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Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 548.01/A1

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

Support: NIH Grant EY027003
NSF Grant IOS-1457126

Title: Mutations in protocadherins impact neural circuit assembly

Authors: *S. LIGHT, J. JONTES;
Neurosci., The Ohio State Univ., Columbus, OH

Abstract: Protocadherins (pcdhs) belong to a diverse family of homophilic cell adhesion molecules involved in a variety of developmental processes that are critical for establishing appropriate brain structure and function. Mutations in pcdhs are associated with neurodevelopmental diseases including autism spectrum disorder, schizophrenia, and epilepsy. Our lab has previously shown that zebrafish with mutations in various pcdhs display subtle defects in neurogenesis, neuronal organization of the optic tectum, and visually-guided behaviors. To further characterize individual pcdh mutants, we employed *in vivo* imaging of spontaneous neuronal activity to investigate the development of network architecture and neuronal connectivity. We performed whole-brain multiplane two-photon calcium imaging of wild type, pcdh19 mutant, and pcdh1a mutant larvae during the first developmental week, which represents a critical period of circuit assembly and structural maturation. The evolution of network topology was evaluated with graph theory, which allowed us to easily compare wild type and mutant networks. This novel approach proved to be an efficient and reliable way to quantify dynamic network properties over time. In both pcdh mutants, we observed robust alterations in the trajectory of network development, as measured by clustering, transitivity, and small world organization. These changes in complex network measures reflect a dysregulation in neuronal architecture and synaptic maturation at the circuit level that leads to altered activity patterns across the brain. Using transient BAC injections, truncation constructs, and non-adhesive pcdh mutants in conjunