brain temporal latencies

Authors: *S. PAJEVIC[1], A. V. AVRAM[2], A. S. BERNSTEIN[3], R. COPPOLA[7], R. D. FIELDS[4], M. HALLETT[8], Z. NI[5], A. C. NUGENT[7], A. C. SIMMONS[4], F. VIAL[6], P. J. BASSER[4]
[1]OIR/CIT, [2]Natl. Inst. of Biomed. Imaging and Bioengineering, NIH, Bethesda, MD; [3]NICHD, NIH, Rockville, MD; [4]NICHD, [5]Natl. Inst. of Neurolog. Disorders and Stroke, NIH, Bethesda, MD; [6]Human Motor Control Section, NIH, Chevy Chase, MD; [7]MEG Core Facility, NIMH, Bethesda, MD; [8]Human Motor Control Sec, Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD

Abstract: Time-delays in communication between brain regions greatly impact brain function, which requires precise timing of the arrival of neural spikes and signals that propagate along axons. Our aim is to develop methods for measuring and estimating brain network latencies. Here, axon diameter distribution (AAD) measured via MRI are used to estimate conduction velocities, while transcranial magnetic stimulation (TMS) evoked potential (EP) via electroencephalography (EEG), as well as time-series analysis of the magnetoencephalography (MEG) and EEG recordings, provide complementary information with which to estimate latencies. The connectivities and latencies obtained from time-series analysis are typically inferred from time-shifted signals compared in a pairwise manner. Establishing connectivity usually relies on Wiener-Granger causality, which ascribes the improvement in linear prediction or information gain to the inclusion of the potential “causal” source time-series. Our approach is different, as we rely on unpredictable events in time-series and treat them as perturbations for which we try to infer the propagation of their influences. These events are defined as the time points where the time-series falls outside a very stringent confidence interval (e.g., z>5 or larger) for any prediction scheme that we use. Our latency estimation procedure has three steps: 1) identifying “trigger” times at which the onset of unpredictable event occurs; 2) using bi-variate analysis on the count data to determine significant pairs and temporal delays at which the “casual” propagation occurs; 3) using tri-variate mediation analysis to remove the “indirect causes”. We previously tested this procedure on simulated data (a non-linear network of neurons, using only auto-regressive linear prediction) and showed that very long recordings of activity

(many hours) can lead to the correct identification of the majority of the intrinsic latencies in the network. Here, we extend this analysis to a variety of machine learning prediction schemes and ultimately apply all these methods to 4-hour EEG recordings. In these pilot studies, we were able to identify significant latencies, but only in the range between 100 and 300 ms, and with the uncertainty that is larger than 10 ms. In trying to measure latencies, it is important to distinguish between the temporal differences in neural events and delays incurred solely by signal conduction, which we seek to infer. Our results further emphasize the need to supplement time-series analysis with the structural axon diameter and conduction velocity information and with TMS+EEG measurements.

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Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.16/LLL34

Topic: I.06. Computation, Modeling, and Simulation

Support: CFREF, 2016-2023

Title: Eyes open or closed: Synchrony and complexity in a resting state brain network

Authors: *A. GHADERI[1,2], B. BALTARETU[3]
[1]Iranian Neurowave Lab., Najafabad, Iran, Islamic Republic of; [2]Ctr. for Vision Res., [3]Biol., York Univ., North York, ON, Canada

Abstract: Recently, there has been an increase in neuroimaging studies applying graph theoretical analysis (*GTA*) to resting state activity. In the resting state, no task is performed, yet brain activity is affected by visual information, which is why we would expect different brain activity patterns when the eyes are open or closed for example. GTA has been used to determine topological properties (statistical features) of functional brain networks; but, there is little knowledge about dynamical properties, such as synchrony and complexity, in these networks. Our aim here was to develop methodology to investigate these dynamical properties and to uncover them. To investigate the dynamics of the resting state network for eyes closed (*EC*) and eyes open (*EO*) conditions, we used the following measures for data obtained using electroencephalography (EEG): maximum eigenvalue (*ME*), graph energy (*E*) and Shannon entropy (*S*). For each participant (N=45; 8-45 years of age), coherence values from data obtained from 19 EEG channels were calculated. Then, dynamical measures (Laplacian matrices) were

compared by nonparametric permutation test, for each participant. A k-mean approach was used to separate data based on conditions. We did this for delta, theta, alpha, beta, and high beta frequencies. Our results indicate that there were significant differences in all three band frequencies tested. In the alpha band, higher value of *S* was observed in *EO* (p=0.00001), while *EC* exhibits higher *E* (p=0.00001) and *ME* (p=0.00002). In the alpha and beta bands, higher *E* (p=0.00000) and *ME* (p=0.00004) was observed in *EC*. In the high beta band, *EC* exhibits significantly higher *E* (p=0.0002) and lower *S* (p=0.0030) than *EO*. We also found a statistically significantly negative correlation between *E* and *S* (p=0.0195). The k-mean results in 83% accuracy for the *EC* clustering, when alpha measures were used as inputs. According to our results, dynamical properties of resting state network are changed based on whether the eyes are open or closed. Consistent with previous findings about alpha band activity, our findings of higher *ME* and *E* in *EC* can be viewed in terms of increased thalamo-cortical synchrony. This effect has been also observed in beta band, which in turn may be related to higher order cortical processing of visual inputs. The lower *S* in *EC* indicates decreased complexity and information processing in the resting state brain network. Lastly, the negative correlation between *S* and *E* suggests that synchrony predicts complexity in an inverse manner within the brain network. Overall, we have developed a method of analyzing dynamical properties of functional brain networks for resting state activity.

Disclosures: A. Ghaderi: None. **B. Baltaretu:** None.

Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.17/LLL35

Topic: I.06. Computation, Modeling, and Simulation

Title: Local mutual information estimator of functional connectivity on EEG source sparse time series

Authors: *A. OJEDA GONZALEZ[1], R. MARTINEZ-CANCINO[2], K. KREUTZ-DELGADO[3], P. A. VALDES-SOSA[4,5], J. MISHRA[1]
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Abstract: An important goal of translational neuroscience is to characterize brain circuit dysfunctions leading to neuropsychiatric disorders. Such knowledge has potential for developing

non-invasive therapies based on brain-computer interfaces (BCI). However, most attempts to use BCI to rehabilitate impaired cognition fall short due to the use of suboptimal brain imaging technology with low spatiotemporal resolution and oversimplified assumptions of linearity and stationarity of brain interactions. In this work, we address these shortcomings by estimating EEG source time series using a recently developed, real-time, sparse Bayesian learning algorithm followed by the characterization of source functional connectivity using an estimator of local mutual information (LMI). We simulate ground truth functional connectivity patterns and EEG source activity using a biologically inspired large-scale dynamic causal model of the brain. Our simulations show that LMI can successfully track functionally relevant brain network states from the sparse nonlinear time series of online estimated EEG sources.

Disclosures: A. Ojeda Gonzalez: None. **R. Martinez-Cancino:** None. **K. Kreutz-Delgado:** None. **P.A. Valdes-Sosa:** None. **J. Mishra:** None.

Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.18/LLL36

Topic: I.06. Computation, Modeling, and Simulation

Support: Ministry of Science and ICT Grant 20170010980011001

Title: Automatic elimination of EEG artifact using convolutional neural network, ICA features, and dipole source location

Authors: *G. KANG[1], D. KIM[2], S. KANG[3]
[1]Imedisyn, Seoul, Korea, Republic of; [2]iMediSyn, Seoul, Korea, Republic of; [3]Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Electroencephalogram (EEG) signals can be distorted by unwanted noise sources such as eye blinks, horizontal eye movements, muscle activity, line noise and heart signal. Therefore, it is important to identify and remove them to avoid serious misinterpretation. Independent component analysis (ICA) is a statistical method, which is popular to separate the artifacts from EEG signals. Features extracted from ICA are topographic maps, power spectrum and dipole sources. Topographic mapping of the EEG often reflects source localization. Power spectrum can be specifically useful to identify EMG signals. Dipole source localization is used to estimate the location of sources of electrical activity in the brain. One major problem with ICA is that it needs visual inspection by EEG experts. In this study, a new method was developed for automatically classifying and eliminating EEG artifacts using image recognition of image patterns of ICA features using the convolutional neural network (CNN). The EEGs recorded from 841 healthy

subjects were used in this study. Subjects were between the ages of 4 and 80, with 6732 men and 884 women. The pipeline for EEG artifacts removal consists of pre-processing including filtering, common average referencing and ICA. Data for training and testing the CNN model were obtained from manual inspection of the ICA features by EEG experts. Since the volume of data was important for the CNN, generation of additional data was implemented as follows. The pre-processed signals were divided into several segments to extend data for the CNN. ICA was then applied to the segments and ICA features were generated. The CNN was then used to classify neural signal and 3 different artifacts including EMG, horizontal eye movements (eye blinks), and vertical eye movements. The CNN applied to the ICA features presented its effectiveness to automatically classify and remove the EEG artifacts. An accuracy rate of 93.01±2.09% was obtained and eye blinks were most effectively classified with a recognition rate of 98.29±4.76%. The error rates of missing neural signals and artifacts were 4.21±3.16% and 6.60±1.89% respectively. Finally, the execution time of the system was acquired for real-time applicability. In conclusion, a method of the CNN applied to ICA features has been presented to identify and remove EEG artifacts. The results demonstrate that the proposed method can effectively, automatically remove EEG artifacts in EEG signals. This study supports that the deep learning is capable of strong potential for removing EEG artifacts resulting high quality of EEG signal analysis without manual inspection by EEG experts.

Disclosures: G. Kang: None. **D. Kim:** None. **S. Kang:** None.

Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.19/LLL37

Topic: I.06. Computation, Modeling, and Simulation

Support: US Army Research Laboratory under Cooperative Agreement under Grant W911NF-10-2-0022.

Title: Cross-session transfer learning for brain-computer interfaces based on steady-state visual evoked potentials

Authors: *K.-J. CHIANG[1], C.-S. WEI[3], M. NAKANISHI[4], T.-P. JUNG[2]
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Abstract: Brain-computer interfaces (BCIs) based on steady-state visual-evoked potentials (SSVEPs) have been applied to high-speed spellers that allow typing without moving a finger or

speaking a voice. The high efficiency of SSVEP-based BCI speller is established upon the use of individualized training data and advanced detection methodology [1]. However, collecting training data could be time-consuming and laborious to ensure the accuracy of SSVEP detection. Cross-session transfer learning could be an effective way to reduce the need for collecting training data from a new session by leveraging the existing data from other sessions. Our previous study [2] has demonstrated the feasibility of transferring SSVEP templates across sessions to minimize the data-collection effort. We herein proposed a cross-session transferring framework that incorporates least-squares transformation (LST) to alleviate the session-to-session variability of SSVEP data within a subject. The experimental data consist of three sessions of 9-channel, 40-stimuli SSVEP recording from eight subjects [2]. The LST is applied to channel-wise SSVEP data from source (other) sessions to a target (new) session, and seeks the transformation across sessions to maximize the similarity between the transformed source SSVEPs and the target SSVEP templates. We then pooled the LST-SSVEP data and target SSVEP data together to expand the training data size for the new session, and performed the SSVEP detection with the state-of-the-art task-related component analysis (TRCA) technique [1]. The cross-validation results suggest that our cross-session LST-based transferring framework can achieve high performance with a small amount of training data from the new session. In sum, we showed that leveraging SSVEP data from other sessions could improve SSVEP detection and significantly reduce the training time without compromising performance. The proposed LST scheme can be further extended to cross-device or even cross-subject transferring in the future. Support: This work was supported in part by the US Army Research Laboratory under Cooperative Agreement under Grant W911NF-10-2-0022. [1] M. Nakanishi, Y. Wang, X. Chen, Y. T. Wang, X. Gao, and T. P. Jung, “Enhancing Detection of SSVEPs for a High-Speed Brain Speller Using Task-Related Component Analysis,” *IEEE Transactions on Biomedical Engineering*, vol. 65, no. 1, pp. 104-112, Jan. 2018. [2] M. Nakanishi, Y. Wang, and T.-P. Jung, “Session-to-Session Transfer in Detecting Steady-State Visual Evoked Potentials with Individual Training Data,” in *Foundations of Augmented Cognition: Neuroergonomics and Operational Neuroscience*, 2016, pp. 253-260.

Disclosures: K. Chiang: None. **C. Wei:** None. **M. Nakanishi:** None. **T. Jung:** None.

Poster

523. Computation, Modeling, and Simulation: EEG, Evoked Potential, and Electrophysiology

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 523.20/LLL38

Topic: I.06. Computation, Modeling, and Simulation

Support: 2 R01 NS047293-09A1
W911NF-10-2-0022

Title: Skull conductivity and source location estimation (SCALE) to high-resolution EEG source imaging

Authors: *Z. AKALIN ACAR, S. MAKEIG
Inst. for Neural Computation, Univ. of California San Diego, La Jolla, CA

Abstract: We have published a novel iterative Skull Conductivity And source Location Estimation (SCALE) algorithm for simultaneously estimating head tissue conductivities and brain source locations (Akalin Acar et al., 2016). SCALE uses a realistic FEM head model and scalp maps of near-dipolar sources identified using independent component analysis (ICA) decomposition of sufficient high-density EEG data. Our simulations have shown that skull conductivity is the most important impediment to high-resolution EEG source imaging (Akalin Acar et al., 2013). Until now, there has been no widely accepted and used method for non-invasively measuring skull conductivity in individual subjects. We propose that using SCALE, functional EEG source imaging can become routine and accurate. Figure 1 shows scalp maps and estimated source distributions.

We applied SCALE to nine (9) subjects, ages 19-25 years. We collected 256-channel EEG data with 3-D digitization of electrodes while they performed either a video game-playing experiment, dart throwing, and/or an arrow flanker task. Table 1 shows the estimated brain-to-skull conductivity ratios (BSCR values) and (in parentheses) the number of ICs used for SCALE for these subjects' different experiments. For the 3 subjects with two experiment data sets (FR, JH, and SE), the estimated BSCR values for the two experiments were very close (mean within-subject difference <9% versus 33% between-subjects). These preliminary results indicate the robustness of the SCALE approach across experimental sessions and paradigms, and suggest this approach can make EEG a portable, low cost modality for accurately imaging EEG brain activity.

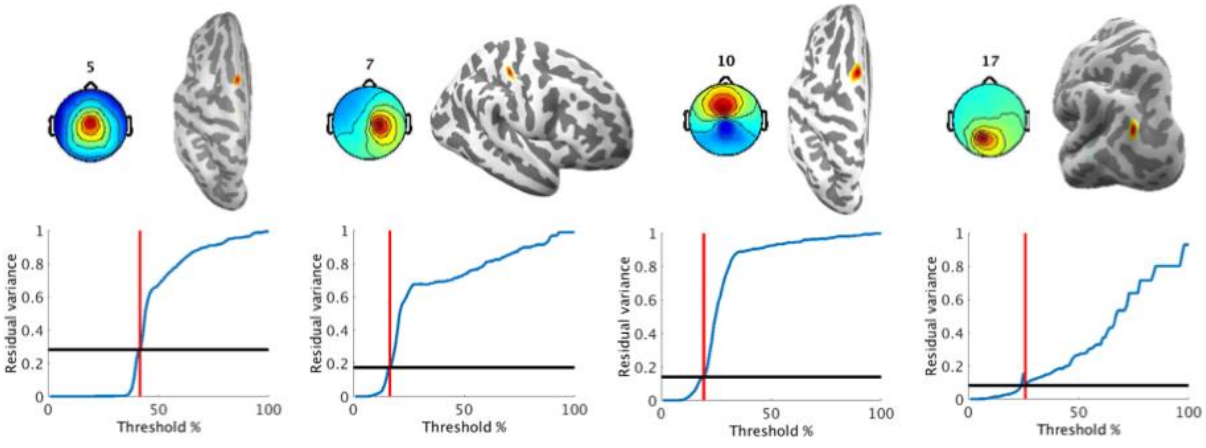


Figure 1 *(Top row): Scalp map, estimated source distribution (plotted on the subject's semi-inflated cortical surface) of 4 independent component sources dominating an Error-Related Negativity (ERN) feature of the event-related potential (ERP) time-locked to erroneous finger button responses in an Eriksen flanker task session recorded from 128 scalp channels. Bottom row: Residual scalp map variance of the percentage thresholded SCALE-converged best-fitting source distribution. The red line shows the threshold used for these source distributions.*

Table 1: BSCR values for 9 subjects									
	BD	FR	AV	RB	LH	GV	AS	JH	SE
STRUM	28 (10)	43 (14)	30 (13)	68 (15)		31 (11)	63 (12)	48 (15)	31.5 (15)
Darts		45 (14)			20 (16)				
Arrow Flanker								54 (13)	34 (13)

Disclosures: Z. Akalin Acar: None. **S. Makeig:** None.

Poster

524. Computation, Modeling, and Simulation: Informatics and Database

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 524.01/LLL39

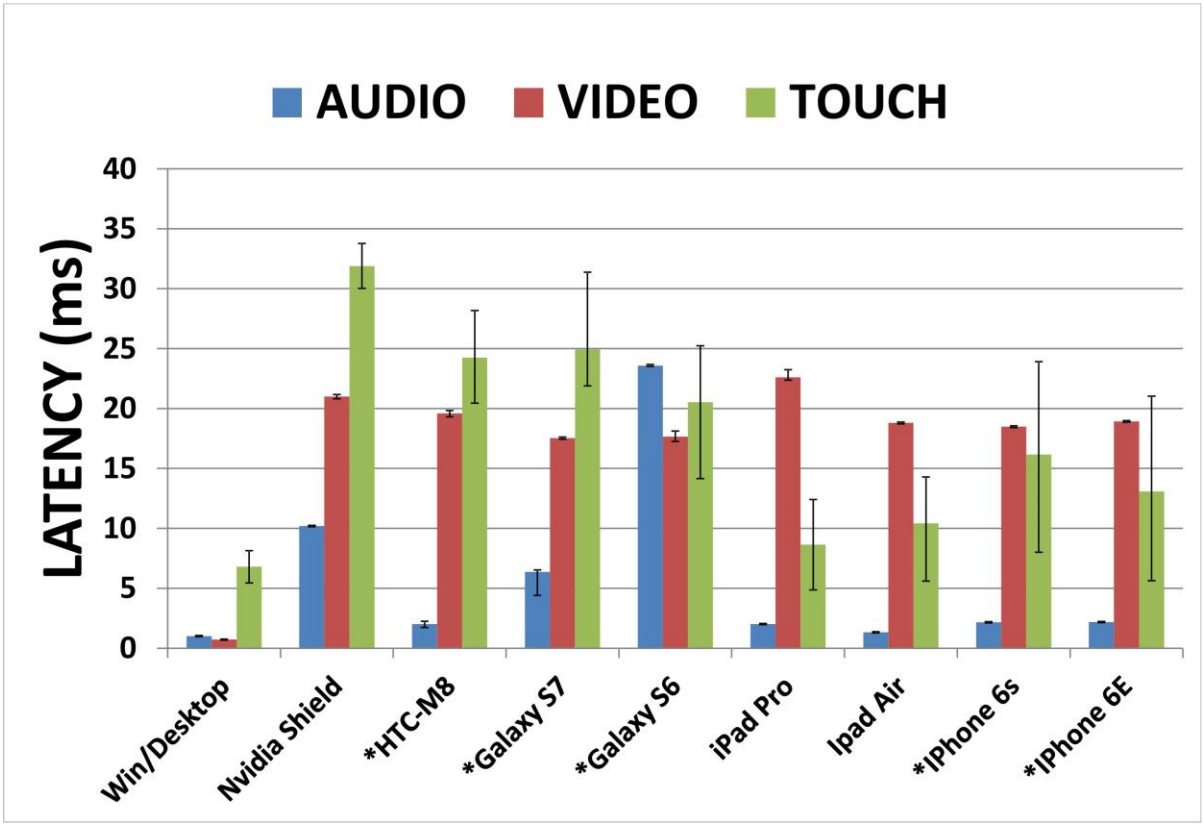
Topic: I.06. Computation, Modeling, and Simulation

Title: Calibrating the timing of neuroscientific apps on mobile devices

Authors: M. I. W. GRIVICH, 94704-1151, P. A. W. PEBLER, 94704-1151, *D. L. WOODS Neurobehavioral Systems, Inc., Berkeley, CA

Abstract: Neuroscientists wishing to use mobile apps in their research face two major obstacles: (1) High-precision mobile apps are challenging to program, and require different development environments for the iOS and Android operating systems (OSs); (2) App timing calibration is a challenge because mobile devices lack the hardware ports necessary to connect with traditional calibration systems. Here, we describe (1) Presentation® Mobile, which enables the rapid programming of mobile apps that execute on both iOS and Android devices; and (2) The LabStreamer, a device which enables paradigm timing calibration through wired connections or over wireless networks using the Lab Streaming Layer (LSL) network-timing protocol. METHODS. We measured timing delays of Presentation Mobile calibration tests on iOS and Android tablets and smartphones by comparing the time of stimulus occurrence reported by the mobile OS and the actual time of stimulus occurrence measured from photodiode and microphone inputs. Touch latencies were measured by stimulating touches with an electrode attached to the mobile-device screen. RESULTS: Figure 1 shows median latencies and 95% confidence intervals for different mobile devices (* = smartphone) and a Windows desktop computer. We found a range of OS- and device-specific latency delays for both auditory and visual stimulus delivery and touch-response registration. However, delays showed little temporal jitter (e.g., within-device standard deviations were less than 0.4 ms for auditory stimulus delivery and less than 0.8 ms for visual stimulus delivery). DISCUSSION: Accurate physiological and

behavioral data can be recorded from mobile devices connected over wireless networks if corrections are made for device-specific delays in stimulus delivery and response registration.



Disclosures: **M.I.W. Grivich:** A. Employment/Salary (full or part-time):; Neurobehavioral Systems, Inc. **P.A.W. Pebler:** A. Employment/Salary (full or part-time):; Neurobehavioral Systems, Inc. **D.L. Woods:** A. Employment/Salary (full or part-time):; Matthew I. Grivich, Neurobehavioral Systems, Inc..

Poster

524. Computation, Modeling, and Simulation: Informatics and Database

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 524.02/LLL40

Topic: I.06. Computation, Modeling, and Simulation

Title: The SONATA data format: A new file format for efficient description of large-scale neural network models

Authors: *A. ARKHIPOV[1], E. B. MULLER[2], K. DAI[1], Y. N. BILLEH[4], J.-D. COURCOL[3], S. L. GRATIY[1], J. HERNANDO[2], A. DEVRESSE[2], M. GEVAERT[2], J. G. KING[5], W. VAN

GEIT[2], D. NACHBAUER[2], A. POVOLOTSKIY[2]
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Abstract: Increasing computing power and availability of high-performance computing (HPC) resources have made it easier for neuroscientists to simulate and visualize large-scale brain network models. However, one bottleneck for building, simulating, and sharing large-scale networks is the lack of efficient data formats. A widespread practice is to represent models with simulator specific code such as hoc, SLI or python. XML based formats have been proposed as a solution. But the use of XML quickly becomes problematic when scaling up to large realistic networks.

Thus, an open specification is needed that is compact, computationally fast, yet also easy to read and edit. To meet these demands, the Allen Institute (AI) and the Blue Brain Project (BBP) have jointly developed the SONATA (Scalable Open Network Architecture TemplAte) Data Format - an open-source framework for representing neuronal circuits. The framework utilizes both organizations' expertise with large-scale HPC network simulation, visualization and analysis. It was designed for memory and computational efficiency, as well as to work across multiple platforms. We provide the specification documentation, open-source reference APIs, and model and simulation output examples with the intention of catalyzing support and adoption of the format in the modeling community.

In the SONATA format, properties of nodes (cells) and edges (synapses/junctions) of a network are stored in table-based data structures, hdf5 and csv, using indexing procedures for fast and parallelizable lookup. The use of hdf5 provides both efficiency in space and read-time. The format provides naming conventions for node and edge properties, but also allows for extensions to include additional properties.

Besides network representation, SONATA includes representation of simulation output, which is optimized for memory and read/write performance. This permits efficient storage of variables such as spike times, membrane potential, and Ca2+ concentration. Lastly, to bring together network models, simulation output, and various run-time conditions (duration, time step, temperature, etc.), SONATA includes a JSON-based file format for configuring simulations.

The rapid advancement in neuroscientific data generation, large-scale data-driven modeling, and simulation capabilities makes the development of standards for network simulations necessary. The SONATA Data Format and framework (https://github.com/AllenInstitute/sonata) are open to the community to use and build upon with the goal of achieving such a standard data format.

Disclosures: A. Arkhipov: None. **E.B. Muller:** None. **K. Dai:** None. **Y.N. Billeh:** None. **J. Courcol:** None. **S.L. Gratiy:** None. **J. Hernando:** None. **A. Devresse:** None. **M. Gevaert:** None. **J.G. King:** None. **W. van Geit:** None. **D. Nachbauer:** None. **A. Povolotskiy:** None.

Poster

524. Computation, Modeling, and Simulation: Informatics and Database

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 524.03/LLL41

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF 1458495
NSF 1458840

Title: The Neuroscience Gateway: Enabling large scale modeling and data processing in neuroscience

Authors: *N. T. CARNEVALE[1], S. SIVAGNANAM[2], K. YOSHIMOTO[2], A. MAJUMDAR[2]
[1]Neurosci., Yale Univ. Sch. Med., New Haven, CT; [2]San Diego Supercomputer Ctr., Univ. of California San Diego, La Jolla, CA

Abstract: We review the origin and evolution of the Neuroscience Gateway (NSG; http://www.nsgportal.org) as a high performance computing (HPC) resource for neuroscientists. When it first became available to users in 2013, NSG's design goal was to provide neuroscientists free and easy access to simulation software installed on HPC hardware for their increasingly complex models of biological neurons, neural circuits, and systems. More recently we have expanded it to also serve cognitive and experimental neuroscientists facing large scale data analysis problems (e.g. fMRI processing, connectome pipelines). It is also being used for educational purposes in neuroscience courses and workshops. The diverse and growing set of modeling and data analysis tools currently available via NSG includes BluePyOpt (from the European Human Brain Project), Brian, CARLsim, DynaSim, EEGLAB, Freesurfer, Human Neocortical Neurosolver (HNN), Large Scale Neural Modeling Simulator, MATLAB, MOOSE, NEST, NetPyNE, NEURON, Octave, PGENESIS, PyNN, Python, R, TensorFlow, and The Virtual Brain Personalized Multimodal Connectome Pipeline. These can be accessed either through a web portal or programmatically through a RESTful API. NSG allows a wide range of use cases: individual users with NSG accounts can work directly with individual tools, or with packaged pipelines, or configure their own pipelines; users of community projects that take advantage of NSG's RESTful API (e.g. OpenSourceBrain) can employ HPC resources via NSG without having to leave their familiar working environment or even obtain their own NSG accounts; software developers can use NSG for dissemination of their projects, e.g. BluePyOpt, CARLSim, DynaSim, EEGLAB, HNN. NSG is being used by neuroscience researchers, educators, and students at institutions and laboratories around the world, and its user base is currently >600 and still growing. Based on increasing demand and usage, we have successfully obtained progressively larger allocations of HPC resources through the competitive peer review process of the Extreme Science and Engineering Discovery Environment (XSEDE) program.

Developing and operating the NSG has given us a unique opportunity to understand the diverse HPC needs of neuroscientists and explore associated issues and needs for collaboration, data sharing/management and various forms of computing. Supported by NSF 1458495 (NTC) and NSF 1458840 (SS, KY, AM).

Disclosures: S. Sivagnanam: None. **K. Yoshimoto:** None. **A. Majumdar:** None.

Poster

524. Computation, Modeling, and Simulation: Informatics and Database

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 524.04/LLL42

Topic: I.06. Computation, Modeling, and Simulation

Support: European Community Grant H2020-720270 (Human Brain Project SGA1)

Title: Systematic statistical validation of data-driven models in neuroscience

Authors: *S. APPUKUTTAN[1], P. E. GARCIA-RODRIGUEZ[1], L. SHARMA[1], S. SÁRAY[2], S. KÁLI[2], A. P. DAVISON[1]
[1]Unité de neurosciences, information et complexité, Ctr. Nationale De La Recherche Scientifique, Gif-sur-Yvette, France; [2]Inst. of Exptl. Med., Hungarian Acad. of Sci., Budapest, Hungary

Abstract: The expansion of knowledge in neuroscience has resulted in a myriad of models to represent the multi-level complexity of the brain, from the subcellular scale, through multi-compartment neurons, microcircuits to network level models. An essential element of scientific modeling is validation of the model with respect to experimental data. Until recently this has most often been done in an ad hoc way, with most studies reporting only qualitative comparisons between simulation results and experimental findings, and different modeling studies using different datasets for validation, which makes comparison of models difficult.
Inspired by quality control methods from software engineering, SciUnit (Omar, Aldrich & Gerkin, ICSE 2014) is an attempt to remedy these problems by providing a software framework for quantitative validation testing that explicitly supports applying a given validation test to different models. By defining interfaces to which models must adhere, tests can be model agnostic and used to validate any compatible model despite differences in their internal structures, the language used and/or the simulator employed.
Building on the SciUnit framework, we have developed suites of validation tests for biophysically and morphologically detailed neuron models, and for circuit models of different brain regions. HippoUnit, CerebUnit and BasalUnit are validation suites catering to neuron activity models of hippocampus, cerebellum and basal ganglia, while MorphoUnit targets testing of neuronal reconstructions and network structures. Each test is implemented as a class in the

Python language, and comprises a specification of the required model capabilities, the location of the reference dataset, and data analysis code to transform the variables recorded from simulations (such as membrane potential, action potentials) into a format (for example a histogram) that allows the simulation results to be directly compared to the experimental data through a statistical test.
We have further developed a web services framework to support the management of models, tests, and validation results. It is accessible via web apps within the Human Brain Project Collaboratory and through a Python client. The framework enables tracking the evolution of models over time, as well as comparison against other models in the domain.
This work was performed as part of the Human Brain Project (HBP), in collaboration with colleagues modeling the brain regions mentioned above.

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Poster

524. Computation, Modeling, and Simulation: Informatics and Database

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 524.05/LLL43

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF IIS-1636893
NSF BCS-1734853
Microsoft Research Award
Indiana University Areas of Emergent Research initiative “Learning: Brains, Machines, Children.”
NSF ACI-1445604
NSF IIS-1550320

Title: A public cloud platform for large-scale data analysis, visualization and sharing of reproducible neuroscience research

Authors: *F. PESTILLI[1], L. KITCHELL[2], B. MCPHERSON[4], D. BULLOCK[5], B. A. CARON[2], E. GARYFALLIDIS[2], R. HENSCHEL[2], O. SPORNS[3], L. WANG[6], A. J. SAYKIN[7], I. DINOV[8], S. HAYASHI[2]
[1]Psychology, Neuroscience, Cognitive Sci. and Network Sci., Indiana Univ., Bloomington, IN; [2]Indiana Univ., BLOOMINGTON, IN; [3]Psychological and Brain Sci., Indiana Univ., Bloomington, IN; [4]Psychological and Brain Sci., Indiana Univ. Bloomington, Bloomington, IN; [5]Psychological & Brain Sciences; Neurosci., Indiana Univ. - Bloomington, Bloomington, IN; [6]Psychiatry, Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [7]Radiology and Imaging

Sci., Indiana Univ. Sch. of Med., Indianapolis, IN; [8]Univ. of Michigan Sch. of Nursing, Ann Arbor, MI

Abstract: Neuroscience is engaging at the forefront of science by dissolving disciplinary boundaries and promoting transdisciplinary research. This is a process that, in principle, can facilitate discovery by convergent efforts from theoretical, experimental and cognitive neuroscience, as well as computer science and engineering. To assure the success of this process the current lack of established mechanisms to guarantee reproducibility of scientific results must be overcome. Promoting open software development and data sharing have become paramount in the quest to achieve reproducibility. We present brainlife.io, a platform addressing challenges of neuroscience reproducibility by providing integrative mechanisms for publishing data, and algorithms while embedding them with computing resources to impact multiple scientific communities.We present three main technological results for widespread impact on neuroscience research and discovery. First, we demonstrate that platform can capture brain data, publish algorithms as reproducible applications, and perform data-intensive computing on Clouds. Second, we present novel algorithms for mapping brain networks using Clouds. The algorithms will enhance discovery by leveraging on the online platform for data-intensive processing of large datasets. Third, we publish test-retest brain datasets and derived data (processed), such as connectome matrices, multi-parameters tractography models, cortical segmentation and functional maps. These datasets can be used as a reference or to develop algorithms for functional mapping, anatomical computing, and optimization.The platform presents a unique method and technology for publishing the full set of scientific research assets in a study comprising data and analyses code as well as all provenance information, embedded in a series of reproducible, open cloud platform web-services that allow collaborative tracking of the scientific process. We demonstrate that the core platform functionally including software, data, and analyses to reproduce major published results in neuroscience. To promote a grassroots approach to open neuroscience, brainlife.io allows scientists to publish data and reproducible analyses with seamless access to national supercomputers. In sum, the brainlife.io platform provides access to algorithms, data and computing resources to trainees, and faculty nationally. The entire platform and all technologies developed with it are freely available and open-source to contribute to the wide community of users, and researchers in the neurosciences.

Disclosures: F. Pestilli: None. **L. Kitchell:** None. **B. McPherson:** None. **D. Bullock:** None. **B.A. Caron:** None. **E. Garyfallidis:** None. **R. Henschel:** None. **O. Sporns:** None. **L. Wang:** None. **A.J. Saykin:** None. **I. Dinov:** None. **S. Hayashi:** None.

Poster

524. Computation, Modeling, and Simulation: Informatics and Database

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 524.06/LLL44

Topic: I.06. Computation, Modeling, and Simulation

Title: Neuroglia: A Python library for analyzing large scale electrophysiology and calcium imaging with scikit-learn machine learning pipelines

Authors: *J. KIGGINS, M. D. OLIVER, S. MANAVI, C. MOCHIZUKI, N. CAIN, S. R. OLSEN
Allen Inst. for Brain Sci., Seattle, WA

Abstract: Applying modern machine learning techniques to the analysis of neurophysiology data requires the researcher to extract relevant features from the continuous time-varying activity of populations of recorded neurons. For example, to apply supervised classification techniques to population activity for a decoding analysis, the researcher must create a population response vector for each stimulus to decode. Depending on the scientific question and recording modality, this response vector could be the mean calcium signal in a window during each stimulus or the time to first spike after the stimulus onset. We have developed an open source Python package, *neuroglia*, to aid neuroscientists in incorporating these common transformations into machine learning pipelines. In *neuroglia*, these transformations between these core data structures are defined as scikit-learn compatible transformers—Python objects utilizing a standardized fit, transform, and predict methods, allow them to be chained together into scikit-learn pipelines. Here, we illustrate the core design principles of the package and demonstrate how the package facilitates applying modern machine learning to population neurophysiology datasets. We demonstrate its use on both large scale Neuropixels recordings and 2-photon calcium imaging data.

Disclosures: J. Kiggins: None. **M.D. Oliver:** None. **S. Manavi:** None. **C. Mochizuki:** None. **N. Cain:** None. **S.R. Olsen:** None.

Poster

524. Computation, Modeling, and Simulation: Informatics and Database

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 524.07/LLL45

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH R44 NS074540
NIH U24 EB023398

Title: Nih funded NITRC's triad of services: Software, data, compute

Authors: *D. N. KENNEDY[1], N. PREUSS[2], C. HASSELGROVE[3]
[1]Psychiatry, U. Massachusetts Med., Worcester, MA; [2]TCG, Inc., Washington, DC; [3]Univ. of Massachusetts Med. Sch., Worcester, MA

Abstract: Aim of Investigation: NeuroImaging Tools and Resources Collaboratory (NITRC) is a neuroinformatics knowledge environment for MR, PET/SPECT, CT, EEG/MEG, optical imaging, clinical neuroinformatics, computational neuroscience, and imaging genomics tools and resources.
Methods: Initiated in 2006 through the NIH Blueprint for Neuroscience Research, NITRC's mission is to foster a user-friendly knowledge environment for the neuroinformatics community. By continuing to identify existing software tools and resources valuable to this community, NITRC's goal is to support its researchers dedicated to enhancing, adopting, distributing, and contributing to the evolution of neuroinformatics analysis software, data, and compute resources.
Results: Located on the web at www.nitrc.org, the Resources Registry (NITRC-R) promotes software tools and resources, vocabularies, test data, and databases, thereby extending the impact of previously funded, neuroimaging informatics contributions to a broader community. NITRC-R gives researchers greater and more efficient access to the tools and resources they need, better categorizing and organizing existing tools and resources, facilitating interactions between researchers and developers, and promoting better use through enhanced documentation and tutorials—all while directing the most recent upgrades, forums, and updates. All services freely downloadable, NITRC-R offers 1,000 public resources; NITRC-Image Repository (NITRC-IR) offers 9,924 imaging sessions, and NITRC Computational Environment (NITRC-CE) provides cloud-based computation services downloadable to local machines or via commercial cloud providers such as Amazon Web Services and Microsoft Azure.
Conclusions: In summary, NITRC is now an established knowledge environment for the neuroimaging community where tools and resources are presented in a coherent and synergistic environment. NITRC is a trusted source for the identification of resources in this global community. With over 5,600 citations on Google Scholar, NITRC has supported over 23,900 registered users, served up 10.7 million total, and of that, 9.7 million data downloads, to over 1 million users generating 2.2 million sessions. We encourage the neuroinformatics community to continue providing valuable resources, design and content feedback and to utilize these resources in support of data sharing requirements, software dissemination and cost-effective computational performance.

Disclosures: N. Preuss: None. **C. Hasselgrove:** None.

Poster

524. Computation, Modeling, and Simulation: Informatics and Database

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 524.08/LLL46

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant R24MH114793

Title: A volumetric brain data repository for neuroscience research

Authors: *A. J. ROPELEWSKI[1], A. W. WETZEL[1], G. P. HOOD[1], D. SIMMEL[1], K. BENNINGER[1], J. A. CZECH[1], A. M. WATSON[3], S. C. WATKINS[3], M. P. BRUCHEZ[2]
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Abstract: Capabilities to image the Brain in terms of both resolution and capture speed of optical microscope have pushed the boundaries of what was once thought possible. High resolution cameras, which easily generate gigabytes of data/second, have been integrated into multiple systems. There is also a growth in very fast resonant scanning confocal (ribbon scanning) and multiphoton microscopy. In each case these platforms generate very large data sets, generally multi-terabytes per specimen. While these acquired data can be immediately housed and processed using local storage systems, individual labs frequently must decide the value of data immediately after collection and its value for reuse and long-term storage.
The Brain Image Library is an NIH funded resource to store volumetric brain data, along with essential information about the experiment. BIL has direct connectivity to Internet2, multiple commodity internet providers and direct peering with other networking providers. This high-bandwidth connectivity makes BIL an ideal distribution site for imaging data compliant with FAIR (Findable, Accessible, Interoperable, and Reusable) standards. BIL provides citable identifiers for the submitted data to facilitate tracking of contributed data used by others in publications. BIL deposits serve as a backup function for high-value data that submitting sites desire to be preserved off-site. BIL also provides high performance computing resources that can be used to process staged data prior to submission and supports access control capabilities, including data embargoes until publication.
A unique feature of BIL is that it can provide assistance in moving multi-terabyte brain datasets to the library and help diagnose and resolve network issues related to file transfer speeds. A help desk (bil-support@psc.edu) is available to data submitters to access this service and provide other assistance to sites submitting data to the library.

Disclosures: A.J. Ropelewski: None. **A.W. Wetzel:** None. **G.P. Hood:** None. **D. Simmel:** None. **K. Benninger:** None. **J.A. Czech:** None. **A.M. Watson:** None. **S.C. Watkins:** None. **M.P. Bruchez:** None.

Poster

524. Computation, Modeling, and Simulation: Informatics and Database

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 524.09/LLL47

Topic: I.06. Computation, Modeling, and Simulation

Support: Intelligence Advanced Research Projects Activity (D16PC00005)

Title: Cloud processing and web visualization of petabyte images

Authors: *W. SILVERSMITH, I. TARTAVULL, S. SEUNG
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Abstract: When image datasets fit on one machine, it's easy to see your data, compute metrics, and share entire copies. However, once datasets grow to hundreds of gigabytes, it becomes difficult to view them, and it takes powerful hardware to compute on them. Today, multi-terabyte and even petabyte electron microscopy datasets require storage and computation on a large number of machines. Some labs cannot even see their data, which is critical for analysis and quality assurance.

Within the next year, the iARPA MICrONS program plans to acquire a petavoxel image to study nanoscopic details of neural microcircuitry on the order of a cubic millimeter. The eventual ambition of the connectomics field is to analyze entire brains. This upward pressure has resulted in the development of increasingly sophisticated tools for viewing volumetric images (Saalfeld et al. 2009, Boergens et al., 2016, Knowles-Barley et al. 2016).

Recently, Neuroglancer (an unofficial Google product) has become a popular web app to view large volumetric datasets and associated 3D objects due to its responsive interface, simple and manipulable architecture, and hyperlinked interactive views. Neuroglancer provides interfaces to many server based backends (e.g. NDstore, DVID, Render), but it also defines the "Precomputed" format, a serverless chunk-based format suitable for local storage, Google Cloud Storage, and AWS S3. Precomputed obviates the need to deploy and manage potentially bottlenecking servers. However, Neuroglancer does not provide a client that can read or write Precomputed.

We introduce CloudVolume, a Python client that uses an array-like interface to access arbitrarily sized images in the cloud or locally as numpy arrays. It uses a configurable number of processes, doesn't touch disk unnecessarily, and discards downloaded image chunks after painting to keep a low memory profile. We've witnessed 1.8 Gbps read speeds of gzipped 1024x1024x1 8-bit images on a 16 core Google Compute Engine instance.

We also introduce Igneous, a Python/Numpy based task execution system that can generate image hierarchies, meshes, remap segmentations, and contrast correct images. Igneous pulls dependency free JSON specified tasks off Amazon Simple Queue Service, is based on Kubernetes and CloudVolume, and scales to at least 1600 cores. It has generated five levels of eight bit image hierarchies for a 59 teravoxel image in less than an hour.

Neuroglancer, CloudVolume, and Igneous comprise a system for visualizing and accessing petascale biomedical images collaboratively and are available to the community as open source tools. Used in combination, sharing, computing, and seeing your data are easy again.

Disclosures: W. Silversmith: None. **I. Tartavull:** None. **S. Seung:** None.

Poster

524. Computation, Modeling, and Simulation: Informatics and Database

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 524.10/LLL48

Topic: I.06. Computation, Modeling, and Simulation

Title: Anatomical variability of brain structures in the allen mouse brain common coordinate framework

Authors: *M. D. NAEEMI, N. S. GRADDIS, Q. WANG, S. MIHALAS, J. ROYALL, Y. LI, L. NG, J. A. HARRIS
Allen Inst. for Brain Sci., Seattle, WA

Abstract: The Allen 3D Reference Atlas segments the adult mouse brain among 840 anatomical structures drawn natively within a 3D reference space, the Common Coordinate Framework (CCF). Using these segmentations, we analyzed the neuroantomical variation in 2859 male and female C57BL/6J mice. The dataset consisted of 2-photon image stacks registered to the CCF. Our aim was to find the variability in the volumes of each structure across our mouse population, identify the most variable structures, and analyze the contribution of gender and hemisphere asymmetry to that variability. The CCF is a symmetric 3D reference space generated by the registration and averaging of 1,675 brains imaged from male and female C57BL/6J mice at 2.5 months of age. Annotation of this average template was done by assigning each voxel in the reference space to a brain structure using multi-modality datasets registered to the template. To systematically investigate neuroanatomical variation in our mice, we first triangulated the voxel segmentations of brain structures within our CCF space to produce reference meshes describing the surface of each structure. We deformed these meshes to match the structures in individual subjects, and obtained a set of meshes characterizing the specific anatomy of each individual mouse. The deformed meshes could then be used to calculate surface areas and volumes of all structures in the brain of each individual mouse. Due to the range in the scale of structures in the brain, the coefficient of variation was used as a standardized metric for volume variability. To account for surface area effects, we modeled the coefficient of variation as a function of the surface area to volume ratio. This model was used to evaluate a standardized neuroanatomical variability, accounting for the effects of structure shape and size. We used a generalized linear model to evaluate the effects of gender and hemisphere asymmetry on this standardized variability and found no significant differences. We also measured the variability in the deformation of each voxel in each individual mouse brain when registered to the CCF. Our results show the neuroanatomical variability for each structure in CCF space, and compare it to the variability of voxel deformation from the registration process.

Disclosures: M.D. Naeemi: None. **N.S. Graddis:** None. **Q. Wang:** None. **S. Mihalas:** None. **J. Royall:** None. **Y. Li:** None. **L. Ng:** None. **J.A. Harris:** None.

Poster

524. Computation, Modeling, and Simulation: Informatics and Database

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 524.11/LLL49

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH SPARC 1 OT3 OD025348-01

Title: Open online platform and functionalized anatomical models for computational modeling and integration of NIH SPARC initiative data and models

Authors: *N. KUSTER[1], E. NEUFELD[2], N. CHAVANNES[2], A. M. CASSARA[2], B. LLOYD[2], P. CRESPO[2], M. GUIDON[2], O. MAIZ[2], W. KAINZ[3]
[1]ETH Zurich & IT'IS Fndn., Zurich, Switzerland; [2]IT'IS Fndn., Zurich, Switzerland; [3]Ctr. for Device and Radiological Hlth., U.S. Food and Drug Admin., Silver Spring, MD

Abstract: Advances in neuro-engineering have opened up new avenues for 'electroceuticals' – devices that affect organ function through neuromodulation. For their rapid development, an improved understanding of neural dynamics, nerve mapping, organ electrophysiology, interaction mechanisms, and the design of safe and effective implantable devices is crucial. Computational life sciences (CLS) and *in silico* tools are the method of choice to study interaction mechanisms, targeting optimization, side-effect minimization, treatment personalization, and closed loop control of such devices. Recently, the NIH SPARC initiative was established, an important research endeavour which aims to "transform the understanding of nerve-organ interactions" and "advance the neuromodulation field towards precise disease treatment". A key component of SPARC is a freely accessible online platform (o^2S^2PARC) to support modeling-related activities. o^2S^2PARC will allow to study the interaction of physical stimuli with the human body and its physiology via multi-physics/-scale simulations.o^2S^2PARC is an open-source framework to create, host, connect, and execute computational models, as well as solvers for anatomical model-centred multi-physics simulations. At the core of o^2S^2PARC are detailed, human and animal models which are functionalized with dynamic nerve models and will serve as integration centres for computational (tissue/organs/⋯) models and measurement data and as context for physical modeling. The modeling/coupling originates from a mechanistic electrophysiology perspective. The platform will support image-based- and meta-modeling and quality assurance (chain of custody, traceability, reproducibility, V&V, certification). Prototypes of the o^2S^2PARC platform (front/back-end, communication, and compute services) were realized. Critical solvers (e.g., for electromagnetic and coupled neuronal dynamics modeling) were developed, verified against reference models, and successfully applied to study a range of

therapeutic applications. Anatomical models were functionalized with peripheral nerves (currently: cranial, sacral, brachial, lumbar plexi) based on high-resolution cryosection images (female & male human, monkey). First organ physiology models from SPARC teams could be executed within containerized services and the use of our CLS platform Sim4Life as a service was explored.The evaluated technologies demonstrate that the ambitious vision of o^2S^2PARC is feasible. The final software will be a crucial contribution towards open and extendable simulation platforms for electroceuticals/ neuroprosthetics research.

Disclosures: **N. Kuster:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ZMT Zurich MedTech AG. **E. Neufeld:** A. Employment/Salary (full or part-time):; ZMT Zurich MedTech AG. **N. Chavannes:** A. Employment/Salary (full or part-time):; ZMT Zurich MedTech AG. **A.M. Cassara:** None. **B. Lloyd:** A. Employment/Salary (full or part-time):; ZMT Zurich MedTech AG. **P. Crespo:** None. **M. Guidon:** None. **O. Maiz:** None. **W. Kainz:** None.

Poster

524. Computation, Modeling, and Simulation: Informatics and Database

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 524.12/LLL50

Topic: I.07. Data Analysis and Statistics

Support: National Key Research and Development Program of China 2017YFA0105203

Title: Pair-wise interactions in gene expression determine a hierarchical transcription profile of the brain

Authors: *J. HUA, Z. YANG, T. JIANG, S. YU
Inst. of Automation, Chinese Acad. of Sci., Beijing City, China

Abstract: Expression of individual genes are not independent with each other, therefore characteristics of each gene and gene-gene interactions determine the transcription profile of the genome. Similarly, transcription profiles in different areas of the brain are not independent with each other, so transcription characteristics of each area combined with interactions among different areas determine the global transcription profile across the brain. Together, this is a hierarchical organization traversing from the level of individual genes to the entire brain, which governs how the brain is shaped by genes' transcription. In this study, we are aiming at revealing the quantitative nature of this organization. By studying gene transcription profiles across different areas of human brain in six individuals (the Allen Brain Transcription dataset), we found that such a two-level, hierarchical organization is mainly determined by pairwise interactions. Specifically, we found that the first- and second- order statistics of gene expression profile, corresponding to the likelihood of individual genes expressing and pairwise correlation

in the expression patterns between genes, respectively, could accurately predict the collective features of transcription of the whole genome. Meanwhile, the number of genes been expressed in individual areas, and pairwise correlation in the gene expression patterns between areas could be combined to accurately approximate the collective features of the transcription profile across the entire brain. Our results reveal how the pairwise interactions in gene expression determine the hierarchical transcription profile of the brain, providing a framework to better understand the mechanisms by which complex interactions among genes give rise to brain's structural and functional organizations.

Disclosures: **J. Hua:** Other; Inst. of Automation, Chinese Academy of Sciences. **Z. Yang:** None. **T. Jiang:** None. **S. Yu:** None.

Poster

524. Computation, Modeling, and Simulation: Informatics and Database

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 524.13/LLL51

Topic: I.07. Data Analysis and Statistics

Support: NIH grant MH111099

Title: Large scale analysis of cell type specific changes in whole tissue expression profiles

Authors: *O. MANCARCI[1], L. TOKER[1], S. TRIPATHY[1], P. PAVLIDIS[2]
[1]Psychiatry, Univ. of British Columbia, Vancouver, BC, Canada; [2]Psychiatry, Univ. British Columbia, Vancouver, BC, Canada

Abstract: Analysis of gene expression in whole tissues remain an important tool for the study of neurological disorders. These types of analyses are complicated by the heterogeneity of brain tissues due to difficulties in differentiating cell type specific differences from global changes in gene expression. Recently, we published a method for summarizing expression of cell type markers using principal component analysis (marker gene profiles) and demonstrated that they reflect cell type proportion changes in select datasets. We now expand the scope of our analysis by examining ~400 manually curated, previously published whole tissue datasets to discover cell type specific changes not analyzed by the original studies. The data allows us to compare cell type compositions of mouse and human brains under a wide variety of conditions such as different developmental stages or various neurological diseases. Finally, to ensure the accuracy of our findings, we introduce quality metrics to our marker gene profiles. These quality metrics examine the effect size, the number of correlating cell type markers and how much variance is explained by the first principal component of marker gene expression. In select datasets, we show that quality metrics are useful in differentiating between true (whole tissue studies with

known differences in cell type proportions) and false positives (studies where no cell type proportion differences are expected)

Disclosures: O. Mancarci: None. **L. Toker:** None. **S. Tripathy:** None. **P. Pavlidis:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.01/LLL52

Topic: I.06. Computation, Modeling, and Simulation

Title: Realistic spatial modeling of vesicle trafficking in neurons

Authors: *A. R. GALLIMORE, I. HEPBURN, S. Y. NAGASAWA, E. DE SCHUTTER
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Abstract: The trafficking of vesicles inside neurons plays a number of critical roles: the packaging and release of neurotransmitters on the presynaptic side and the trafficking and sorting of membrane receptors during plasticity on the opposite side of the synapse, for example. Complex subcellular networks coordinate the trafficking of vesicles and their cargo to and from the membrane, and through the cytosol and endosomal system. Despite its central importance in many aspects of neuronal function, and even though computational models of subcellular neuronal processes are becoming increasingly important in neuroscience research, realistic models of vesicular trafficking are almost non-existent. This is largely because the modeling tools for detailed spatial modeling of vesicles are not available. Although spatial modeling has advanced in recent years, with voxel-based molecular simulators such as STEPS incorporating spatial effects - diffusion and probabilistic interactions between molecules within realistic neuronal mesh structures[1] - there has been no explicit account of molecule size or excluded volume effects. Such a simplified approach has the advantage of computational performance and accuracy for small molecules and ions, but these assumptions break down for complex structures of large size such as vesicles and a new modeling approach is required. Extending the STEPS simulator, we have pioneered spherical ‘vesicle’ objects that occupy a unique excluded volume and sweep a path through the tetrahedral mesh as they diffuse through the cytosol. Our vesicles incorporate endocytosis, exocytosis, as well as fusion and budding to and from intracellular membranes, allowing us to model the complete vesicular cycle. In addition, interactions between vesicular proteins and cytosolic and plasma membrane proteins allow us to model vesicular processes, such as membrane docking and endosomal sorting events at an unprecedented level of spatially-realistic and biochemical detail. Our preliminary models using this technology have successfully replicated experimental studies revealing the role of specific Ras-family proteins in the expression of plasticity in the cerebellum[2,3]. In the future, we envisage that this new methodology will open up entirely new avenues of modeling research in all areas of

neuroscience and cell biology in which the regulation of vesicle trafficking and function plays a role. 1. Hepburn, I., Chen, W., Wils, S., De Schutter, E. **2012**, *BMC Syst. Biol.* 6, 36. 2. Kim, T., Yamamoto, Y. & Tanaka-Yamamoto, K. **2017**, *Nat. Comm.* 8, 16. 3. Gallimore, A.R., Kim, T., Tanaka-Yamamoto, K. & De Schutter, E. **2018**, *Cell Rep.* 22, 722-733.

Disclosures: A.R. Gallimore: None. **I. Hepburn:** None. **S.Y. Nagasawa:** None. **E. De Schutter:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.02/LLL53

Topic: I.06. Computation, Modeling, and Simulation

Title: Brain modeling toolkit (BMTK): An open-source package for multiscale modeling of brain circuits

Authors: *K. B. DAI, Y. N. BILLEH, S. L. GRATIY, M. BUICE, N. CAIN, F. BAFTIZADEH, D. FENG, N. W. GOUWENS, R. IYER, S. MIHALAS, C. KOCH, A. ARKHIPOV
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Abstract: The field of neural circuit modeling currently utilizes a variety of different levels of resolution, from biophysically-detailed and point-neuron based networks to population-level and more abstract types of models. Each have their own benefits and drawbacks depending on the questions being investigated. And though it's sometime necessary to bridge these network models, the fact that different levels of resolution use different set of tools and formats can make doing so difficult. To this end the Allen Institute has developed the Brain Modeling Toolkit (BMTK), a open-source software framework for building, simulating and analyzing neural circuit models of various levels of resolution.
The BMTK provides a single and unified package for creating and simulating large-scale network for multiple simulators. Modelers can build a network once, or use an existing network, and run it across a range of different simulators without having to write converters or adaptors. The toolkit provides interfaces to the NEURON simulator for biophysically detailed network, NEST simulator for point-neuron network, DiPDE for populational statistical simulation, LGNModel for filter models, and TensorFlow for convolutional neural networks. The BMTK also uses the SONATA data format that has been jointly developed by the Allen Institute and Blue Brain project. SONATA, a open-format for representing circuit files, simulation parameters and simulation output, allows BMTK to work interchangeably with other software. Software that implements the SONATA standard can reuse networks/simulations built on the BMTK and vice-versa, thus providing a powerful platform for reproducibility and collaboration. And finally the BMTK can work on scales from circuits of a few cells up to circuits of millions of scales and

automatically handle parallelization for cluster computing.
The BMTK, using the SONATA data format, provides a way of integrating a diverse collection of tools and software into a single platform. By unifying different levels of resolution not only does it allow individual modelers to expand upon their own work, but also makes it easier for modelers working across levels to share and collaborate.

Disclosures: Y.N. Billeh: None. **S.L. Gratiy:** None. **M. Buice:** None. **N. Cain:** None. **F. Baftizadeh:** None. **D. Feng:** None. **N.W. Gouwens:** None. **R. Iyer:** None. **S. Mihalas:** None. **C. Koch:** None. **A. Arkhipov:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.03/LLL54

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF GRF Grant DGE-1232825
NSF Grant 1540916

Title: Exploring nuclear connectivity and function within the primate amygdala using the neural engineering framework

Authors: *K. D. FISCHL[1], T. C. STEWART[2], K. M. GOTHARD[3], A. G. ANDREOU[1]
[1]Johns Hopkins Univ., Baltimore, MD; [2]Univ. of Waterloo, Waterloo, ON, Canada; [3]Univ. Arizona, Col. Med., Tucson, AZ

Abstract: The Neural Engineering Framework (NEF) offers a structure and methodology to explore internal dynamics of ensembles of spiking neurons that perform specific computations. The NEF provides the equations that govern neural dynamics and is simulated using Nengo, a graphical and scripting-based Python simulation environment. In Nengo, neural populations are defined such that the collective activity of each population represents a vectored value to be decoded in later computations by way of connections to other populations within the model. The necessary connection weights to implement the desired functions are determined using least squares optimization. We employ Nengo to create a biologically realistic model of the amygdala i.e., a model that reproduces the stimulus-selectivity and the temporal spiking patterns (phasic or tonic responses to stimuli) of the component neurons. Existing models of the amygdala seldom consider biological plausibility due, in part, to the complexity of neuronal types and connections and also to the almost exclusive focus on associative learning (fear conditioning).
Our first attempt at the primate amygdala model focuses on the three main nuclei: lateral, basal/accessory basal, and central. To enable a direct comparison with neural data recorded from the primate amygdala, the model employs simplified abstractions for the experimental setup and

stimuli used to record the activity of small groups of single neurons. Neural data were classified using temporal features and a clustering algorithm. Neurons were categorized as: (1) responsive to the cue, (2) responsive to stimulus onset, (3) responsive to stimulus offset, and (4) tonically responsive during stimulus presentation. The firing patterns of the simulated and real-life neurons were then compared. Using these metrics, we found that the experimental and simulated data were highly correlated. The prevalence of the response patterns of the simulated neurons matched those of the real data for 98.8%, 81.5%, and 92.6% of the responses, respectively by nucleus. These results were obtained after varying model parameters and model size to observe effects on neural response patterns.
The results obtained with the NEF are encouraging and warrant further exploration of this modeling approach, specifically to develop more detailed models of connectivity and function for the main nuclei of the amygdala and of the amygdala as a whole. The results presented in this work come from simulations of our model with visual stimuli, but future work will include simulation with multi-sensory inputs.

Disclosures: K.D. Fischl: None. **T.C. Stewart:** None. **K.M. Gothard:** None. **A.G. Andreou:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.04/LLL55

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF DMS 1361145
Washington Research Foundation

Title: Dynamic worm: Moving model of *Caenorhabditis elegans* worm controlled by the nervous system

Authors: *J. KIM[1], E. SHLIZERMAN[2]
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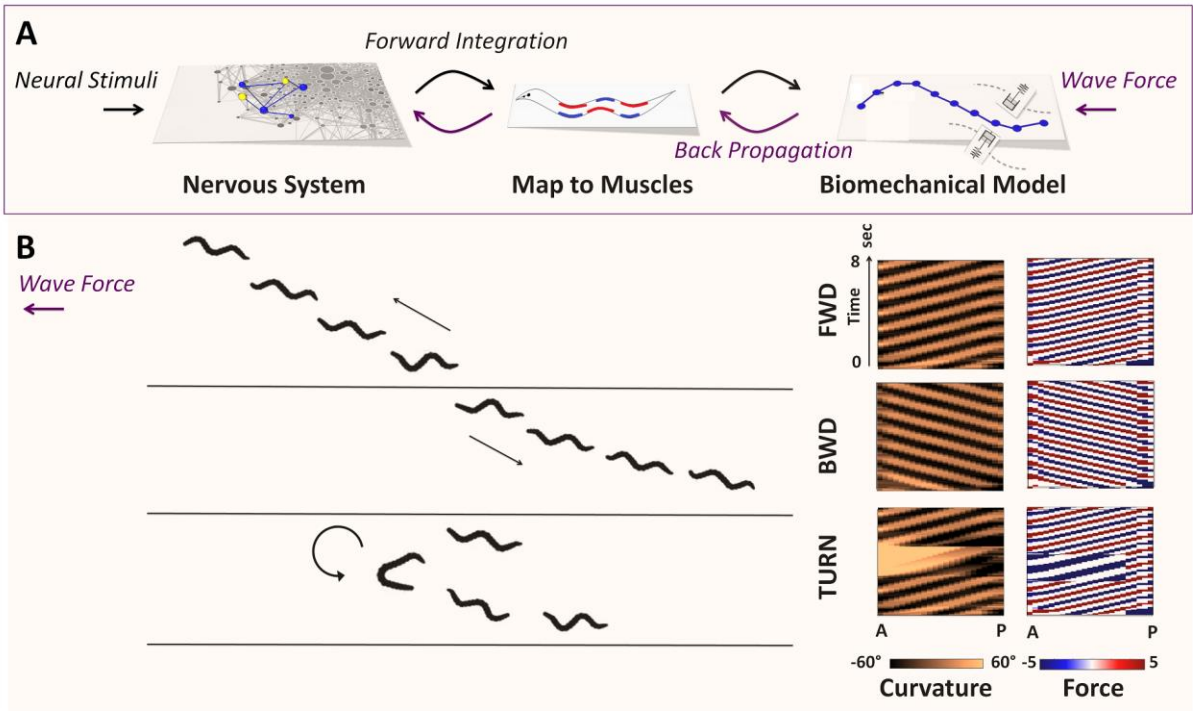
Abstract: Neural circuits generate body movements using rhythmic signals, however, little is known about characteristics of these signals, and their transformation to behavior. Here, we implement the dynamic worm, an in-silico model for the nematode *Caenorhabditis elegans,* to understand how the nematode's nervous system transforms stimuli to behavior. The model emulates the response of the nervous system to stimuli, translates neural activity to muscle forces and muscle impulses to body movements, and implements feedback to account for environmental entrainment. We validate the dynamic worm in both signal propagation directions; back propagating external force applied to the body, and investigate touch response

behaviors by injection of current into sensory and inter neurons. We are able to generate locomotion behaviors typical to the nematode from external force waves and identify a set of stimuli that generate coherent locomotion. In particular, we show that only precise combinations of both sensory and inter neurons generate coherent movements, such as crawling forward, backward and turns. The characteristics of the movements resemble experimentally identified locomotion patterns. We show that neural dynamics associated with distinct movements can be mapped and classified using low dimensional space, but even more importantly, we show that the transformations between the layers of the model are dynamic and require full simulation for each stimulus. By exploring the effect of the environment on locomotion, we find that specific environmental parameters facilitate typical locomotion behavior, and environmental sensory feedback can entrain, sustain and switch between movements. Taken together, our results show that the nervous system encompasses mechanisms of movement initiation, activated by constant stimulation, and mechanisms of movement sustainment through entrainment by the environment.



Disclosures: E. Shlizerman: None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.05/LLL56

Topic: I.06. Computation, Modeling, and Simulation

Support: Sandia LDRD 180885
Sandia LDRD 151345

Title: N2A: A language and software tool for large-scale modeling

Authors: *F. ROTHGANGER
Sandia Natl. Labs., Albuquerque, NM

Abstract: Sharing models and data is doubtless a prerequisite for progress toward a full understanding of brain function. The Neuroscience Information Framework (NIF) does this for many forms of descriptive data. Interchange languages such as NeuroML/LEMS provide a simulator-agnostic description of models, and repositories such as NeuroML-DB and ModelDB make them searchable and accessible.
However, exchanging models and data is not sufficient. It is also necessary to assemble those shared models into larger functional units, ultimately reaching the level of an entire nervous system. From all these details we hope to form abstract descriptions of function. The modeling system must be capable of crossing many scale levels, and component models should be expressed in a form suitable for automated analysis.
N2A is an effort toward these challenging goals. It treats models as data rather than code. This declarative approach describes a model as a set of attributes and equations, without specifying a step-by-step procedure for simulation. It emphasizes the relationships between values within a model and the relationships between models in a larger functional unit.
The declarative approach allows one model to directly extend and modify another, simply by referencing the parent model and declaring new values for specific attributes and equations. A model may also incorporate other models as components, allowing the assembly of arbitrarily deep systems. We will demonstrate an open-source implementation of N2A.

Disclosures: F. Rothganger: A. Employment/Salary (full or part-time):; Sandia National Labs.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.06/LLL57

Topic: I.06. Computation, Modeling, and Simulation

Support: Intel Corporation

Title: Neuromorphic synapses with reconfigurable voltage-gated dynamics

Authors: J. WANG[1], A. AKININ[2], G. CAUWENBERGHS[3], *F. D. BROCCARD[3]
[1]Bioengineering, [3]Inst. Neural Computation, [2]UCSD, La Jolla, CA

Abstract: Synapses are fundamental elements for computation and information processing in neural systems. Although biological synapses express a large variety of receptors in the neuron's membrane, the current hardware implementation of neuromorphic synapses often rely on simple models ignoring the heterogeneity of synaptic transmission. Here we describe a biophysical model of a chemical synapse with reconfigurable pre-synaptic and post-synaptic voltage-gated dynamics implemented on a neuromorphic VLSI chip, and evaluate its versatility with measurements from the chip reproducing the response characteristics of five different ionotropic conductances for both excitatory (AMPA, NMDA) and inhibitory ($GABA_A$, $GABA_C$, glycine) receptors. A neuromorphic implementation of an electrical synapse is also presented. Finally, we discuss applications of the reconfigurable dynamic clamp capabilities of the neuromorphic synapses for the creation of biohybrid circuits between biological and silicon neurons.

Disclosures: J. Wang: None. **A. Akinin:** None. **G. Cauwenberghs:** None. **F.D. Broccard:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.07/LLL58

Topic: I.06. Computation, Modeling, and Simulation

Support: EPFL Blue Brain Project Fund
ETH Board Funding Blue Brain Project Fund

Title: In-silico anatomical reconstruction of astrocytic microdomains

Authors: *E. ZISIS[1], D. KELLER[2], H. MARKRAM[3]
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Abstract: Astrocytes in the brain form anatomically exclusive territories that minimally overlap with neighboring astrocytes. In these domains, each cell establishes connectivity with vasculature and neuronal synapses. In order to investigate the bidirectional dynamics in the neurovascular unit, an accurate anatomical model of such organization is essential. To create the structural geometry of astrocyte domains, we used a weighted tessellation model with volumetric constraints acquired from the literature. Use of a weighted model allowed for non-equidistant boundaries, allowing territories to be affected by the size of the cell.
We distributed astrocytic somata in a rectangular space to match the average cell densities in the rat neocortex as well as the nearest neighbor and radius distributions. Cell positions were co-localized with the reconstruction of the neocortical vasculature and neuronal somata. Next, we

used a Laguerre tessellation model to construct the domains and optimized to match the experimental volume distribution. Extended boundaries were then constructed in order to take into account the required expansion of the domain to account for the overlap with neighbors. Using the geometry of the domains, we extracted the pairwise connections between astrocytes and the vasculature and between astrocytes and neuronal synapses. Finally, the connectivity and the geometrical boundaries set the foundations for in-silico growth of the astrocytic morphologies into their predetermined space using space-filling algorithms.
The presented anatomical reconstruction pipeline forms the basis for future functional models of energy provision to the neuronal microcircuit. Furthermore, the indirect communication of neuronal synapses through the astrocytic syncytium could provide us with insights on the plasticity dynamics in the neuronal-vascular-glial ensemble. Finally, calcium induced intra-cellular and inter-cellular wave simulations require the geometry of domains, the morphologies and the overlap with their neighbors. The workflow generates the anatomical architecture that renders possible all of the above.

Disclosures: E. Zisis: None. **D. Keller:** None. **H. Markram:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.08/LLL59

Topic: I.06. Computation, Modeling, and Simulation

Support: Swiss Commission for Technology and Innovation CTI 25290.1 PFLS-LS
Korean Institute for Advancement of Technology

Title: Neuroman: implementing neuro-functionalized computational human body models

Authors: *B. LLOYD[1], S. FARCITO, 8004[1], A. M. CASSARA[1], E. NEUFELD[1], E. HUBER[1], B. S. CHUNG[2], J. S. PARK[3], M. S. CHUNG[2], N. KUSTER[4]
[1]IT'IS Fndn., Zurich, Switzerland; [2]Dept. of Anatomy, Ajou Univ., Suwon, Korea, Republic of; [3]Dept. of Anatomy, Dongguk Univ., Gyeongju, Korea, Republic of; [4]ETH Zurich & IT'IS Fndn., Zurich, Switzerland

Abstract: There is a growing trend within the neuroscience community and the medical and health industries towards bioelectronics medicine: applying electrical modulation to the nervous system to control and modify physiological functions of the body. These so-called “electroceuticals” include numerous types of neurostimulation devices. While computational techniques to quantify electromagnetic exposure, power absorption, and thermal consequences are well established, predictive tools to study nerve electrophysiology within the complex human anatomical environment and estimate the risk of peripheral nerve stimulation (PNS) are lacking.

To this end, we are developing reference human and animal (rat, monkey) anatomical models, with unprecedented details in the peripheral nervous system and connectivity to organs and muscles, functionalized with compartmental nerve models to investigate interactions with neuronal electrophysiology.
Cryosection image data is being used as the basis for the new monkey and human male and female phantoms due to the unique resolution (i.e. 0.1 × 0.1 × 0.2 mm in the human female) and quality of these images. For the rat, high-resolution magnetic resonance images will be acquired.
To segment important peripheral nerves, a nerve tracing tool has been developed, which allows to semi-automatically extract smooth nerve trajectories by specifying sparse (start/end) points along a nerve in the cryosection image stack. Functionalization is achieved by assigning electrophysiological models of myelinated and unmyelinated axons to trajectories within nerve models based on histological investigations documented in the literature.
The computational phantoms will continue evolving, but already over 1000 different tissues and structures have been segmented in the human datasets, including more than 320 muscles. The following major nerves are or will soon be completed: the vagus nerve and other cranial nerves as well as the lumbar, brachial and sacral plexus. To ensure high quality standards, we follow an internal/external review approach similar to that of the Virtual Population models V3.x.
The NEUROMAN models are expected to significantly impact the scientific community and the field of PNS research and will enable multi-scale modeling studies with realistic anatomies and electrophysiology. The obtained neuro-functionalized models will provide experimental test-beds for new therapeutic approaches and devices, and allow studying safety aspects, providing a tool to facilitate regulatory submissions and standardization activities.

Disclosures: B. Lloyd: None. **S. Farcito:** None. **A.M. Cassara:** None. **E. Neufeld:** None. **E. Huber:** None. **B.S. Chung:** None. **J.S. Park:** None. **M.S. Chung:** None. **N. Kuster:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.09/LLL60

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant MH 086638

Title: Building, simulating, and visualizing reaction-diffusion models with NEURON's enhanced rxd module

Authors: *R. A. MCDOUGAL[1], A. NEWTON[1], M. L. HINES[1], W. W. LYTTON[2,3]
[1]Neurosci., Yale Univ., New Haven, CT; [2]SUNY Downstate, Brooklyn, NY; [3]Kings County Hosp., Brooklyn, NY

Abstract: Intracellular phenomena -- e.g. calcium waves, protein interactions, etc -- play key roles in modulating brain activity through their interactions with electro-chemical signaling between neurons. Quantitative models used as tools for pre- and post-dictive studies of neural functioning have incorporated these phenomenon using the mathematical formalism of reaction-diffusion kinetics. NEURON (neuron.yale.edu) has long provided a Python module -- *rxd* -- for these kinetics that provides a separation between model specification and numerical implementation. We describe recent developments that enhance the usability and performance of this module: just-in-time (JIT) compiled reactions accelerate simulation. A redesigned graphical reaction-diffusion builder allows modifying reaction schemes on the fly, parameter changes, and more numerical simulation options including 3D simulation. Graphical display enhancements allow selecting and visualizing reaction-diffusion states alongside electrophysiological ones. We describe the underlying methods and demonstrate the enhancements with a study of calcium wave entry (or non-entry) into the soma.

Disclosures: R.A. McDougal: None. **A. Newton:** None. **M.L. Hines:** None. **W.W. Lytton:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.10/LLL61

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant U01EB017695
NYS DOH Grant DOH01-C32250GG-3450000
NIH Grant R01EB022903
NIH Grant R01MH086638

Title: NetPyNE: A GUI-based tool to build, simulate and analyze large-scale, data-driven network models in parallel NEURON

Authors: *S. DURA-BERNAL[1], B. A. SUTER[2], A. QUINTANA[3], M. CANTARELLI[4], P. GLEESON[5], F. RODRIGUEZ[6], S. A. NEYMOTIN[7], M. L. HINES[8], G. M. SHEPHERD[9], W. W. LYTTON[6]
[1]Physiol. and Pharmacol., State Univ. of New York Downstate Med. Ctr., Brooklyn, NY; [2]IST Austria / Jonas Group, Klosterneuburg, Austria; [3]EyeSeeTea Ltd, London, United Kingdom; [4]Metacell, Oxford, United Kingdom; [5]Neuroscience, Physiol. & Pharmacol., Univ. Col. London, London, United Kingdom; [6]SUNY Downstate, Brooklyn, NY; [7]Dept. Neurosci., Brown Univ., Providence, RI; [8]Neurobio., Yale Univ., New Haven, CT; [9]Dept Physiol., Northwestern Univ., Chicago, IL

Abstract: Transforming experimental data into solid conclusions and theory requires integrating and interpreting disparate datasets at multiple scales. The BRAIN Initiative 2025 report highlights this requires rigorous theory and modeling. The widely used NEURON simulator allows researchers to develop biophysically realistic models of neurons and networks. However, building and running parallel simulations of complex brain networks usually requires years of highly technical training. Here we present NetPyNE (www.netpyne.org), a tool that extends NEURON's capabilities and makes it accessible to the wider scientific community. NetPyNE provides both a programmatic and graphical interface that facilitates the definition, parallel simulation and analysis of data-driven multiscale models. Users can provide specifications at a high level via its standardized declarative language, e.g. a probability of connection, instead of millions of explicit cell-to-cell connections. With a single command, NetPyNE can then generate the NEURON network model and run an efficiently parallelized simulation. The user can then select from a variety of built-in functions to visualize and analyse the results, including connectivity matrices, voltage traces, raster plot, local field potential spectra or information transfer measures. The graphical user interface was developed using state-of-the-art technology (www.geppetto.org) and allows users to more intuitively access all NetPyNE functionalities: specifying model parameters using drop-down lists or autocomplete forms, interactively visualizing the 3D network, running parallel simulations or plotting results. NetPyNE models can be imported/exported to NeuroML specifications, facilitating model sharing and simulator interoperability. As a case-study we present the development of a multiscale model of mouse primary motor cortex (M1) microcircuits. The model simulates a cylindrical volume of cortical tissue with over 10,000 biophysically detailed neurons and 30 million synaptic connections. Neuron densities, classes, morphology and biophysics, and connectivity at the long-range, local and dendritic scale were derived from published experimental data. NetPyNE enabled the integration of these complex experimental datasets and in silico exploration of the microcircuit neural dynamics, information flow and underlying biophysical mechanisms.

Disclosures: S. Dura-Bernal: None. **B.A. Suter:** None. **A. Quintana:** None. **M. Cantarelli:** None. **P. Gleeson:** None. **F. Rodriguez:** None. **S.A. Neymotin:** None. **M.L. Hines:** None. **G.M. Shepherd:** None. **W.W. Lytton:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.11/MMM1

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant MH105174
NIG Grant NS094288
Simons Foundation Grant 542971

Title: Assessing goodness-of-fit of neural population models using marked point process time-rescaling

Authors: *K. ARAI[1], L. TAO[2], K. WEBER[2], U. EDEN[2]
[2]Mathematics & Statistics, [1]Boston Univ., Boston, MA

Abstract: The assessment of the goodness-of-fit to the observed data is a critical step of any statistical modeling procedure. For neural spike train models of individual neurons, many goodness-of-fit measures rely on the time-rescaling theorem to assess the statistical properties of rescaled spike times. Recent interest in building a single model for the population spiking activity has also necessitated a goodness-of-fit measure for the population model. Classically, such models have used spike sorted data to describe relationships between the identified neurons, but more recently single clusterless models have been used to describe the spiking activity of a population of neurons. Here we develop a generalization of the time-rescaling theorem that enables a comprehensive goodness-of-fit analysis for both traditional spike sorted and clusterless population models. We model the population spiking using the theory of marked point processes, and show that under the correct model, each spike can be rescaled individually to generate a uniformly distributed set of events in time and the space of spike marks. After rescaling, the assessment problem for complicated population spiking models can be simplified to the assessment of various properties of the rescaled spikes using multiple well-established statistical tests. We demonstrate applications of our assessment methods to models of sorted spikes and clusterless models of population spiking with and without history, of the same simulated spiking data. Further we illustrate our methods to real neural population spiking data from CA3 of a rat performing alternating spatial navigation task. All code is available via github.
Figure Rescaling analysis for unsorted spikes and their marks from rat CA3: **A**. Marks of time-rescaled spikes from each of the 4 tetrode channels. The same spikes appear in each of the 4 panels at the same rescaled time, but at different mark values. **B** The corresponding KS plot.

Disclosures: K. Arai: None. **L. Tao:** None. **K. Weber:** None. **U. Eden:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.12/MMM2

Topic: I.06. Computation, Modeling, and Simulation

Support: CRCNS Grant 610-4011100-60041050

Title: Improving the convergence of multiobjective optimization for morphologically realistic neuron models

Authors: *A. ABOUZEID[1], W. L. KATH[2]
[2]Applied Mathematics, [1]Northwestern Univ., Evanston, IL

Abstract: Evolutionary multiobjective optimization (EMO) techniques are receiving increasing interest in neuroscience, as technical advances are providing more detailed morphological and electrophysiological data that can be used to constrain large-scale neuron models. Although computing power has simultaneously grown, the problem of fitting large numbers of parameters to satisfy multiple simultaneous constraints has remained challenging. Here we present a method for improving the speed and convergence of the widely-used NSGA-II algorithm [Deb et al. 2002], and we illustrate the approach by fitting the parameters of a model CA1 pyramidal cell with full dendritic morphology.

EMO strategies are designed to maximally explore the Pareto-optimal front of solutions, which represents inherent trade-offs among the objectives being optimized. NSGA-II as originally developed by Deb et al. (2002) attempts to balance these trade-offs by computing a crowding distance among solutions in error space, preferentially emphasizing those from more sparse regions. This creates selection pressure that guides the solution set into regions where at least one of the objectives has large error values. Although such solutions satisfy the criterion for Pareto-optimality, they may not be the most useful in applications where small error values across all the objectives would be preferred. Moreover, we show that this biasing effect toward the extreme-valued fringes of the Pareto front occurs at the expense of solutions near the origin of the error space, where error values are small across all objectives.

By performing a projection of the error vectors prior to the crowding distance calculation, the "outward" pressure of the NSGA-II crowding distance operator can be counteracted while preserving its role in promoting solution diversity. Specifically, we perform stereographic projection of errors onto the n-dimensional unit sphere before calculating the crowding distance. This rescales the error space such that distances between points near the origin remain essentially unchanged, while distances between points with large error values become compressed, thus biasing the evolution "inward" toward the origin in error space.

Using a model CA1 pyramidal cell with full dendritic morphology as a case study, we show that the modified NSGA-II algorithm converges more rapidly than the standard algorithm as measured by the L1 norm on the original error space. Furthermore, solutions produced with the projection method "dominate," in the Pareto sense, those found using the unmodified algorithm, suggesting that the standard algorithm may become trapped by local minima of the objective function.

Disclosures: A. Abouzeid: None. **W.L. Kath:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.13/MMM3

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant U01 GM104604
NIBIB Grant P41 EB001978
ONR Grant N00014-13-1-0211

Title: A point-process approach for dendritic morphology generation

Authors: *Z. Z. CHOU, G. J. YU, T. W. BERGER
Dept. of Biomed. Engin., USC, Los Angeles, CA

Abstract: Biologically realistic dendritic morphologies are critical to developing meaningful simulations of neuronal activity. In particular, the length of dendritic branch segments and the overall arborization of the dendritic tree largely determine how a neuron integrates input signals. Here, we present a non-parametric approach that uses a point-process filter and Expectation-Maximization (EM) to estimate the branching rate of a rat dentate granule cell dendrites as it changes according to distance from the soma. We use the estimated branch rate to randomly generate morphologies that match several aspects of the branching behavior of real cells.
We model dendritic branching as a simple discretized Poisson generalized linear model with an exponential conditional intensity function. We use a point-process filter and smoother, combined with the EM algorithm to simultaneously solve for an estimate of the branching rate and the model parameters. These algorithms were run on a set of 42 histological reconstructions of rat dentate gyrus granule cell morphologies to provide an estimate for the branching rate. 50 randomly generated morphologies were created using by spike thinning a Poisson point-process at the maximum branch rate. The distributions of key metrics for branching behavior were quantified for both the real and the generated morphologies, namely the branch pathlength, total dendritic length, a Scholl analysis, and the total number of bifurcations.
The generated morphologies closely matched the distributions of all measured parameters, but there was a mild overestimation of shorter pathlengths and underestimation of early branching. The model is able to capture many of the important characteristics of granule cell dendritic branching dynamics, and shows significant advantages over stochastic generation algorithms. We can use these more biologically accurate morphologies in our existing large-scale model of the dentate gyrus to achieve more meaningful simulations. In future work, additional elements can be added to the state-space model to account for the history of branching events along neighboring processes.

Disclosures: Z.Z. Chou: None. **G.J. Yu:** None. **T.W. Berger:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.14/MMM4

Topic: I.06. Computation, Modeling, and Simulation

Support: Provost's PhD Fellowship (University of Southern California)
NIH Grant U01 GM104604
NIBIB Grant P41 EB001978
ONR Grant N00014-13-1-0211

Title: An evolutionary multi-objective optimization approach for constraining biophysical properties for neuron models in a large-scale neuronal network model of the hippocampus

Authors: *P. K. GUNALAN, G. J. YU, T. W. BERGER
Biomed. Engin., USC, Los Angeles, CA

Abstract: One of the major applications for the large-scale neuronal network model of hippocampus we are developing is to investigate biological and functional differences between healthy and diseased states and to explore electrical and pharmacological treatment therapies. Pathology-driven physiological changes may be modeled by changes in the biophysical properties, such as the distribution of ion channel conductances of neurons, which must therefore be constrained to simulate healthy and diseased networks. As direct measurements of all ion channel conductances that comprise a neuron are difficult to obtain, electrophysiological responses of neurons due to stimulation can be used to constrain parameters as certain stimulation paradigms reveal specific electrophysiological responses that can largely be mediated by certain subsets of ion channels. Here we provide a method for constraining the biophysical properties of granule cells using a multi-objective genetic optimization algorithm to increase the speed of optimizing such models.

A three-dimensional multi-compartmental model of a granule cell with representations of dendrites, soma, axon initial segment, and axon was implemented in the NEURON simulation environment using the Python interpreter [Hines and Carnevale 2001; Santhakumar 2004]. The conductances of sodium and multiple types of potassium and calcium ion channels were optimized. To decrease the number of parameters that are necessary to optimize for a model, we assumed that each ion channel conductance decreases linearly as a function of distance from the soma, so the total number of parameters optimized per granule cell was twenty-two. Defined objectives include the amplitude and duration of threshold, input resistance, resting membrane potential, spike frequency adaptation, and slow, medium and fast afterhyperpolarizations. An Evolutionary Multi-Objective Optimization (EMOO) algorithm was used to minimize error between the computational model's stimulation response values and experimental values found in literature and to determine parameter values [Bahl 2012]. Parallelization decreased the duration of runs.

We demonstrate the EMOO algorithm can be used to constrain model parameters to satisfy all the electrophysiological objectives. This general approach can be used to generate models for additional hippocampal cell types and additional objectives can also be added in future work.

Disclosures: P.K. Gunalan: None. **G.J. Yu:** None. **T.W. Berger:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.15/MMM5

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH Grant U01 GM104604
NIBIB Grant P41 EB001978
ONR Grant N00014-13-1-0211

Title: A generalized linear model to capture the nonlinear dynamics of neural ensembles within a large-scale neuronal network model of hippocampus

Authors: *G. J. YU[1], D. SONG[2], J.-M. C. BOUTEILLER[2], T. W. BERGER[2]
[2]Biomed. Engin., [1]USC, Los Angeles, CA

Abstract: We are developing a three-dimensional, large-scale neuronal network model of the hippocampus with multi-compartmental representations of each neuron and the goal of representing every neuron and synapse in a single hemisphere of the rat hippocampus. The current version of the large-scale model includes the entorhinal cortex, dentate gyrus, and CA3 and a majority of their cell types and offers a unique platform through which the propagation and transformation of spatio-temporal patterns can be investigated. As such, new techniques are necessary to describe and characterize the nonlinear transformations performed by these neural regions. Furthermore, given the scale, methods need to be developed to characterize a neural system at a physical scale beyond the neuronal level and towards a network/circuit level.
The generalized linear model (GLM) framework, in combination with Laguerre basis functions, has been used to capture the nonlinear input-output transformations performed by single neurons. The kernels that can be constructed from the GLM model capture the dynamics that result from direct and indirect synaptic activations that are caused by an input.
Using a GLM, an input-output model was created for neural ensembles that were organized into neural modules based on anatomy. In this work, the dentate gyrus was discretized into square spatial bins based on the septo-temporal and transverse axes with a size of 0.5 mm. The spatial bins were referred to as neural modules. The input and output signals were defined as the total number of spikes elicited by a cell population and discretized into 10 ms bins. An input to the neural module consisted of the sum of all unique presynaptic events received by the neurons within the neural module and was divided between the neurons of the medial and lateral entorhinal cortex. The output of the GLM consisted of the sum of all spike times elicited by the principal neurons of the subfield, i.e., dentate granule cells, within the neural module. A Poisson GLM with a log-link function was selected, and 4^{th} order Laguerre basis functions and 2^{nd} order self-kernels were used for the feedforward and feedback kernels. Cross validation was performed

using an 80:20 split with 32000 training samples and 8000 validation samples. The out-of-sample prediction achieved an NRMSE of 0.48.
The GLM of neural modules offers a method by which the nonlinear spatio-temporal transformation properties of neural ensembles can be quantified. Given that the GLM sufficiently predicts the output of the model, it could then be used as a generative model for simulating long periods of time after being initially trained using the large-scale neuronal network model.

Disclosures: G.J. Yu: None. **D. Song:** None. **J.C. Bouteiller:** None. **T.W. Berger:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.16/MMM6

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH U01 GM104604
NIH P41 EB001978

Title: Multi-scale modeling of complex nonlinear synaptic dynamics using sparse laguerre-volterra network

Authors: E. HU, *J.-M. C. BOUTEILLER, G. YU, D. SONG, V. Z. MARMARELIS, T. W. BERGER
Biomed. Engin., USC, Los Angeles, CA

Abstract: Synapses constitute key specialized structures through which interneuronal communication takes place. They are also critical specialized structures in which long term potentiation, the cellular substrate of learning and memory occurs. This critical role is done through a large number of biochemical processes that result in complex nonlinear dynamics. Yet, computational models of large-scale neuronal systems often rely on highly simplified linear representations of synaptic dynamics. This is partly because the nonlinear complexity of synaptic dynamics leads to a prohibitively heavy computational load in network models comprised of a large number of neurons.
Here we present a solution for the multi-scale modeling of a glutamatergic CA3 to CA1 hippocampal synapse through the use of nonlinear dynamic system modeling. More specifically, we develop an “input-output” (IO) model using the Volterra functional series that is trained using the mechanistic (kinetic) models of the ionotropic receptors AMPAr and NMDAr.
We compare the input-output model to the original mechanistic models and demonstrate that the IO model replicates the nonlinear dynamics with a high degree of accuracy. Then, we further improve the computational efficiency of the IO model by adopting a Laguerre-Volterra Network (LVN) structure, and demonstrate improved performance in both runtime and memory usage in

large scale simulations. Finally, we measure the network activity obtained from large scale network simulations comprised of either linear (exponential) or nonlinear (IO model) synapse models subjected to the same patterns of stimulation; We compare the network spiking activities - outlining the effects of nonlinear synaptic connections on network-level response.
The methodology presented constitutes an efficient solution for bridging subcellular to network scales, enabling relevant information to be passed across levels while maintaining low computational load. Incorporation of such pertinent subcellular nonlinear dynamics will undoubtedly improve the validity of large-scale simulations. The methodology is general and may be adapted to other types of subcellular (physiological and pathological) processes, furthering our understanding of the large number of interdependent processes that take place in the brain, and how they shape brain function and dysfunctions.

Disclosures: E. Hu: None. **J.C. Bouteiller:** None. **G. Yu:** None. **D. song:** None. **V.Z. marmarelis:** None. **T.W. berger:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.17/MMM7

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH P41 EB001978
NIH U01 GM104604

Title: A computational study of the effects of muscarinic m1-mediated cholinergic modulation on ca1 pyramidal cell excitability

Authors: *A. MERGENTHAL, J.-M. C. BOUTEILLER, T. W. BERGER
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Abstract: Projections from the basal forebrain provide extensive cholinergic modulation to the hippocampus. This modulation has been established to play an important role in attention, learning, and synaptic plasticity, while its disruption has been linked to various neural disorders (e.g. Alzheimer's Disease). The primary cell type of the CA1 region of the hippocampus, the pyramidal neuron, expresses M1 muscarinic receptors throughout their morphology. We have developed a computational model of these receptors and their downstream modulatory effects of ionic channels in the soma of the pyramidal cell. We verify that this computational model replicates CA1 pyramidal cell behavior observed after in vitro acetylcholine exposure. We then demonstrate how the increased excitability measured during acetylcholine exposure alters the way the cell model integrates synaptic inputs. Through these developments, we propose to use this simulation framework to investigate how cholinergic modulation alters cell function in

normal function, and in pathological situations (e.g. following a decrease in cholinergic modulation as reported in AD, or as a result of exposure to organophosphates), and identify potential ways to re-establish normal function. The model presented will also serve as essential building block for a large scale model network of the CA1 region to extend our investigations to network-level observables.

Disclosures: A. Mergenthal: None. **J.C. Bouteiller:** None. **T.W. Berger:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.18/MMM8

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF CAREER Award 1653080
Craig H. Neilsen Foundation Grant 314980
NIH NIBIB Grant U18EB021760
NIH Grant UL1TR000433
NIH Grant UL1TR002240

Title: Three-dimensional reconstructions of dorsal root ganglia morphometry and cell distribution

Authors: *Z. J. SPERRY[1,2], N. PECK-DIMIT[1,2], R. D. GRAHAM[1,2], S. F. LEMPKA[1,2], T. M. BRUNS[1,2]
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Abstract: We created realistic quantitative computer models of dorsal root ganglia (DRG) anatomy using cross-sections taken from felines and non-human primates. DRG contain the cell bodies for primary sensory neurons in spinal nerve roots and hold significant potential as sites for neural interfacing. Existing commercial therapies deliver electrical stimulation near the DRG or spinal roots to provide targeted pain relief or improved bladder control. On-going animal research suggests that electrical recordings from DRG could be used as sensory feedback for neuroprosthetic devices. Devices for spinal cord injury patients, for instance, could utilize sensory feedback from limb proprioceptors or bladder mechanoreceptors below the level of their injury, accessed with electrodes in or on relevant DRG. Design of these therapies will benefit from a detailed and quantitative understanding of DRG anatomy. We have previously presented quantitative descriptions of cell body distribution in feline lumbosacral DRG at a single medial location. Here we extend this study to include multiple sections per DRG as well as non-human primate DRG as an alternative translational animal model. Following intracardiac perfusion with paraformaldehyde, lumbar and sacral spinal roots of either feline or rhesus macaque subjects

were exposed via spinal laminectomy, removed, and fixed in 10% formalin. The roots were bisected in the transverse plane and embedded in paraffin. Roots were sectioned at closely spaced intervals (4-50 µm) and the sections stained for neurofilament-heavy polypeptide and counterstained with hematoxylin. This stain allows for high contrast imaging of the pseudounipolar neurons of the DRG, both cell bodies and axons. A custom MATLAB GUI was developed to allow for semi-automated segmentation and alignment of the sections, as well as identification and quantification of cell component properties. By interpolating the profiles of the spinal root components in a CAD program, we reconstructed the 3D geometry of each DRG and ventral root within the overall spinal root. By combining these models with realistic tissue electrical properties, it may be possible to predict and improve experiment outcomes. We also quantified the distribution and location of different cell component sizes across the length of the DRG, utilizing a polar transformation to normalize for different spinal root profiles across samples. By combining these spatial soma/axon density maps across sides and levels, we produced a map showing the organization of cells within the DRG that could be useful for future device development.

Disclosures: Z.J. Sperry: None. **N. Peck-Dimit:** None. **R.D. Graham:** None. **S.F. Lempka:** None. **T.M. Bruns:** None.

Poster

525. Computation, Modeling, and Simulation: Neuron/Network Modeling

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 525.19/MMM9

Topic: I.06. Computation, Modeling, and Simulation

Support: Wellcome Investigator Award 204788/Z/16/Z

Title: Bayesian inference of spontaneous neuronal assemblies

Authors: *G. DIANA[1], T. SAINSBURY[2], M. MEYER[1]
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Abstract: Brain function emerges from the coordinated activation of neuronal populations. Descriptions of population dynamics will provide important insights into how brain computations are distributed across neural networks. The proliferation of experimental techniques for recording the activity of neuronal populations calls for a comprehensive statistical method to describe, analyze and characterize these high dimensional datasets. Here we develop a new Bayesian inference method based on a stochastic model of pattern activity to describe spontaneously active neural ensembles throughout the tectum of larval zebrafish. Unlike heuristic methodologies employed to detect neural assemblies, our framework provides rigorous statistical estimates of composition and dynamics of these neural populations. Furthermore, we

have derived a message-passing algorithm to boost computational performance, which extend the applicability of our method to the analysis of long recordings of thousands of neurons. Within our model we can show how data sufficiency is constrained by the balance between noise and neuronal activity, providing robust estimates of the recording time required to capture the ensemble structure of large neural populations. Our method allows to make statistical inference on the spatio-temporal organization of neuronal ensembles their composition and the logic of their interactions.

Disclosures: G. Diana: None. **T. Sainsbury:** None. **M. Meyer:** None.

Poster

526. Computation, Modeling, and Simulation: Optical Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 526.01/MMM10

Topic: I.06. Computation, Modeling, and Simulation

Support: R24 OD016474

Title: Generating a post-twitching developmental atlas for *Caenorhabditis elegans*

Authors: *R. CHRISTENSEN[1], A. BOKINSKY[2], A. SANTELLA[3], M. MOYLE[4], Y. WU[1], M. GUO[1], E. ARDIEL[6], W. DUNCAN[1], B. HARVEY[1], M. LEVIN[1], N. KARAJ[1], A. LAUZIERE[1], E. MCCREEDY[2], W. MOHLER[7], D. A. COLÓN-RAMOS[5], Z. BAO[3], H. SHROFF[1]
[1]NIBIB, [2]Ctr. for Information Technol., NIH, Bethesda, MD; [3]Mem. Sloan Kettering Cancer Ctr., New York, NY; [5]Cell Biology; Program in Cell. Neuroscience, Neurodegeneration and Repair, [4]Yale Univ., New Haven, CT; [6]Harvard Univ., Cambridge, MA; [7]Univ. of Connecticut Hlth. Ctr., Farmington, CT

Abstract: The *Caenorhabditis elegans* embryo is a useful model for studying tissue morphogenesis and complex developmental events due to its small number of cells and experimental accessibility. Development is well characterized in pre-twitching embryos, but halfway through embryogenesis morphological changes and muscular motion combine to make data analysis difficult. To remedy this problem, we developed software that computationally untwists embryo images, allowing for detailed analysis of developmental time series in a common reference frame. We are applying our software to generate a developmental map of cell position in the *C. elegans* embryo, with an eventual goal of covering the position of all 558 embryonic nuclei from the beginning of twitching until hatching. Currently, the atlas covers 65 nuclei including 20 seam cells, 20 E lineage intestinal cells, and 11 neurons with each modeled position derived from cell positions in three individual embryos. We are also interested in mapping out major neuronal tracts and the outgrowth of neurites in the post-twitching regime, with the atlas currently incorporating neurite outgrowth from the ALA neuron. Finally, we

implement a re-twisting capability which allows the positions of cells from our model to be matched to the configuration of a specific embryo volume, potentially allowing for identification of unknown cells in embryo images. These tools should allow the generation of a computational map showing the position of all nuclei as well as neurite position and outgrowth in the *C. elegans* embryo from the beginning of twitching until hatching.

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Poster

526. Computation, Modeling, and Simulation: Optical Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 526.02/MMM11

Topic: I.06. Computation, Modeling, and Simulation

Support: Hertz Foundation Graduate Fellowship
NSF Graduate Fellowship

Title: High-throughput, cellular resolution neural circuit mapping with closed-loop adaptative experimental design

Authors: *B. SHABABO[1], S. CHEN[2], K. KILBORN[4], X. DENG[3], A. SHARMA[2], J. FRIEDRICH[5], H. ADESNIK[6], L. PANINSKI[2]
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Abstract: Circuit-mapping experiments combining whole-cell electrophysiology with two-photon optical stimulation of potentially presynaptic neurons have produced rich data on cell type-specific monosynaptic connectivity of neural circuits. However, mapping large volumes of densely-packed neurons (e.g. cortical excitatory neurons) at cellular resolution with two-photon optogenetics has proven challenging because of two main problems: 1) stimulation sensitivity and resolution varies across cells due to differential opsin expression and intrinsic excitability, making the precise localization of connected neurons difficult, and 2) experimental time is severely limited compared to the number of potential connections to map. We present a method which overcomes these limitations using statistical modeling, online experimental design, and the combination of a fast, high-potency soma-targeted opsin (st-ChroME) with computer generated multi-target holography. To infer posterior distributions for connectivity parameters (e.g. probability of synaptic transmission or short-term dynamics) and per cell parameters for the

excitability of the local population (e.g. opsin expression level, spatial opsin distribution), we fit a generative model with three main components: a neural response model which predicts presynaptic spike rates given the power and location of stimulation targets, a connectivity model which filters presynaptic spike rates into a postsynaptic event rate, and a postsynaptic model which converts the postsynaptic event rate into a voltage-clamp observation. To improve mapping efficiency, we implement a closed-loop parallel computational system which designs batches of stimulation targets online based on fast stochastic variational inference of these posteriors. Specifically, stimulation design for each neuron automatically switches between coarser (multi-target) and finer (single-target) protocols depending on the posteriors. This approach allocates high-resolution single-target stimuli only at locations of evoked connections and ambiguous responses. Furthermore, our experimental system allows us to collect data at 20 trials per second for a large portion of experimental time while analyzing data in the background. We demonstrate the efficacy of our method by mapping excitation onto both excitatory and inhibitory cells in layer II/III of cortex in acute mouse brain slices.

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Poster

526. Computation, Modeling, and Simulation: Optical Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 526.03/DP15/MMM12

Topic: I.06. Computation, Modeling, and Simulation

Support: Simons Foundation

Title: Empirically constrained population models of whole brain cell-resolution activity

Authors: *M. RUBINOV[1], Y. MU[1], C. WANG[1], N. VLADIMIROV[2], D. BENNETT[1], P. KELLER[1], M. AHRENS[1]
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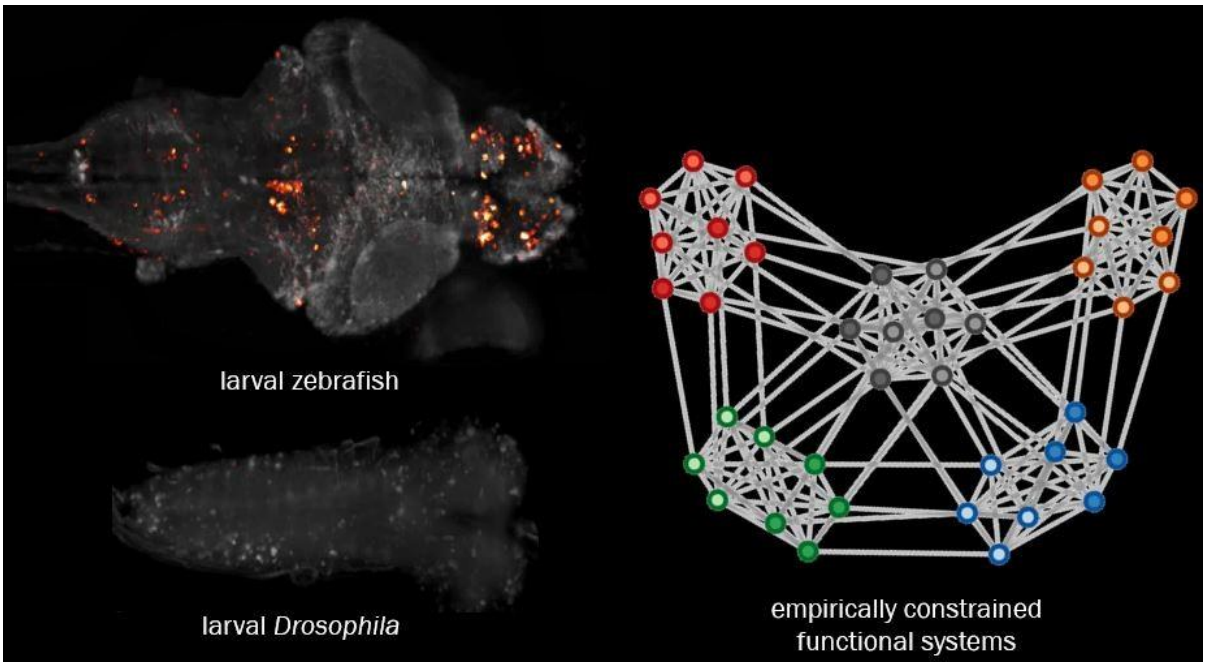
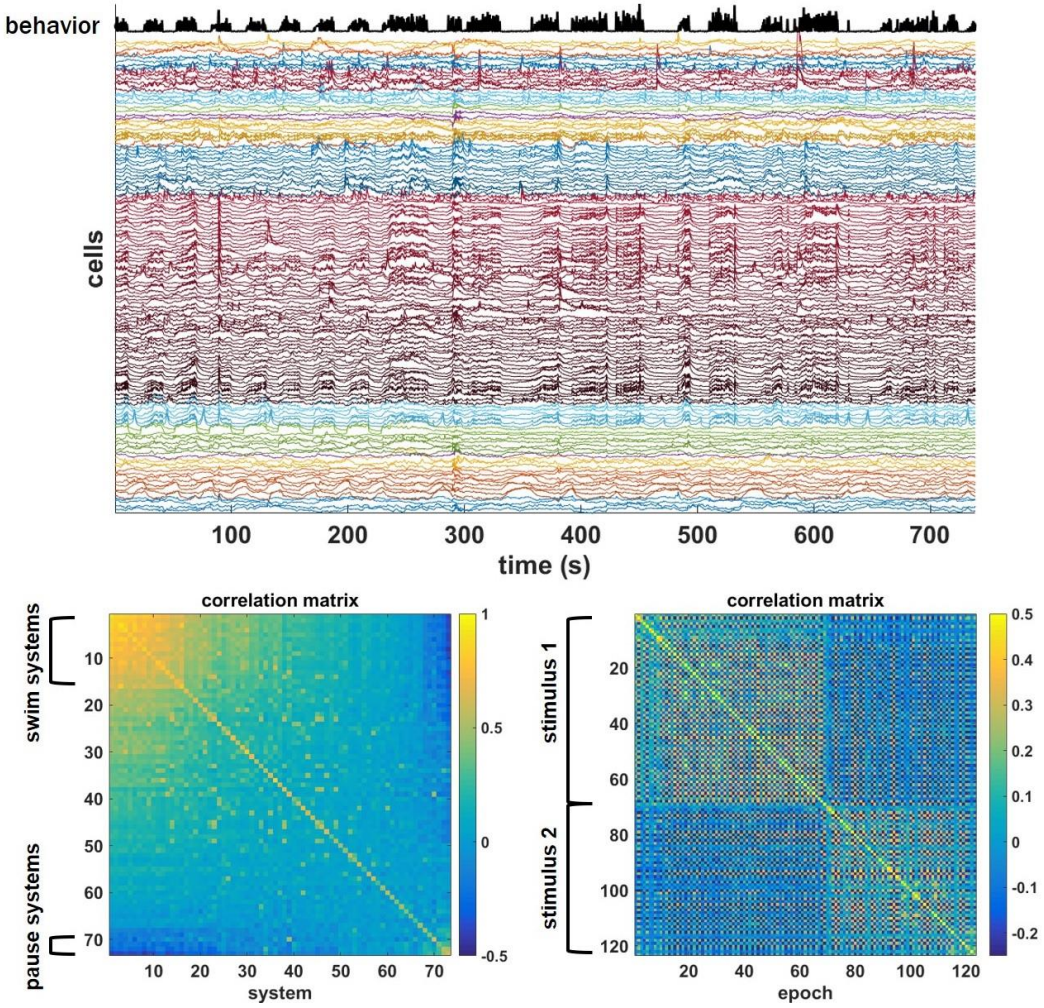
Abstract: The combined single-cell resolution and brain-wide coverage of light-sheet microscopy calcium imaging has provided a spatiotemporally unmatched view into vertebrate and invertebrate brain activity. However, data generated using these imaging tools have thus far been little analyzed or modeled integratively at the level of the whole brain (Figure 1). Here, we developed population models of neuronal network dynamics that allowed us to characterize the activity of all cells in the brain or nervous system of vertebrate (larval zebrafish) and invertebrate (larval *Drosophila*) organisms. Our models describe individual cell activity in terms of correlations of each cell to its largest system (group of co-activated cells), and in terms of

average correlations of cells between system hierarchies (Figure 2). Numerical solutions for these constraints provide accurate and ultra-compact (order of magnitude smaller than current state of the art) representations of whole-brain single-cell resolution activity. We demonstrated the utility of these representations, by showing that the coarse system correlation structure distinguishes between global underpinnings of behavioral states, links these global changes to differences in activity of individual cells and predicts the effects of interrogating these systems with ablation and stimulation experiments. Our approach provides a bridge between big functional imaging data sets and empirically grounded mechanistic formulations of whole-brain activity.





Disclosures: M. Rubinov: None. **Y. Mu:** None. **C. Wang:** None. **N. Vladimirov:** None. **D. Bennett:** None. **P. Keller:** None. **M. Ahrens:** None.

Poster

526. Computation, Modeling, and Simulation: Optical Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 526.04/MMM13

Topic: I.06. Computation, Modeling, and Simulation

Support: HHMI
DARPA

Title: EXTRACT: Automated cell sorting for large-scale neural calcium imaging based on the framework of robust statistics

Authors: *H. INAN[1], C. SCHMUCKERMAIR[1], B. AHANONU[2], M. A. ERDOGDU[3], M. J. SCHNITZER[4]
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Abstract: Fluorescence calcium imaging is a widely used methodology for tracking the simultaneous activity patterns of large numbers of neurons in awake behaving animals. High-fidelity computational extraction of individual neurons and their activity time traces from the raw calcium video datasets is important for attaining reproducible, high-quality biological results. However, most calcium imaging datasets acquired in behaving animals contain substantial sources of non-stationary noise and signal contamination, such as from brain motion, neuropil activation, or clustered patterns of neural activation. Although previous research has considered the effects of such contamination under limited circumstances, there has not been a general framework treating its effects on the statistical estimation of calcium signals. Here we propose a new cell sorting approach based on the statistical framework of robust estimation. Using approaches from the theory of statistical estimation, we find a statistically optimal objective function for estimating neurons' spatial locations and the time-dependent activity traces. This objective function leads to substantial improvements in estimation accuracy, even in cases with large-amplitude signal contamination caused by noise sources, including neuropil activation and spatiotemporal overlap with other background activity. The resulting algorithm for automated cell sorting, which we call EXTRACT, enables rapid estimation of cells' images and fluorescence dynamics. By implementing EXTRACT on graphical processing units (GPUs), we further decrease the required runtimes for cell extraction. Using simulated and real datasets, we showcase several advantages of our robust estimation approach as compared to other commonly used algorithms for cell sorting. EXTRACT also enables fast and accurate analyses of large-scale neural calcium imaging datasets acquired in freely behaving mice. To share EXTRACT with other labs in the neuroscience community, we have created a github repository enabling researchers to apply our software to datasets generated using a wide variety of calcium imaging techniques.

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Poster

526. Computation, Modeling, and Simulation: Optical Methods

Location: SDCC Halls B-H

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Program #/Poster #: 526.05/MMM14

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH-TRA 1R01NS092474
R01NS094499
R01MH111768
R24NS092991
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Allen Institute for Brain Sciences
National Science Foundation

Title: An array tomography exploration tool: Exploring synapses from FMR1 knockout mice

Authors: *A. K. SIMHAL[1], K. D. MICHEVA[2], Y. ZUO[3], R. J. WEINBERG[4], S. J. SMITH[5], G. SAPIRO[1]
[1]Electrical Engin., Duke Univ., Durham, NC; [2]Molec Cell. Physiol, Stanford Univ. Sch. Med., Stanford, CA; [3]UC Santa Cruz, Santa Cruz, CA; [4]Cell Biol. & Physiol., Univ. North Carolina, Chapel Hill, NC; [5]Synapse Biol., Allen Inst. for Brain Sci., Seattle, WA

Abstract: Array tomography is a powerful imaging tool that can address a variety of important but hitherto-intractable biological questions. Array tomographic study of the brain can generate high-dimensional data sets containing markers for different cell types (neurons, glia), neuronal compartments (dendrites, axons) and subcellular structures (synapses, mitochondria, myelin), but the power of this tool presents unique challenges for understanding and quantifying the produced data. The output of array tomography is three-dimensional multi-channel immunofluorescence (IF) images, where the number of channels range from four to thirty or more. Manually identifying brain substructures and their relationships with each other by visually inspecting thirty channels is a daunting task. Recent work in this area focusing on computational synapse detection represents one step toward a general approach to comprehensive analysis of the complex and diverse elements of neuropil.
We developed a framework comprising a suite of computer vision methods designed to facilitate the exploration of array tomography data, the Array Tomography Exploration Tool (ATET). The goal of this framework is to use computer vision methods to segment and quantify various properties such as size and shape of subcellular structures, and the relationship between them. For example, the tool, detects traditional synapses with specific subtype accuracy, as well as "tripartite" synapses—defined by the presence of an astrocytic process in close apposition to the synapse. By extracting morphology from the AT data, ATET can identify which axon a synapse

originates from, and which dendrite it terminates upon, whether a synapse contains mitochondria, or an axon is ensheathed in myelin.
To illustrate the value of this tool, we imaged the somatosensory cortex from FMR1 (a gene associated with Fragile X Syndrome) knockout mice and from wild-type mice. Each was processed using standard array tomography techniques and imaged with a variety of synaptic and nonsynaptic neuropil markers. We used this data to validate the tool by comparing the output to the results of previous studies, as well as to discover previously unreported features of this Fragile X Syndrome mouse model.
Developing the ATET to explore the relationship between brain substructures will allow for holistic analysis of array tomography at scale. The tool is developed in Python and will be open sourced upon publication.

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Poster

526. Computation, Modeling, and Simulation: Optical Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 526.06/MMM15

Topic: I.06. Computation, Modeling, and Simulation

Support: U01MH114824

Title: Improved deconvolution and image processing for oblique light sheet tomography

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[1]Neurosci., Cold Spring Harbor Lab., Great Neck, NY; [2]Neurosci., [3]Osten Lab., [4]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [5]Biomed. Engin., Stony Brook Univ., Stony Brook, NY

Abstract: Oblique Light Sheet Tomography (OLST) is a light-sheet fluorescence microscopy (LSFM) method designed for volumetric imaging of larger specimens at a high-spatial resolution, high imaging speed and dynamic range with low photobleaching and noise. OLST utilizes XYZ translation stages and vibratome tissue sectioning to achieve high speed and consistently high resolution throughout large specimen volumes. The current OLST setup produces whole mouse brain imaging at 0.4 micron XY resolution and 2.5 micron Z-spacing between oblique planes in approximately 14 hours. The Z-resolution is restricted by the thickness of the light sheet, but Gaussian blur also occurs in the X-Y plane. This blur results from the

optical transfer function (OTF), and causes fluorescently labelled point-sourced objects to appear larger than they are. The OTF's blur is from several inevitable factors, including Abbe's diffraction limit, the collection objective's NA, and camera properties. To reduce this blur, deconvolution is implemented before image volume reconstruction. Signal to noise is improved as deconvolution reduces the effects of stray fluorescence (from source autofluorescence, camera artifact, and photon scattering) in the illumination plane. We modeled a custom 3D Gaussian point spread function (PSF) specifically suited to counter the PSF of detected blur. This was calculated from experimental beam parameters, 5 microns at the center and 20 microns near the edges. The modeled PSF is used for pixel-wise deconvolution. This addition results in significant noise reduction and narrower pixel PSFs. In this manner, the new software employs Lucy-Richardson Deconvolution to decrease background, improve resolution, and create sharper halo-reduced images. In addition to image processing, it was also necessary to develop and implement an image transformation model to produce the coronal section series. A shear transform is used to permute and shear the oblique image stacks. Custom software for OLST image stitching, better suited than previous techniques, was also developed. These additions and their optimizations, including reconstruction, deconvolution, shearing, permuting, and stitching, reduce processing time and produce superior image quality.

Disclosures: J. Mizrachi: None. **A. Narasimhan:** None. **K. Umadevi Venkataraju:** None. **P. Osten:** None.

Poster

526. Computation, Modeling, and Simulation: Optical Methods

Location: SDCC Halls B-H

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Program #/Poster #: 526.07/MMM16

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF PoLS PHY-1305537
NIH R01-MH112694
Skoltech Award 1911/R

Title: Phenotypic profiling of neuronal synapses using highly multiplexed fluorescence imaging and quantitative analysis

Authors: *E. W. DANIELSON[1], M. BATHE[1], S.-M. GUO[1], S. GORDONOV[1], R. VENEZIANO[1], M. TOMOV[1], M. STONE[2], V. KULIKOV[4], A. GOODMAN[2], E.-C. WAMHOFF[1], V. LEMPITSKY[4], A. CARPENTER[2], L. L. RUBIN[5], J. R. COTTRELL[3]
[1]Biol. Engin., MIT, Cambridge, MA; [2]Stanley Ctr., [3]Broad Inst., Cambridge, MA; [4]Skoltech, Moscow, Russian Federation; [5]Stem Cell and Regenerative Biol., Harvard Univ., Cambridge, MA

Abstract: The transmission of information between neurons occurs at specialized contact zones called synapses. Synapses are complex structures comprised of a dense network of several hundred different protein types, which can exhibit functionally important variation between distinct synapses and within single synapses over time. Fluorescence imaging is the principal means of measuring protein localization within intact developing neuronal circuits, but is limited by the spectral overlap of fluorophores in conventional microscopy to assaying three to four protein targets within a given sample. To facilitate high-content confocal imaging of neurons without the limitation imposed by this spectral limit, we turned to modified antibodies and developed an imaging platform (PRISM: **Pr**obe-based **I**maging for **S**equential **M**ultiplexing) that sequentially utilizes high affinity Locked Nucleic Acid (LNA) probes to enable highly multiplexed and high throughput confocal imaging compatible with 384-well plate imaging formats. Using this approach, we can stain for over a dozen protein targets to create detailed profiles of cellular and synaptic features, characterizing individual synapses and different neuronal subtypes. Here, we apply this method to examine synaptic protein expression in rat neuronal cultures before and after chemical induction of long-term potentiation (cLTP), classifying subclasses of neuronal synapses and examining changes in synaptic protein expression and localization. To accomplish this, we apply a neural network approach for synapse identification, using supervised learning trained on user annotated synapses and applying these results to improve synapse segmentation and feature extraction. Further, with recent developments in human stem cell derived neural cultures that can recapitulate neurodevelopmental conditions *in* vitro, we have also developed a panel of markers that characterize neural stem cell differentiation in 3D cultures *in vitro,* highlighting PRISM's promise as a high content assay platform for drug discovery and developmental studies.

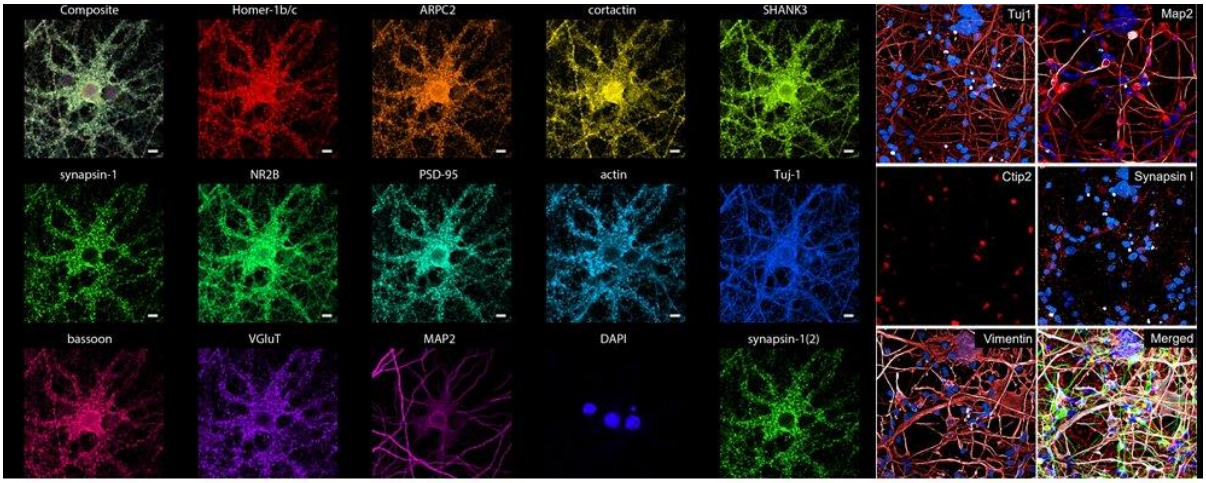

Figure 1. (Left) 13-marker confocal fluorescence image of E18 rat hippocampal neuronal culture obtained using PRISM. (Right) 6-Marker confocal fluorescence image of iPSC-derived human cortical neuron microglial co-cultures collected using PRISM

Disclosures: E.W. Danielson: None. **M. Bathe:** None. **S. Guo:** None. **S. Gordonov:** None. **R. Veneziano:** None. **M. Tomov:** None. **M. Stone:** None. **V. Kulikov:** None. **A. Goodman:** None. **E. Wamhoff:** None. **V. Lempitsky:** None. **A. Carpenter:** None. **L.L. Rubin:** None. **J.R. Cottrell:** None.

Poster

526. Computation, Modeling, and Simulation: Optical Methods

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 526.08/MMM17

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF CAREER Award (IIS-1150186)
Simons Collaboration on the Global Brain (SCGB AWD1004351)
NIH NRSA Training Grant in quantitative neuroscience (T32MH065214)
NRSA F32NS077840-01
NIH Grant 5R01MH083686-08
Simons Grant 328057

Title: Robust identification and removal of false transients in calcium fluorescence imaging data

Authors: *J. L. GAUTHIER, A. S. CHARLES, J. W. PILLOW, D. W. TANK
Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Two-photon calcium imaging has become an important source of insight into neural circuit function, and advances in large scale imaging have created the need for high throughput analysis methods. These consist largely of algorithms designed to isolate the activity of individual neurons within a large field of densely-stained tissue. However, automated inference methods can be susceptible to misattribution of fluorescence activity. For example, if two neurons overlap, but only one is known to the algorithm, or even if a part of one cell's spatial extent is not fully included in the model, activity from the "missed" cell can contaminate the found cell. Such cross-talk has the potential to affect scientific conclusions about population activity. To address these cases of misattribution, we have developed a generative model that explicitly describes the interfering activity. In our framework, missed cells are modeled as the sum of small Gaussian-shaped kernels, allowing the activity of found cells to be estimated through likelihood maximization. This effectively prevents the contamination of found cells by accounting for the spatial structure of missed cells. In its basic form, our method may be run independently on a frame-by-frame basis, allowing for efficient parallel computation. To further improve the estimation quality, we also expand our model to incorporate the expectation of temporal continuity, a key feature for helping to discriminate cellular activity from photon shot noise. The augmented model includes temporal consistency information via sparsity-aware dynamical filtering techniques from the signal processing literature. These techniques modify the base probabilistic model to include a dynamics function describing how activity changes over time, and incorporate this dynamic information into the likelihood estimation procedure, resulting in augmented LASSO and weighted LASSO procedures. In addition to this refined methodology for estimation procedures, we describe how Bayesian optimization techniques can

be used for efficient parameter fitting under the new probabilistic model. Together, these improvements enhance the ability to discriminate different sources of variability in calcium-imaging movies, providing a more veridical estimate of neural activity.

Disclosures: J.L. Gauthier: None. **A.S. Charles:** None. **J.W. Pillow:** None. **D.W. Tank:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.01/MMM18

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant R15S088776

Title: A comparison of the avisoft (5.2) and ultravox (2.0) recording systems: Implications for early life communication and vocalization research in mouse models

Authors: *M. BINDER, C. HERNANDEZ-ZEGADA, C. POTTER, J. LUGO
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Abstract: Alterations in early life communicative behaviors are a common feature of neurodevelopmental conditions such as autism and epilepsy. One way communication can be investigated in murine models is through analyzing ultrasonic vocalizations. These vocalizations are commonly recorded with either the Avisoft (5.2) or the Ultravox (2.0) recording programs. However, since no study has compared whether the systems are equally sensitive, the findings in one program may not be reproducible in the other. To directly compare the two programs, we elicited vocalizations from male and female 129SvEvTac and C57BL/6 mouse pups via the maternal isolation paradigm, recording vocalizations simultaneously with both systems. We held the detection parameters identical for each system and found that the Avisoft (5.2) program detected more calls emitted at 50, 60, and 70 kHz, than the Ultravox (2.0) program, $p < .05$. No statistically significant difference was present at 80 kHz. These findings demonstrate that different recording systems do not detect the same quantity of vocalizations as one another, even when detection parameters are congruent. Therefore, it may be useful to revisit previous negative results obtained with Ultravox (2.0) and repeat the experiments using the Avisoft (5.2) system. Ultimately, ultrasonic vocalizations are a valuable tool capable of examining early life phenotypes, however, a more thorough understanding of the relationships between recording systems is necessary in order to achieve a more comprehensive, reproducible, assessment of vocalizing behaviors.

Disclosures: M. Binder: None. **C. Hernandez-Zegada:** None. **C. Potter:** None. **J. Lugo:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.02/MMM19

Topic: I.07. Data Analysis and Statistics

Support: 'BrainLinks-BrainTools' Cluster of Excellence (DFG Grant EXC 1086)

Title: Semi-automated quantification of the CNS immune response at the probe-tissue-interface

Authors: *M. JOHNSTON[1,2], T. BÖHM[3,4,2], K. JOSEPH[5,2], M. ASPLUND[3,2], U. G. HOFMANN[5,2], S. THIELE[3,4,2], C. A. HAAS[1,6,2]
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Abstract: The design of microelectrodes for electrical stimulation or recording of neuronal activity increasingly focuses on biocompatibility. Still, implantation of a cortical probe evokes a sustained sterile inflammatory response (SIR) within brain tissue. This manifests in activation of microglia, astrocytic scarring, neurodegeneration, and other molecular and morphological changes that may ultimately lead to failure of the device.
To visualize the extent of the spatially limited tissue response, immunohistochemistry (IHC) is the well-established method of choice. But while qualitative assessment of resulting microscopic images can be easily accomplished, quantitative analysis poses a larger challenge to the investigator. This is partly due to the large number of images required to adequately represent the SIR, but also accounted for by high variability within and across tissue sections and animals. To this point there have been several publications that employed custom-built codes for quantification of IHC signals at the implantation sites of cortical electrodes. However, these differ greatly with respect to their evaluation methods and are not provided for open access. Hence, it is difficult to compare the extent of the SIR across different or even identical electrode types utilized by different groups. We therefore aimed at creating a semi-automated quantification method that allows fast and flexible delineation of the signal-intensity distribution from the site of lesion towards healthy brain tissue, based on the widely used software tools ImageJ and MATLAB.
In this study cortical implantation of lithographically fabricated, flexible polyimide probes (10µm thickness with iridium oxide electrodes) was performed on adult Sprague Dawley rats.

After different survival times transversal tissue sections were immunohistochemically stained and imaged with an epifluorescence microscope. Subsequent signal quantification was performed in concentric distance bins with flexibly adaptable size (the shape of the latter is determined by the respective cavity shape of the individual image). Processing artifacts can optionally be selected and excluded from the analysis. Apart from that normalization parameters can be modified towards the needs of the study design. This also yields the possibility of using differently processed and/or imaged tissue sections within one experimental population.
Our approach provides a novel, straightforward tool for quantification of IHC-images that is versatile and adaptable for various purposes.

Disclosures: M. Johnston: None. **T. Böhm:** None. **K. Joseph:** None. **M. Asplund:** None. **U.G. Hofmann:** None. **S. Thiele:** None. **C.A. Haas:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

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Program #/Poster #: 527.03/MMM20

Topic: I.07. Data Analysis and Statistics

Support: 1OT3OD025347-01
1R44DA044929-01A1

Title: Blackfynn: Rapid multimodal data integration for the neurosciences

Authors: L. A. GUERCIO, M. HOLLENBECK, *J. B. WAGENAAR
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Abstract: Neurological and mental disorders pose a significant public health concern, representing the leading cause of death and disability in the world today. Moreover, the burden of neurological disorders has increased substantially over the past 25 years. The significant human costs notwithstanding, these conditions also impose overwhelming costs on the global economic system. The current annual costs of neurological and mental health disorders are approximately $2.5 trillion USD, with a projected increase to over $6 trillion USD by 2030. In response to these rapidly expanding costs, there have been significant increases in public and private funding to support research into nervous system disorders. These global initiatives, such as the US BRAIN Initiative or the EU Human Brain Project, have led to expansive and diverse datasets generated through broad, multi-disciplinary research approaches. This underscores the need for sophisticated methods and tools for multi-modal data integration and analysis to enable scientists and clinicians to explore and analyze scientific and clinical data in context.
We have developed a HIPAA-compliant, cloud-based data management, visualization, and analytics platform for the Neurosciences to help accelerate research, foster collaborative efforts,

and ultimately improve clinical care for patients suffering from neurological disorders. The platform enables researchers to explore relationships that are typically difficult to extract from complex, multi-modal datasets. This removes friction in the scientific process, allowing individual investigators and teams to maximally leverage their data and capture their full value. The ability to integrate and analyze a wide variety of data modalities — including genomics data, time series data, imaging data, and behavioral data — in a single platform will significantly improve the ability of the research community to gain insight in the mechanisms of neurological and mental diseases, identify relevant biomarkers, and predict responses to therapy.
The platform is used by a growing number of investigators as part of the NIH Stimulating Peripheral Activity to Relieve Conditions (SPARC) program, the National Institute on Drug Abuse (NIH NIDA) and others. Here, we demonstrate the capabilities of the platform to rapidly provide novel insight into scientific data as well as novel methods to integrate complex meta-data using a graph-based approach to data management, and analysis.

Disclosures: L.A. Guercio: A. Employment/Salary (full or part-time):; Blackfynn Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackfynn Inc. **M. Hollenbeck:** A. Employment/Salary (full or part-time):; Blackfynn Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackfynn Inc. **J.B. Wagenaar:** A. Employment/Salary (full or part-time):; Blackfynn Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackfynn Inc..

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

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Program #/Poster #: 527.04/MMM21

Topic: I.07. Data Analysis and Statistics

Support: NRF-2017M3C7A1049051

Title: Amnet: Multi-modal multi-species network analysis toolbox for animal neuroimaging data

Authors: *J. EO[1], S. JO[2,4], C. PAE[5,2], J. SOHN[5,2], K. JUNG[2,4], J. KANG[2,4], H.-J. PARK[5,3,4]
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Abstract: Preclinical neuroimaging study for animal plays an important role in that it links non-invasive imaging with invasive experiments that cannot be performed on human. As a brain network mining has recently come to the fore in recent science of the human brain, network analysis in the animal is also gaining a spotlight in both clinical and basic science research. It holds great promise for expanding our understanding of the animal brain in relation to principles of brain network organization and its organizational properties associated with pathology. This method of artificial network perturbation in animal brain, which is inapplicable to human, would allow testing and verification of alterations in connectivity through invasive experiments. Despite the importance of brain network analysis in the animal neuroimaging, we still lack simple and automatic pipelines to analyze brain networks using multimodal imaging data. Such pipelines will allow structural-functional integration and data mining. In order to utilize big graph networks, automated pipelines should include the followings: preprocessing steps of raw neuroimaging data, feature extraction and data mining using statistical evaluation or machine learning methods. For this purpose, we have developed a MATLAB-based multimodal network analysis toolbox for animal network analysis, aMNET. aMNET provides both optimal preprocessing modules of resting state functional MRI (rs-fMRI) and diffusion tensor images (DTI) for functional network and structural network, respectively, construction of various types of structural and functional connectivity matrixes with user configurable parameters, extraction of graph theoretical features of each network and structure-function relationships. The tool also includes statistical analysis for group level study and data mining using machine learning techniques such as deep neural network or support vector machine. With the help of its interactive and informative visualization techniques and the integration of invasive approaches and non-invasive imaging, we expect to translate animal experiment results to humans.

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Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

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Program #/Poster #: 527.05/MMM22

Topic: I.07. Data Analysis and Statistics

Title: Frequency-based separation of fast-scan cyclic voltammetry analytes

Authors: K. N. BAUSTERT[1], *E. RAMSSON[2]
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Abstract: With the flourishing use of Fast Scan Cyclic Voltammetry (FSCV) as an analytical technique, the potential for interfering analytes increases. Principle Component Regression (PCR) is a common method used to isolate multiple signals from a complex matrix, however, it

requires the a priori generation of a training set of all species of interest. Even with careful planning, though, it can be difficult to account for all interferents or generate a sufficient training set. While standard training sets can be utilized, this is currently debated within the field. Currently, frequency-based separation is not utilized in FSCV and provides separation of analytes such as dopamine, pH, serotonin, and background drift. This method does not require a training set and can thus prove useful in certain situations.

Disclosures: K.N. Baustert: None. **E. Ramsson:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

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Program #/Poster #: 527.06/MMM23

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant 5R01-NS047293-12
Gift from The Swartz Foundation (Old Field NY).

Title: Analyzing EEG data in EEGLAB: One useful approach

Authors: *R. MARTINEZ-CANCINO, S. MAKEIG, A. DELORME
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Abstract: EEGLAB (sccn.ucsd/eeglab) is an open source signal processing environment for electrophysiological signals running on Matlab (Mathworks, Inc.). Despite the extensive documentation and current widespread use of EEGLAB, implementing reasoned preprocessing of EEG data remains challenging for many users because of the richness and variety of algorithms, plug-in toolboxes and data-specific approaches EEGLAB makes available. There are more than one ways to analyze EEG data; here, from our perspective as EEGLAB developers, we present a reasonable approach to assessing event-related dynamics of source-resolved multichannel EEG data using EEGLAB functions. For this demonstration, we use EEG data made available by Wakeman & Henson (https://openfmri.org/dataset/ds000117/) and apply ICA decomposition (Makeig et al., 1996) to study the dynamics of the effective brain sources following face image presentations and ensuing subject button presses. Preprocessing steps include data import, channel location specification, frequency domain filtering, and 'bad' data removal. We demonstrate decomposition of the preprocessed EEG data into brain and non-brain effective sources. Several visualizations of data measures at the single-subject and group analysis levels are shown. An attempt to interpret the results and conciliate them with previous findings using the same data is done from the effective brain sources perspective.

Disclosures: R. Martinez-Cancino: None. **S. Makeig:** None. **A. Delorme:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

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Program #/Poster #: 527.07/MMM24

Topic: I.07. Data Analysis and Statistics

Support: BMBF Grant 01GQ1302
BMBF Grant 01GQ1509

Title: Achieving reproducible data workflows: Lightweight tools for safe and efficient data management

Authors: C. GARBERS[1], M. SONNTAG[1], A. KOUTSOU[1], C. J. KELLNER[1], J. GREWE[2], *T. WACHTLER[1]
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Abstract: Maintaining reproducible data workflows while keeping data in sync, backed up, and easily accessible from within and outside the lab is a key challenge in research. To minimize time and effort scientists have to spend on these tasks, we provide a suite of tools designed for comprehensive, reproducible and versioned management of scientific data.
Reproducibility and data re-usability require the presence of metadata also providing information about experimental conditions. The odML[1] metadata format is a simple and convenient format to flexibly collect and organize any kind of metadata. It enables comprehensive collection and automated processing of metadata[2], including conversion to other formats such as RDF to utilize semantic web technologies.
To keep data and metadata organized, the NIX[3] data format enables to effectively link data and corresponding analysis results as well as the associated metadata. It supports a wide range of data types, including electrophysiology and imaging data. NIX uses the odML metadata format and is integrated with the Neo[4] Python package for electrophysiology, enabling Neo users to store their data in a common open format.
The GIN[5] services provide versioned data management and collaborative data sharing. Using established versioning technology[6,7], GIN keeps track of changes and provides secure access, making it convenient to work from multiple workplaces while keeping all data available and in sync. Data can be managed from web and file browsers or a command line client, enabling integration into data acquisition or analysis procedures. The service works with any kind of directory structure and file types, keeping previous versions accessible when datasets are updated. It makes it straightforward to share data within a lab or with off-site collaborators and to work on it together.
The tools presented are easy to use, can be combined with other approaches supporting

reproducibility and data sharing[8,9,10], and enable efficient data management that supports the FAIR principles[11]. Combining them for data annotation, organization, and storage allows streamlining data workflows and efficiently sharing well-annotated datasets within the lab, among collaborators, or with the larger scientific community.
[1] http://www.g-node.org/odml
[2] https://doi.org/10.3389/fninf.2016.00026
[3] http://www.g-node.org/nix
[4] http://neuralensemble.org/neo
[5] https://gin.g-node.org
[6] https://git-scm.com
[7] https://git-annex.branchable.com
[8] http://neuralensemble.org/sumatra
[9] http://bids.neuroimaging.io
[10] http://datalad.org
[11] https://doi.org/10.1038/sdata.2016.18

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Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

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Program #/Poster #: 527.08/MMM25

Topic: I.07. Data Analysis and Statistics

Support: A gift by the Swartz Foundation
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R01NS047293

Title: ICLabel: An automated electroencephalographic independent component classifier, dataset, and website

Authors: *L. PION-TONACHINI, K. KREUTZ-DELGADO[1], S. MAKEIG[2]
[1]Electrical and Computer Engin., [2]Inst. for Neural Computation, UCSD, La Jolla, CA

Abstract: Human brain dynamics are now a focus of intense academic research and public interest. Consequently, there is growing interest in electroencephalography (EEG) as a non-invasive, highly time-resolved, and relatively cheap platform for imaging normal and abnormal brain dynamics.While blind source separation (BSS) methods, particularly independent component analysis (ICA), provide demixing estimates of the numerous source-signals summed in each EEG channel signal, they introduce two difficulties into EEG analysis: (1) vulnerability

to large-amplitude, non-stereotyped artifacts and (2) the unknown natures of the retrieved components. The former issue is largely resolvable through readily available signal processing methods; the latter requires expert skill and visual analysis. We present a tool for this problem through the public release of ICLabel, an automated EEG independent component (IC) classifier, as a plug-in for the EEGLAB analysis environment (sccn.ucsd.edu/eeglab) running on MATLAB.The ICLabel project comprises a MATLAB plug-in, an IC dataset, and a tutorial website. The dataset consists of multiple measures (IC scalp topographies, power spectral densities, equivalent dipole models, etc.) for roughly 250,000 ICs decomposed from about 16,000 EEG recordings. The ICLabel dataset also includes nearly 30,000 crowd-sourced labels for over 8,000 ICs contributed by over 240 volunteers through the ICLabel website (labeling.ucsd.edu/tutorial), which remains available for IC classification tutoring and further label contributions. The ICs and accompanying labels have been used to generate multiple candidate IC classifiers using semi-supervised generative adversarial networks. We analyze their efficacy and compare them to other available EEG IC classifiers.

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Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

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Program #/Poster #: 527.09/MMM26

Topic: I.07. Data Analysis and Statistics

Title: Sexrat male: A smartphone and tablet application to record sexual behavior in male rodents

Authors: *A. TAPIA DE JESUS
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Abstract: In behavioral neuroscience studies, it is essential to accurately and easily record rodent sexual behavior either live or in a video. However, current systems are complex or require a computer that hinders their use in situ. The aim of this work is to validate SEXRAT MALE, new software for the recording and quantitative analysis of the sexual behavior of male rodents. It works on smartphones and tablets, both in the Google™, Android™ and in the Apple™ iOS™ operating systems. This software uses a simple algorithm based on chronometry and frequency counting of the behavioral states or events that the user taps on the screen. Its main advantage is that it can record and time a complex sequence of behavioral states by a human observer. SEXRAT MALE can record sexual behaviors such as genital exploration, mounting, intrusion, ejaculation, and also a behavioral event established by the user (i. e. grooming, rearings, etc.). The user can record events by pressing (or tapping) the corresponding keys. SEXRAT MALE is designed primarily for focal sampling with continuous or live recording (continuous recording

for a predetermined time). The value added of SEXRAT MALE is its ability to analyze events, since it could report the times, order, duration at which every event happened, and also the intervals between them, as statistics of all events in the session. This allows the observer to save multiple data from one or several recording sessions. SEXRAT MALE generates two data files in comma-separated values (CSV) format easily importable from any statistical analysis software such as R™, SPSS™, Graphpad™, or spreadsheets such as Excel™, OpenOffice™, Numbers™. To validate SEXRAT MALE, we observed video recordings of the sexual interaction of Wistar rats. Expert and naive observers participated in these recordings, and in turn registered the sexual behavior in the traditional way or with SEXRAT MALE. The groups were counterbalanced between the registration sessions to avoid bias. SEXRAT MALE showed greater precision among both expert and naive observers, decreasing the number of errors and the accurateness of timing data. Additionally, it processes and displays more information than the traditional recording such as order, time of occurrence, and duration of all behavioral events, intervals between them, statistics of all events in the recording session. It is of particular interest that the user can record an event that can be established by a wildcard button; this particular feature expands the options and personalization of the recording session.

Disclosures: A. Tapia de Jesus: None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

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Topic: I.07. Data Analysis and Statistics

Support: Alfred P. Sloan Foundation
Whitehall Foundation Research Grant 2016-08-18
UW Institute for Clinical and Translational Research Pilot Grant UL1TR000427
NIH Grant R03 DC014305

Title: Video tracking module for the real-time experimental control with graphical user interface (rec-gui) framework

Authors: *B. KIM[1], H. LEE[2], H. X. CHAM[3], A. ROSENBERG[1]
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[3]Neurosci., Baylor Col. of Med., Houston, TX

Abstract: The Real-Time Experimental Control with Graphical User Interface (REC-GUI) framework uses a modular design and network-based parallel processing to implement highly flexible and easily extendable neuroscience research (Kim et al., Society for Neuroscience 2017). Here we present a video tracking module for the REC-GUI framework that can track multiple

targets simultaneously. Video tracking systems are widely used to quantify behavioral measurements of head orientation, gait, spatial navigation, social interactions, etc. Specialized commercial systems with high frame capture rates are available on the market, but may be cost prohibitive or overpowered for certain needs. The REC-GUI video tracking module paired with a USB webcam or other lower-end camera provides a low-cost, practical alternative to such systems for experiments where lower capture rates (~ 60Hz) will suffice. The tracking algorithm consists of three simple stages that are applied to each frame in real-time, utilizing color information to isolate and track multiple targets simultaneously. First, the Red, Green, and Blue (RGB) components of every pixel in the frame are extracted. Second, the RGB triplet of every pixel in the frame is compared to pre-acquired distribution(s) of RGB values defining the tracking target(s). Pixels that match a target within a user-defined tolerance are isolated as part of the target. Third, the center of mass of isolated pixels within each frame is defined as the tracking result. In this way, multiple targets with different colors can be tracked in real-time. The module is coded in Python using the OpenCV library. Because Python is a cross-platform language, the module will run on different operating systems as well as small, single board computing environments like Raspberry Pi. The module includes a simple and intuitive user interface, and fully integrates with the REC-GUI framework using internet protocols to provide a simple and affordable video tracking system for neuroscience applications.
This work was supported by the Alfred P. Sloan Foundation, Whitehall Foundation Research Grant 2016-08-18, UW Institute for Clinical and Translational Research Pilot Grant UL1TR000427, and NIH Grant R03 DC014305.

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Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

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Program #/Poster #: 527.11/MMM28

Topic: I.07. Data Analysis and Statistics

Support: KAVLI Foundation, NWB-4-HPC
NIH Grant 1R01MH105174-01
NIH/SBIR

Title: NWB:N: Advances towards an ecosystem for standardizing neurophysiology

Authors: *O. RUEBEL[1], A. TRITT[2], N. H. CAIN[3], B. DICHTER[4], J.-C. FILLION-ROBIN[5], D. OZTURK[5], L. M. FRANK[6], E. F. CHANG[7], F. T. SOMMER[8], K. SVOBODA[9], M. GRAUER[5], W. SCHROEDER[5], L. NG[3], K. BOUCHARD[10]
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Abstract: Neurodata Without Borders: Neurophysiology (NWB:N) is an emerging unified data standard for neurophysiology data, focused primarily on the dynamics of groups of neurons measured under a large range of experimental conditions. Here we describe recent advances in the NWB:N data standardization ecosystem with a particular focus on data organization, advanced data input/output (I/O), schema extension, and community building. We have enhanced the NWB:N specification language and extension APIs via support for compound data types, enabling storage of complex data types, e.g., tables. In addition, object/region references provide advanced mechanisms for explicit cross-referencing of data. Together, these methods have enabled significant improvements in the organization of complex metadata in NWB:N, e.g., for describing electrodes and ROIs. To support advanced data I/O needs, we have extended the PyNWB Python API for NWB:N to support optimization of the layout of data arrays on disk via chunking and compression, enabling significantly reduced I/O and storage cost. PyNWB also enables the use and creation of external links, facilitating modular storage and enhanced organization of large data collections across files. Finally, we have extended PyNWB via novel, customizable interfaces for iterative data write with broad applications to data streaming, on-the-fly data generation, and progressive, out-of-core conversion of large data arrays. As part of our community engagement efforts, more than 65 users from more than 20 different laboratories have participated this year in NWB:N development and user training hackathon events organized by Lawrence Berkeley National Laboratory (LBNL), the Allen Institute for Brain Science, and Kitware. Here we demonstrate the application of our system to diverse neurophysiology use cases by the Frank Lab (USCF), Chang Lab (UCSF), Bouchard Lab (LBNL) and the Allen Institute for Brain Science among others. The NWB:N software ecosystem empowers users to easily access, use, and analyze NWB:N data, integrate NWB:N with user code bases, and develop new extensions for NWB:N. This work builds the critical foundation towards advanced methods for data management, provenance, query/discovery, and advanced, high-performance visualization and analysis.

Disclosures: O. Ruebel: None. **A. Tritt:** None. **N.H. Cain:** None. **B. Dichter:** None. **J. Fillion-Robin:** None. **D. Ozturk:** None. **L.M. Frank:** None. **E.F. Chang:** None. **F.T. Sommer:** None. **K. Svoboda:** None. **M. Grauer:** None. **W. Schroeder:** None. **L. Ng:** None. **K. Bouchard:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.12/MMM29

Topic: I.07. Data Analysis and Statistics

Support: ONR MURI N000141310672
ONR MURI N000141612829

Title: A method for the precise detection and validation of spindle timing in rodents

Authors: *B. HARPER[1], J.-M. FELLOUS[1,2,3]
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Abstract: The automatic and temporally precise detection of cortical sleep spindles is critical to basic research on memory consolidation in humans and rodents. Existing studies of algorithm performance have not included systematic parameter variations or validated detection accuracy in rodent data. We propose a method to systematically tune and validate algorithm parameters in automatic spindle detection algorithms using a small number of human raters. Tuning was based on a 2.5-hour recording from an adult male Brown Norway rat. Six human raters with basic training in spindle scoring extracted spindles from this recording, and a ground truth was constructed at 10-millisecond resolution using agreement between any three raters. The bandpass filter, extraction threshold, smoothing window, and rejection criterion of a Hilbert transform-based algorithm were varied in a parameter sweep for comparison to ground truth. This procedure identified a parameter set yielding 84% recall and 80% precision, falling within the range of human agreement with the ground truth. Both human and algorithm failures with respect to ground truth tended to arise from disagreement in spindle temporal boundaries rather than in spindle occurrence. We explore options for post-extraction artifact rejection. With no additional tuning, the algorithm performed similarly in recordings from different days or rats. We discuss measures of recording quality associated with detection performance. The tuned Hilbert transform algorithm in our study performed better than most algorithms in prior reports using human data. Overall, these results suggest that a systematic approach to algorithm parameter tuning can enhance detection reliability in studies relying on precise spindle timing in rats.

Disclosures: B. Harper: None. **J. Fellous:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

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Program #/Poster #: 527.13/MMM30

Topic: I.07. Data Analysis and Statistics

Support: NIF via NIH NIDA U24 DA039832

dkNET via NIH NIDDK U24 DK097771
ReproNim via NIH NIBIB P41 EB019936
ODC-SCI via the Craig H. Nielsen Foundation
ODC-SCI via the US Department of Veterans Affairs I01 RX002245
BCDC via NIH NIMH U24 MH114827

Title: InterLex: A community lexicon for crowd sourcing common data elements and terminologies in support of fair data

Authors: *J. S. GRETHE, T. H. GILLESPIE, T. M. SINCOMB, J. GO, M. E. MARTONE
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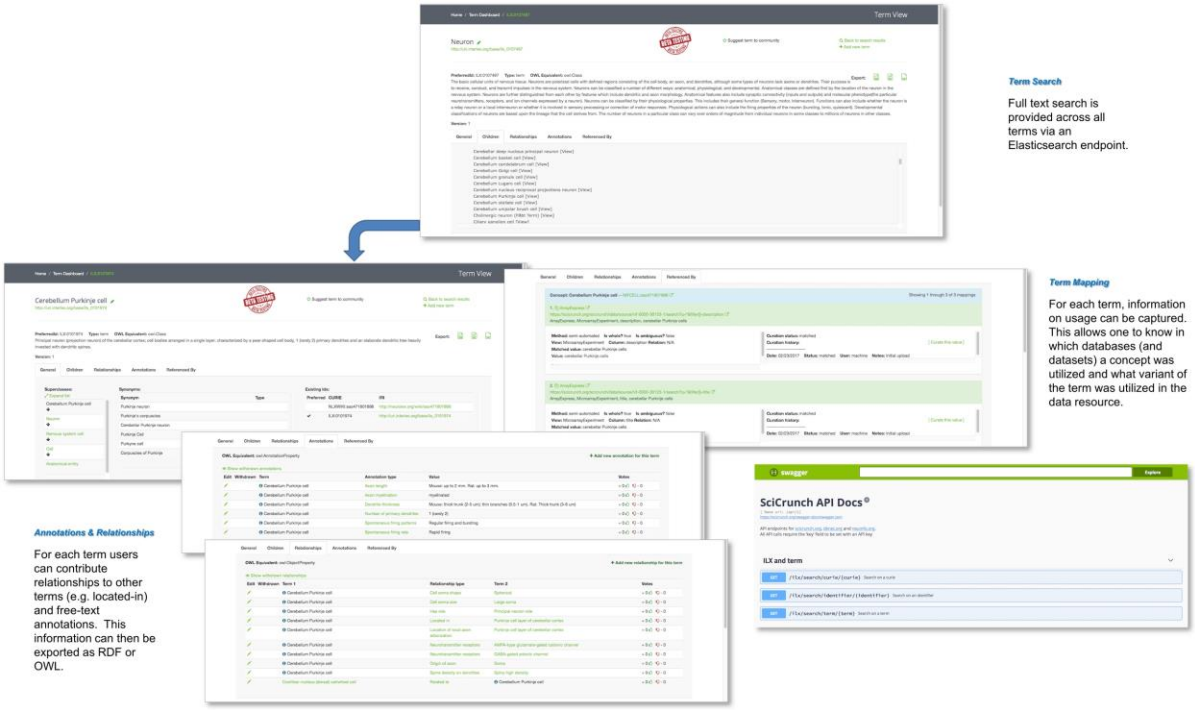
Abstract: InterLex (interlex.org) is a dynamic lexicon, initially built on the foundation of NeuroLex, of biomedical terms and common data elements designed to help improve the way that biomedical scientists communicate about their data, so that information systems like the Neuroscience Information Framework (neuinfo.org), the Center for Reproducible Neuroimaging Computation (repronim.org), and the Open Data Commons for Spinal Cord Injury (odc-sci.org) can find data more easily and provide more powerful means of integrating data across distributed resources. One of the big roadblocks to data integration and making data FAIR - Findable, Accessible, Interoperable and Reusable - is the inconsistent use of terminology and data elements. InterLex allows for the association of data fields and data values to common data elements and terminologies enabling the crowdsourcing of data-terminology mappings within and across communities. A primary goal of InterLex is to provide a stable layer on top of the many other existing terminologies, lexicons, ontologies (i.e. provide a way to federate ontologies for data applications), and common data element collections and to provide a set of inter-lexical and inter-data-lexical mappings. As part of the ReproNim project, InterLex has been expanded to include the full NIMH Data Archive (NDA) CDE library. Through available RESTful web-services, InterLex is supporting alignment of data elements and terminology through PyNIDM which is meant to simplify creation, editing, and querying of NIDM documents. Within the ODC-SCI, InterLex is integrated into the portal platform allowing users to align their data elements to CDEs thereby improving the interoperability and reusability of the data in support of FAIR.

Figure 1: InterLex portal showing term search and term information



Disclosures: J.S. Grethe: None. **T.H. Gillespie:** None. **T.M. Sincomb:** None. **J. Go:** None. **M.E. Martone:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.14/MMM31

Topic: I.07. Data Analysis and Statistics

Support: CONACYT GRANT 259846

Title: pyTral: Open source tool for time series by fractal figures

Authors: *P. GONZALEZ-GASPAR[1], F. M. MONTES-GONZALEZ[1], C. MORGADO-VALLE[2], L. BELTRAN-PARRAZAL[2], C. ISLAS-MORENO[3], B. A. ITZA-ORTIZ[4], F. MENENDEZ-CONDE[4], R. LEONEL-GOMEZ[4], M. TETLALMATZI-MONTIEL[4], J. VIVEROS-ROGEL[4], E.-E. RODRIGUEZ-TORRES[4]
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DE INVESTIGACION EN MATEMATICAS, UNIVERSIDAD AUTONOMA DEL ESTADO DE HIDALGO, MINERAL DE LA REFORMA, Mexico

Abstract: The study of several temporal processes such as temperature, humidity and atmospheric pressure changes in meteorology, rhythmic fluctuations in physiological processes, and nonlinear vibrations in physics, generate time series that are non-linear in general, making difficult the detection of a trend or relationship between points. However, using such time series it is possible to define a map as fractal figure, where groups of points with a similar behavior can be observed. We developed a tool (pyTral) that generates a fractal figure based on time series. User can select just a subset of points on the fractal figure and then recovery the corresponding points of the original time series. In addition, this tool generates a Poincare plot of the time series, which is used as visual tests of chaos within time series. PyTral was developed on Python programming language with a graphical user interface programming in pyqtgraph, which allow portability of the tool.

Disclosures: P. Gonzalez-gaspar: None. **F.M. Montes-gonzalez:** None. **C. Morgado-Valle:** None. **L. Beltran-parrazal:** None. **C. Islas-moreno:** None. **B.A. Itza-ortiz:** None. **F. Menendez-conde:** None. **R. Leonel-gomez:** None. **M. Tetlalmatzi-montiel:** None. **J. Viveros-rogel:** None. **E. Rodriguez-torres:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.15/MMM32

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant R24MH114799

Title: A framework for pipeline optimization and deployment for large neuroscience datasets

Authors: E. C. JOHNSON[1], M. WILT[1], R. NORMAN-TENAZAS[1], L. RODRIGUEZ[1], J. DOWNS[1], E. REILLY[1], M. HUGHES[1], J. MATELSKY[1], N. DRENKOW[1], C. RIVERA[1], B. WESTER[1], E. L. DYER[2], K. P. KORDING[3], *W. R. GRAY RONCAL[1]
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Abstract: There is much excitement in the neuroscience community about new large-scale datasets and high-throughput imaging modalities. At nanoscale resolution, single synapse connectivity maps may radically improve our understanding of neuronal microcircuitry. Coarser resolution datasets provide complimentary approaches and aim to reveal whole-brain connectomes. Insights from these data, and fusion between them, promise to elucidate the

function of healthy brains and reveal the neural basis of disease.
Computational pipelines for working with these datasets are limited in scale, scope, and accessibility. For many pipelines developed to process neuroscience data, the approach does not scale to terabyte-sized datasets. Many tools are developed for specific datasets, and the results do not generalize to new datasets without extensive development. Finally, research groups often lack the computational expertise to deploy these pipelines for their datasets. We need reproducible tools to simplify and streamline the discovery process.
Our framework abstracts many of the computer science challenges that are commonly associated with testing neuroscience hypotheses on modern datasets. The framework consists of: 1) canonical tools and pipelines for processing data and benchmarking performance, 2) workflow execution engines for deployment on datasets of varying sizes, and 3) optimization routines to facilitate the application of pipelines to new datasets. We have incorporated ideas and code from open source solutions such as Common Workflow Language, the Galaxy Project, and Apache Airflow. We have developed a robust, reproducible framework for science, specifically for large neuroimaging datasets (e.g., Electron Microscopy, X-ray Microtomography, optical microscopy). We apply this framework to extract connectivity graphs from Electron Microscopy data and cellular densities from 3D volumes of X-ray Microtomography data. We demonstrate how this framework can be easily configured, how a pipeline can be optimized on a small training dataset, and how the resulting pipeline can be deployed at the scale of hundreds of gigabytes or terabytes. To improve the optimization process, we also present results on parameter optimization and reusing methods for new datasets. Overall, this framework aims to provide accessible, reproducible computational neuroscience for a wide range of problems, with an initial focus on large, neuroanatomical datasets.

Disclosures: E.C. Johnson: None. **M. Wilt:** None. **R. Norman-Tenazas:** None. **L. Rodriguez:** None. **J. Downs:** None. **E. Reilly:** None. **M. Hughes:** None. **J. Matelsky:** None. **N. Drenkow:** None. **C. Rivera:** None. **B. Wester:** None. **E.L. Dyer:** None. **K.P. Kording:** None. **W.R. Gray Roncal:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

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Program #/Poster #: 527.16/MMM33

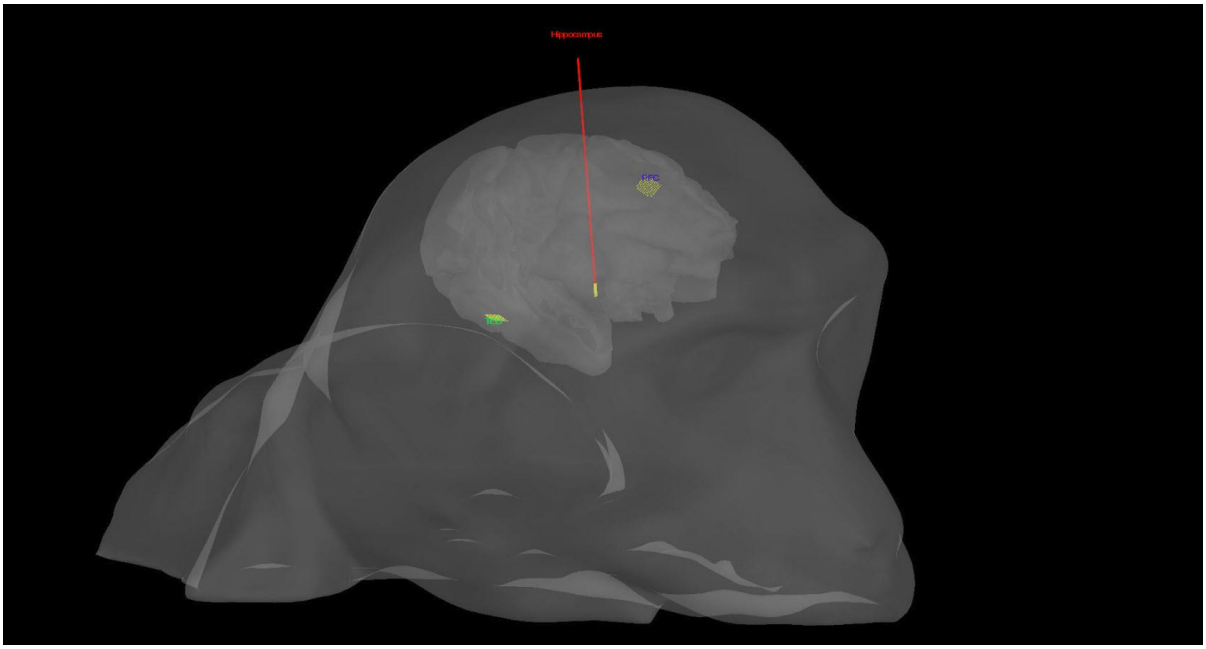
Topic: I.07. Data Analysis and Statistics

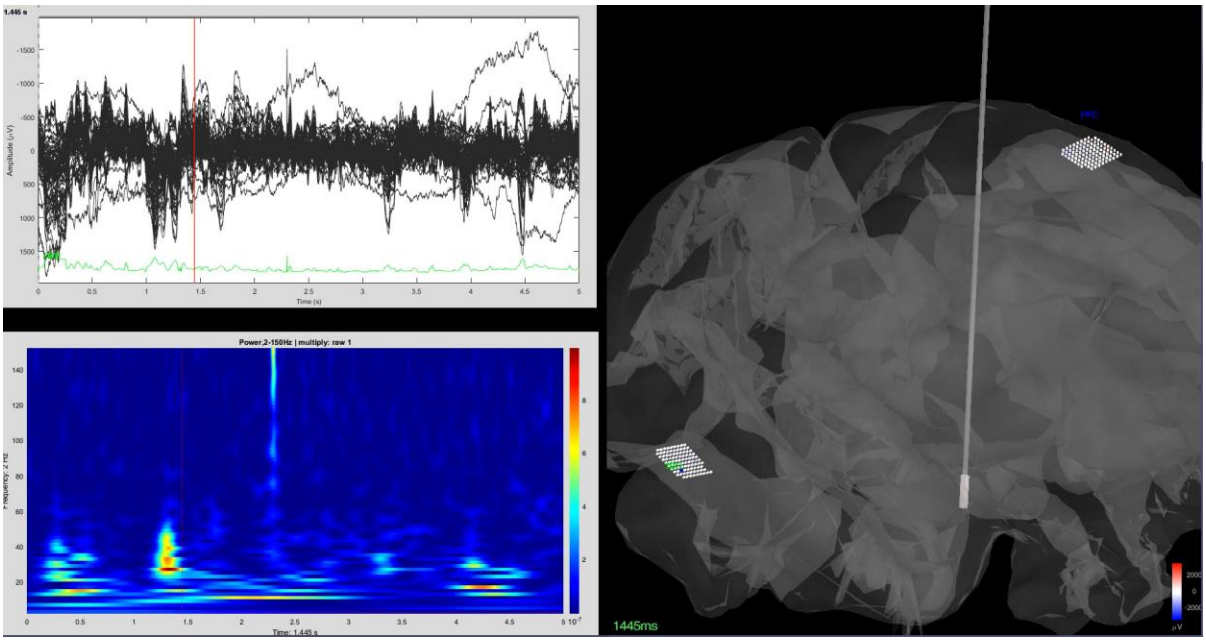
Support: NSERC RGPIN/341534-2012
NSERC 436355-13
NIH 2R01EB009048-05
Platform Support Grant PSG15-3755

Title: Make electrophysiology great again (MEGA)

Authors: *K. NASIOTIS[1], M. COUSINEAU[2], F. TADEL[3], A. PEYRACHE[1], C. PACK[1], S. BAILLET[1]
[1]Montreal Neurolog. Hosp., [2]Montreal Neurolog. Inst., Montreal, QC, Canada; [3]INSERM, Grenoble, France

Abstract: The methods for electrophysiology in neuroscience have evolved tremendously over the recent years, with a growing emphasis on dense-array signal recordings, often at multiple sites simultaneously.Our goal was to implement a software that is oriented for basic electrophysiology, with a user-friendly graphical interface that allows a user experience that interacts as little as possible with “what is under the hood” unless it is explicitly needed. We introduce a free, open-source software application for integrated and advanced data analytics and visualization in basic e-phys. This tool responds to an unmet need of the large neuroscience community relying on diverse recording techniques, ranging from in vitro slices to free-behaving models. The core notion is that researchers (even without any programming skills) shall rely on a tool in which they can import a raw version of their experimental data and then perform all data analytics (spike sorting, spike analysis, LFP analysis etc.) in a traceable (logged) and reproducible manner.





Disclosures: K. Nasiotis: None. **M. Cousineau:** None. **F. Tadel:** None. **A. Peyrache:** None. **C. Pack:** None. **S. Baillet:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

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Program #/Poster #: 527.17/MMM34

Topic: I.07. Data Analysis and Statistics

Support: NIH R01NS06395
NIH U01NS098976
NIH R25NS070694

Title: Introducing "RAVE" (R Analysis and Visualization of intracranial Electroencephalography), a free, open source software package

Authors: *J. F. MAGNOTTI[1], P. J. KARAS[1], Z. WANG[2], M. LI[2], M. S. BEAUCHAMP[1]
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Abstract: A fast-growing technique in human neuroscience is intracranial electroencephalography (iEEG), the only technique that allows for direct recording of the activity of small population of neurons in the human brain. iEEG includes a range of invasive recording techniques (from subdural strips and grids to penetrating electrodes) that share the common attribute of recording neural activity from the human brain with high spatial and

temporal resolution. While this ability has resulted in many advances in understanding fundamental mechanisms of brain function in health and disease, it generates staggering amounts of data as a single patient can be implanted with hundreds of electrodes, each sampled thousands of times a second for hours or even days. The difficulty of exploring these vast datasets is the rate-limiting step in using them to improve human health. We are overcoming this obstacle by developing an easy-to-use, powerful platform designed from the ground up for the unique properties of iEEG, named RAVE: R Analysis and Visualization of intracranial Electroencephalography. The design philosophy of RAVE is driven by three imperatives. The first is to keep users "close to the data" so that users may make discoveries about the brain without being misled by artifacts. The second imperative is rigorous statistical methodology, with a focus on transparency and reproducibility of analyses. The final imperative is "play well with others", allowing easy integration of new or pre-existing code written in languages other than R (e.g., python, Matlab). We describe the data pre-processing and analysis pipeline we have developed and emphasize how our platform enables both confirmatory and exploratory data analysis. The modular design of RAVE allows for seamless incorporation of new and existing analysis tools, providing non-technical users with GUI-based access to state of the art tools. Users comfortable writing their own software can easily plug-in to the RAVE environment to access the optimized computational routines and data management facilities. By distributing software as a RAVE module, developers gain access to a broader audience for their tools, facilitating dissemination of best practices. More information and free download: https://openwetware.org/wiki/Beauchamp:RAVE

Disclosures: J.F. Magnotti: None. **P.J. Karas:** None. **Z. Wang:** None. **M. Li:** None. **M.S. Beauchamp:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.18/MMM35

Topic: I.04. Physiological Methods

Support: NSFC Grant C0916

Title: Optogenetic approach in the study of synaptic transmission——application and limitation

Authors: X. WANG[1,2], Y. WU[1,2], J. HUANG[1,2], Q. ZHU[1,3], Z. LIU[1,2], Y. YANG[1], S. ZHANG[2,1], *J. SUN[4,2]
[1]Univ. of Chinese Acad. of Sci., Beijing, China; [2]Inst. of Biophysics, CAS, Beijing, China; [3]Solomon H. Snyder Dept. of Neuroscience, Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [4]Chinese Acad. of Sci., Beijing, China

Abstract: As light induced cation influx through channelrhodopsin-2 (ChR2) is able to generate action potentials (APs) at genetically manipulated neurons, ChR2 has become a very important tool in neuroscience study, particularly in the functional study of neuronal circuits both in vivo and in vitro. However, the question how much extent the optogetical stimulation can be equivalent to electrical stimulation in regulating neuronal encoding has never been thoroughly addressed. We studied the synaptic responses under various electrical stimulations and optogenetic stimulations at the Calyx of Held synapses and the Parabrachial neucleus - central amygdala (PB-CeAL) synapses. It was found that electrical presynaptic neural fiber stimulation induced postsynaptic excitatory currents (EPSCs) were significantly smaller than the EPSCs induced by optical stimulation upon the presynaptic nerve terminal. Moreover, we found same intensity of optical stimulation induced different ChR2 channel currents at different extracellular Ca^{2+} concentration. The results suggest that light-evoked action potentials at nerve terminal induce additional calcium influx which may cause the significant change in synaptic transmission and short term plasticity. Our study reveals that direct optical stimulation upon the optogenetically manipulated nerve terminal causes non-physiological change in synaptic transmission and thus calls for further evaluating the scope of application and limitation of optogenetic approach in the study of synaptic transmission as well as neuronal signaling

Disclosures: X. Wang: None. **Y. Wu:** None. **J. Huang:** None. **Q. Zhu:** None. **Z. Liu:** None. **Y. Yang:** None. **S. Zhang:** None. **J. Sun:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.19/MMM36

Topic: I.04. Physiological Methods

Title: Adapting the ‘Patch-seq’ protocol to scaled morphological, electrophysiological, and transcriptomic data generation: Keys to maximizing triple modality data

Authors: *B. R. LEE, K. HADLEY, A. BUDZILLO, T. JARSKY, T. BRAUN, D. HILL, L. KIM, R. MANN, L. NG, A. OLDRE, R. RAJANBABU, R. DALLEY, N. GOUWENS, T. KIM, O. PENN, K. SMITH, S. SORENSEN, B. TASIC, J. TING, Z. YAO, C. FARRELL, J. BERG, G. MURPHY, H. ZENG
Allen Inst. for Brain Sci., Seattle, WA

Abstract: The Patch-seq approach (Cadwell et al. and Fuzik et al., Nature Biotechnology 2016) is a powerful variation of the standard patch clamp technique that allows us to characterize the electrophysiological, morphological, and transcriptomic diversity of individual mouse and human neurons. To bridge existing large scale, publicly accessible datasets of morpho-electric (ME) and transcriptional (T) cell types in the Allen Cell Types Database, we have adapted this

protocol to generate high quality 'MET' data from cortical and subcortical neurons. Through this development process, we have identified key factors that together maximize the chance of generating high quality triple modality data. First, we utilize an adaptive extraction technique, varying extraction and retraction pressures and retraction speed to the individual cell to bias toward nucleated patches, as we have determined that to be the ideal post-patch outcome for obtaining high quality transcriptomic data while maintaining morphological integrity. Second, we built custom modules in an automated electrophysiology acquisition software package that allow us to quickly and efficiently acquire the electrophysiological measurements needed to characterize cell types. These modules include online analysis to abort acquisition when QC criteria are not met, as well as stimuli that automatically adjust to a neuron's intrinsic properties. To accurately track the multiple experimental variables we test, we created the JSON Electrophysiology Metadata (JEM) HTML form for efficient and standardized metadata reporting. Although these adaptations were made for large-scale data generation, the techniques and tools described here can be used in any number of settings to improve data quality and throughput.

Disclosures: B.R. Lee: None. **K. Hadley:** None. **A. Budzillo:** None. **T. Jarsky:** None. **T. Braun:** None. **D. Hill:** None. **L. Kim:** None. **R. Mann:** None. **L. Ng:** None. **A. Oldre:** None. **R. Rajanbabu:** None. **R. Dalley:** None. **N. Gouwens:** None. **T. Kim:** None. **O. Penn:** None. **K. Smith:** None. **S. Sorensen:** None. **B. Tasic:** None. **J. Ting:** None. **Z. Yao:** None. **C. Farrell:** None. **J. Berg:** None. **G. Murphy:** None. **H. Zeng:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.20/MMM37

Topic: I.04. Physiological Methods

Support: NSF BRAIN I/UCRC Center 1650566

Title: Do neurons in the vicinity of chronic neural implants experience mitochondrial dysfunction?

Authors: *V. VOZIYANOV, A. SRIDHARAN, J. MUTHUSWAMY
Bioengineering, Arizona State Univ., Tempe, AZ

Abstract: The goal of this study is to assess any disruption in mitochondria function in the neurons surrounding a brain implant. Mitochondrial activity is an important determinant of neuronal viability and function. Brain tissue in the immediate vicinity of chronic neural implants undergo micromotion induced cyclical mechanical stresses that can potentially induce mitochondrial dysfunction. In these exploratory experiments, we assessed the metabolic activity

of the mitochondria both *in vivo* and *in vitro* using MitoTracker™ Red CMXRos. In the *in vitro* experiments, neuronal cells were cultured on either a hard PDMS (poly-dimethyl siloxane) surface with a hardness similar to that of an electrode implant (elastic modulus of 1-3 MPa) or a novel soft PDMS coating that is designed to match the viscoleastic properties of the brain tissue (elastic modulus of 5-10 kPa). These cell cultures were then cyclically stretched for several hours with a maximum strain rate of 3%. At the end of the stretching, the cells were stained with MitoTracker™ Red CMXRos to assess mitochondrial function. In the *in vivo* experiments, several male Sprague-Dawley rats were implanted with tungsten wires, some of which were coated with the novel soft PDMS coating. After two and four weeks, the animals were sacrificed and the brains sliced for staining with MitoTracker™ Red CMXRos to assess mitochondrial activity. The data gathered from the experiments showed that *in vitro*, the cells on the hard substrate showed an elevation in mitochondrial activity that was proportional to the level of cyclical strain rate whereas cells on the soft PDMS surfaces showed similar levels of mitochondrial activity across all levels of deformation. Assessment of data from our in vivo experiments are still in progress. Preliminary data therefore suggest that the function of the mitochondria is disrupted around neural implants as a potential precursor to neuronal migration or necrosis or other forms of neuronal remodeling around such implants. The data also suggests that the soft PDMS coating could be helpful in mitigating any mitochondrial dysfunction around chronic neural interfaces.

Disclosures: V. Voziyanov: None. **A. Sridharan:** None. **J. Muthuswamy:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

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Program #/Poster #: 527.21/MMM38

Topic: I.04. Physiological Methods

Support: Natural Science Foundation of China (81471164)
Key Research Program of Frontier Sciences of CAS(QYZDB-SSW-SMC056)
Shenzhen basic research grant JSGG20160429190521240
Shenzhen basic research grant JCYJ20160429190927063
Shenzhen basic research grant JCYJ20170413164535041
SIAT Innovation Program for Excellent Young Researchers (2016032)

Title: Electrophysiological properties of SF1 neurons in ventromedial hypothalamus

Authors: *J. SHAO, Y. LIU[1,2], S. CHEN[1,2], D. GAO[1], L. ZHANG[1,3], X. ZHOU[1,2], Q. XIAO[1,2], N. HU[4], X. ZHANG[4], J. TU[1], F. YANG[1]
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Kong, Hong Kong; [4]Shenzhen People's Hospital,Second Clin. Med. College, Jinan Univ., Shenzhen, China

Abstract: Ventromedial Hypothalamus (VMH) plays important roles in the regulation of feeding, energy homeostasis, emotional state and social behaviors. The major neuron type in dorsal medial/central VMH (dm/c VMH) is steroidogenic factor 1 (SF1) expressing neurons, these neurons are involved in the control of glucose metabolism, bone metabolism and defensive state. Previous studies have demonstrated these diversified functions are mediated by anatomically distinct and/or genetically specified ensembles of SF1 neurons in dm/c VMH. However up to now little is known about the diversity of the electrophysiological properties of these SF1 neurons, which is fundamental to understand the important functions of distinct neural ensembles. In the present study, we performed a classification study of dm/c VMH neurons in C57BL 6J mice (3-4 months, male) using whole cell patch-clamp recordings. We found that these neurons vary in electrophysiological properties, and could be divided into three types: small input resistance and low resting membrane potential(rheobase>20pA), or Type I; high resting membrane potential and spontaneous firing, or Type II; large input resistance and low resting membrane potential (rheobase<10pA), or Type III. Obvious potential sag, induced by HCN-mediated Hyperpolarization current, was detected in many Type III neurons when injecting current at -100pA. Interestingly, low threshold response (LTR) had been found in some Type II neurons after hyperpolarization. LTR has been considered to be mediated by pacemaker channels which are important ionic components involved in burst firing. Our study is the first to dissect the diversity of the electrophysiological properties of VMH dm/c SF1 neurons using patch-clamp recording; this information is helpful to the classification of subtypes of SF1 neurons, understanding their electrophysiological mechanisms, and dissecting the important functions of the Ventromedial Hypothalamus.

Disclosures: Y. Liu: None. **S. Chen:** None. **D. Gao:** None. **L. Zhang:** None. **X. Zhou:** None. **Q. Xiao:** None. **N. Hu:** None. **X. Zhang:** None. **J. Tu:** None. **F. Yang:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.22/MMM39

Topic: I.04. Physiological Methods

Support: Eastern Washington University Department of Biology

Title: Increasing FSCV dopamine microelectrode sensitivity with NCAM

Authors: *D. P. DABERKOW, D. GINDER, N. SCHERR, J. SEIER
Biol., Eastern Washington Univ., Cheney, WA

Abstract: Chronic fast-scan cyclic voltammetry (FSCV) dopamine (DA) microelectrodes can potentially monitor DA signaling in the brain for several months. After surgical implantation of chronic FSCV DA microelectrodes, a one-month recovery period is usually required for the microelectrode surface to stabilize and accurately detect DA signals. Signal loss during this recovery period is thought to be due to, at least in part, an immune response around the microelectrode sensor (carbon fiber). Neural cell adhesion molecule (NCAM) has been implicated as a means to reduce gliosis around electrodes implanted in the brain. Therefore, chronic FSCV DA microelectrodes were coated with NCAM to investigate potential ability to improve FSCV microelectrode recovery post-surgery. FSCV microelectrodes (n=6) were first sterilized with 70% alcohol and then exposed to 8M nitric acid, dry toluene (100-98%), 2% solution of (3-mercaptopropyl) trimethoxysilane, 2mM 4-maleimidobutyric acid N-hydroxysuccinimide ester, 100 µg/ml NCAM, and 100µM Poly (ethylene glycol)-NH2. Prior to surgical implantation, FSCV microelectrode sensitivity to DA was assessed *in vitro* (i.e., 1 µM DA flow-injection apparatus) before and after NCAM coating. Interestingly, NCAM treatment of FSCV microelectrodes significantly increased the electrode response to DA *in vitro* (51% increase in current response to 1 µM DA in buffer). Future directions include investigating the impact of NCAM coating on FSCV microelectrode recovery and sensitivity to DA *in vivo*.

Disclosures: D.P. Daberkow: None. **D. Ginder:** None. **N. Scherr:** None. **J. Seier:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.23/MMM40

Topic: I.04. Physiological Methods

Support: NIH Grant EY023173
NIH Grant MH106027
NIH Grant NS102727

Title: Pipette cleaning enables one hundred whole cell recordings with a single pipette

Authors: C. LANDRY[1], I. KOLB[1], W. STOY[1], M. YIP[2], C. LEWALLEN[2], *C. FOREST[3]
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Abstract: The late 1970s saw the birth of patch clamp electrophysiology, and despite being a “gold standard” technique across neuroscience, patch clamping has remained a high-skill manual technique, which limits throughput to approximately five cells per hour (for sufficiently short recordings with a single pipette). While significant advances in patch clamp automation (i.e., closed loop image guidance) and multiplexing (i.e., simultaneous recordings with up to 12

electrodes) have occurred, all patch clamp experiments require replacement of pipettes, fundamentally limiting throughput and scalability. We have previously demonstrated a technique that enabled pipettes to be successfully cleaned and reused up to 10 times, enabling unattended operation of patch clamp experiments for 1-2 hours. Here, we present a new method for cleaning pipettes that enables a practically infinite number of reuses with no measurable change in yield or recording quality at a rate greater than trained humans (12-15 cells per hour) for 4 hours with no human intervention. We will demonstrate this new technology by performing 3 experiments: **1)** show efficacy of cleaning by patching >100 cultured HEK 293 cells with a single pipette, **2)** increase throughput by using cleaning for simultaneous dual-pipette patching experiments (25-30 whole cell recordings per hour), and **3)** demonstrate scalability by a single experimenter operating two electrophysiology rigs simultaneously (estimated 50-60 cells per hour). This technology development will bring new levels of scale to patch clamp electrophysiology, enabling repeatable high throughput experiments across neuroscience that can be readily adapted to fields ranging from *in vitro* phenotypic screening to connectomics.

Disclosures: C. Landry: None. **I. Kolb:** None. **W. Stoy:** None. **M. Yip:** None. **C. Lewallen:** None. **C. Forest:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.24/MMM41

Topic: I.04. Physiological Methods

Support: NIH Grant U01NS099687

Title: Transmission electron microscope study of the foreign body response to implanted polyimide-based gold microelectrode platform under *in vivo* conditions

Authors: *H. EREZ[1,2], N. SHMOEL[1,3], S.-H. HUANG[1,3], M. M. JANKOWSKI[1,4], I. NELKEN[1,4], M. E. SPIRA[1,2,3]
[1]The Dept. of Neurosci., [2]The Charles E Smith Family and Prof. Joel Elkes Lab. for Collaborative Res. in Psychobiolo, [3]The Harvey M. Kruger Family Ctr. for Nanoscience, [4]Edmond and Lily Safra Ctr. for Brain Sci., The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Electrode platform implanted to vertebrate central nervous system elicit a cascade of cell biological events that culminate in a characteristic foreign body response (FBR). The severity of the FBR is classically characterized by confocal microscope imaging of immuno-labeled sections prepared from paraformaldehyde fixed brains after the removal of the electrodes-platform. Whereas this method is sufficient to describe the overall distribution of the cells around the implant at a resolution of tens to hundreds micrometers, detailed information as

to the cell types that in fact adhere to the implant surface and the nature of the contact formed cannot be extracted. Here we developed a protocol that enable to prepare thin section from a polyimide-based (PI) gold electrode-platform together with the surrounding rat cortex tissue for transmission electron microscopic (TEM) analysis. Immunohistological examination of two weeks implanted PI perforated MEA and the surrounding tissue revealed that the platform generated a minimal overall FBR. Nonetheless, both activated microglia and astrocytes are detected in the vicinity of the PI-MEA. These cells and occasionally neurites extend branches into the perforations. Established ultrastructural features were used to differentiate among the different cell types in the TEM images. We found that the PI platform and the surfaces of the gold electrodes were occupied by adhering microglia with a PI/microglia extracellular cleft that ranges between 0 to 50 nm. Although this narrow extracellular cleft could represent tissue shrinking artifact in the order of 5-15% due to the processing, this implies very tight adhesion of the microglia to the implant surface. Interestingly, whereas astrocyte adheres to the microglia in vicinity to the platform they don't form direct contact with the PI surface. Neurites were detected at distances as small as approximately 1 µm from the PI-MEA surface but were separated from the platform by microglia. The dominant adhesion of microglia to the PI platform and gold electrodes mechanically isolate the platform from the astrocytes and neurons and probability electrically insulate the electrode.

Disclosures: H. Erez: None. **N. Shmoel:** None. **S. Huang:** None. **M.M. Jankowski:** None. **I. Nelken:** None. **M.E. Spira:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.25/MMM42

Topic: I.04. Physiological Methods

Title: Multi-modal *in vivo* electrophysiology with integrated glass microelectrodes

Authors: *M. BARBIC[1], D. L. HUNT[2]
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Abstract: Progress in neurobiology has driven increasing demand for diverse modalities of information to gain a cohesive understanding of neural function. Electrophysiology is the most ubiquitous form of functional data collected for basic and clinical neuroscience research, typically limited to a single-mode, intracellular or extracellular recording. The integration of multiple physiological modalities for routine acquisition of multi-modal data would be advantageous for numerous biomedical applications but has been challenging due to the incompatibility of their fabrication methods. Here we present a flexible suite of devices with integrated glass pipette microelectrodes, engineered to simultaneously obtain multi-modal

information (intracellular + extracellular) *in vivo*. Moreover, we extend this platform to include electrochemistry, and capabilities for optogenetic perturbations of neural activity. Utilizing our toolkit of integrated devices to acquire multi-modal signals from the CA1 region of the hippocampus in vivo, we demonstrate how such data can serve as ground-truth validation for the performance of spike-sorting algorithms. Thus, our technologies are applicable for basic neurobiological and clinical discovery, as well as for developing next-generation brain-machine interfaces.

Disclosures: M. Barbic: None. **D.L. Hunt:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.26/MMM43

Topic: I.04. Physiological Methods

Support: ERC
HBP

Title: All in one go: Expression, electrophysiology and imaging within 24 hours using Semliki Forest virus *in vivo* and *in vitro*

Authors: *S. DOMINIAK, J. MÜLLER-PESTER, T. A. ZOLNIK, R. N. SACHDEV, M. E. LARKUM, A. GIDON
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Abstract: During the last two decades, the field of neuroscience has been transformed by our ability to express a wide range of proteins in neurons, often by injecting viral vectors into the living brain. Typically, expression is slow, reaching optimal levels in days to weeks following viral transfection. Consequently, state-of-the-art approaches using opsins or other genetically encoded indicators are intractable for experiments constrained in time e.g. in acute brain slices obtained ex vivo from human patients. Here we used a strategy whereby transfection, expression, recording and/or imaging are achievable within hours using Semliki Forest Virus (SFV), a positively stranded RNA viral vector capable of driving rapid protein expression. We describe a simple technique for delivering SFV *in vitro*, using micro-droplets and/or micro-injection of the virus suspension directly onto acute brain slice preparations. Using this technique *in vitro* as well as standard *in vivo* viral injections, we systematically characterized the viability and function of mouse cortical neurons expressing GFP, channel-rhodopsin, CaMPARI or RCaMP. We found that transfecting with viral particles at low concentrations ($<10^8$ particles/ml) resulted in sparse yet strong expression. Importantly, initial expression began as early as 4 hours after viral transfection and the infected cells had viable electrophysiological behavior at least up to 24 hours

post transfection. In summary, we present “all in one go” strategy providing an easy, fast and efficient way to go from transfection to imaging and electrophysiology.

Disclosures: S. Dominiak: None. **J. Müller-Pester:** None. **T.A. Zolnik:** None. **R.N. Sachdev:** None. **M.E. Larkum:** None. **A. Gidon:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.27/MMM44

Topic: I.04. Physiological Methods

Title: Application of high-throughput automated patch-clamp techniques to the study of neurotransmitter receptor function: From engineered cell lines to cultured cortical neurons

Authors: *M. TOH[1], J. M. BROOKS[1], T. STRASSMAIER[2], S. S. PIN[1]
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Abstract: Drugs that target neurotransmitter systems are immensely important as therapeutic agents and as research tools for neuroscientists seeking to unravel the complexities of neuronal signaling. While there are numerous examples of such drugs there is much room for improvement in terms of potency, selectivity, and efficacy. Automated high-throughput systems that directly measure the activity of ionotropic neurotransmitter receptors will help to enable the discovery of the next generation of drugs and research tools. Traditional approaches rely on the use of engineered cell lines that over-express defined receptor types, but these artificial systems may not always faithfully reproduce the function of all neurotransmitter receptors in their native environment, the neuron. For this reason, we sought to bridge the gap between cell line and neuron using a high-throughput planar patch clamp recording system. We started by studying the effects of reference compounds on recombinant NMDA receptors (NR1/NR2B) expressed in an HEK cell line. NMDAR activity was elicited by application of glutamate/glycine both before and after the application of compounds. The NMDAR activity remained stable over repeated applications of glutamate/glycine (average of 7.5% signal decrease over 5 additions) and was inhibited by CP-101,606 with an IC_{50} of 235 nM and Ro-25,6981 with an IC_{50} of 190 nM. As expected, TCN 213, a selective antagonist of NMDA-NR1/NR2A, had no effect up to 30 μM. We also examined the activity of positive allosteric modulators on responses to glutamate alone; the EC_{50} for glycine was 100 nM and the EC_{50} for D-serine was 160 nM. While spermine also potentiated the glutamate activity the response did not saturate at the highest concentration tested. Finally, we applied the same automated patch clamp technology to acutely-dissociated neurons derived from rat cortex. These neurons display a range of voltage-gated conductances. In addition, preliminary pharmacological studies show that a sub-population of the rat cortical neurons express receptors for GABA.

Disclosures: J.M. Brooks: None. **T. Strassmaier:** None. **S.S. Pin:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.28/MMM45

Topic: I.04. Physiological Methods

Support: Veterans Affairs Rehabilitation Research and Development Service Grant to SDH and SGW
NIH U42 Grant 3U420DO1158 to GCK

Title: Accelerating pain research via human dorsal root ganglia analysis

Authors: *M. W. VONDRAN[1], S. SHAD[1], G. KOPEN[1], T. J. BELL[1], S. G. WAXMAN[2,3], S. DIB-HAJJ[2,3]
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Abstract: Species-specific differences in genomic, transcriptomic, and proteomic profiles are emerging as major hindrances for investigators pursuing basic and translational neuroscience research. Analysis on primary human tissues and cells provides an alternative method to overcome this challenge. However due to the experimental and logistical challenges of studying human neurons, this approach is substantially underutilized by investigators. Recent advances in experimental methodologies and procurement practices have ameliorated several key issues. Here we report our advances to provide suitable tissue for state-of-the-art experimental methods. The National Disease Research Interchange (NDRI) is a non-profit organization that serves as the critical link between individuals wishing to donate organs and tissues for research and biomedical investigators. NDRI specializes in using a project-specific approach to design recovery protocols for donor eligibility and tissue collection and preservation procedures. In doing so, the scientist obtains experimental-specific human tissues for their studies. For example, NDRI provides human DRG for pain research that specifically meets the needs of the physiologist. DRGs from NDRI have been utilized to show that the membrane and firing properties of human DRG neurons have several distinct physiological properties compared to rat DRG neurons (Han et el., 2015). Our approach to providing human DRGs and other tissues for rigorous experimental methods such as electrophysiology and RNAseq is presented. For example, as the lead organization for the NIH's Geneotype Tissue Expression project, NDRI applied their project-specific approach to obtain multiple tissues (n=5 to 32) per donor for RNAseq analysis. Due to the escalating nature of experimental questions and techniques that investigators are addressing and pursuing, suitable tissues are needed to enable experimental

success and accurate data. Optimizing tissue collection and preservation methods to the experimental procedures for each scientific study will play a key role in accelerating the development of new pain and other clinical therapies and treatments.

Disclosures: M.W. Vondran: None. **S. Shad:** None. **G. Kopen:** None. **T.J. Bell:** None. **S.G. Waxman:** None. **S. Dib-Hajj:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.29/MMM46

Topic: G.05. Anxiety Disorders

Support: Stanford Neurobiology
Stanford School of Medicine Dean's Fellowship

Title: A novel virtual reality based platform for understanding the mechanism of visually evoked anxiety and habituation in healthy and anxious subjects

Authors: *M. YILMAZ BALBAN[1], A. D. HUBERMAN[1,2,3,4]
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Abstract: Our ability to respond adaptively to different stimuli in our environment is a critical skill for ongoing mental health and overall life progression. Humans rely heavily on vision more than other senses to carry out their daily life functions as well as survival. Habituation to repetitive, inconsequential stimuli, is one mechanism by which the visual system eliminates irrelevant stimuli and therefore responds selectively to salient features in our environment. Defects in habituating to visual stimuli have been to linked a variety of neuro-psychiatric disorders; however, how behaviors and internal states habituate to the repeated presentation of visual stimuli remains poorly understood. The two main goals of this research are (1) to understand how healthy humans respond to repeated and anxiety producing visual stimuli, (2) to understand how these processes are affected in individuals with generalized anxiety disorder. To reach these goals, we built a state-of-the-art Virtual Reality (VR) platform that enables the delivery of realistic and emotionally salient visual environments to humans in the laboratory, while simultaneously measuring their behavioral, physiological and subjective responses. Subjects repeatedly experienced a suite of anxiety-inducing visual stimuli in VR. Peripheral physiology of each subject was continuously recorded by electrocardiogram, electro-dermal activity, respiration and pupil size. Their behaviors were automatically scored in real-time using custom written software. The survey ratings for each stimulus were analyzed as a way to assess subjective perception. Changes in all of the collected responses during consecutive exposures

were evaluated as a measure of habituation.
We discovered that in healthy subjects, there is a pronounced reduction in the number of autonomic and behavioral responses during the second exposure to a stimulus. This finding suggests that changes in baseline reactivity is a robust signature of habituation in this population. By contrast, preliminary data from patients with anxiety show that this population increases their responsiveness to the stimuli (i.e. sensitization) instead of habituating to them. These results suggest that relative sensitization/habituation to repeated exposure to visual stimuli may represent a powerful biomarker for diagnosis of generalized anxiety disorder and a means to reliably measure the efficacy of various treatments. Our VR-based platform enables **objective measurements of the human internal state:** a methodological advance in the field of affective neuroscience, which will lead to a mechanistic understanding of anxiety and other affective disorders.

Disclosures: M. Yilmaz Balban: None. **A.D. Huberman:** None.

Poster

527. Electrophysiological and Behavioral Software and Hardware Tools

Location: SDCC Halls B-H

Time: Tuesday, November 6, 2018, 8:00 AM - 12:00 PM

Program #/Poster #: 527.30/MMM47

Topic: I.06. Computation, Modeling, and Simulation

Support: JSPS KAKENHI Grant Number JP17H02088

Title: A surface design of polystyrene sheet by an inkjet printer for network architecture of cultured neurons

Authors: *S. ISHIDA[1], K. UMETA[2], N. TESHIMA[2], Y. YOSHIMI[3]
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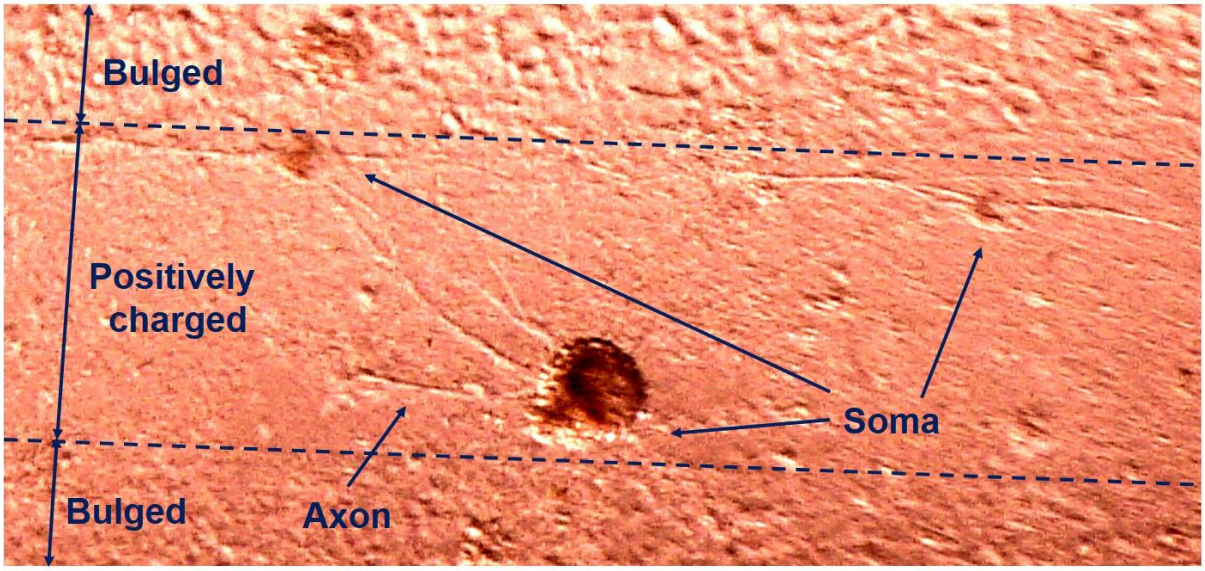
Abstract: Simulating neural network by neurons cultured on the pattered substrate is important for basic study or screening of neurotoxicity of drugs under development.
The purpose of this study is simulating nervous system by patterned culture of neurons on a substrate whose surface is designed by a widely commercialized ink-jet printer. The ink-jet printing can be done economically and flexibly then conventional photolithography.
Firstly, 0.96 wt% cationic polyethylene imine aqueous solution was printed on a polystyrene sheet as the substrate by using a portable inkjet printer (iP100, Canon, Tokyo). The printed area was positively charged and attaches neurons. However, axons grew randomly and extended to the non-printed area.
The results indicate that the axon growth factor would be adsorbed on the polystyrene surface, then the charge patterning is not sufficient for control of the axon growth. Then, we designed a

method to make bulged pattern of the polystyrene surface with the inkjet printer as well by using limonene which is eco-friendly solvent of polystyrene. A mixture of 2: 3 (wt) ethanol-limonene with 0.8 wt% rose bengal was printed on the polystyrene sheet. The polyethylene imine was printed on the interval again. Aplysia neurons were allowed to attach on the interval and were cultured in a mixed medium of SL-15 and Aplysia bodily fluid (1:1 in volume).
As the results the axon of the all neurons extended along the edge of the bulged area.
In addition, 30% of the neurons formed synapse each other.
As a conclusion, a commercialized ink jet printer is a potential tool to create neural networks among the neurons adsorbed on the substrate printed pattern of bulge and charge.



Disclosures: S. Ishida: None. **K. Umeta:** None. **N. Teshima:** None. **Y. Yoshimi:** None.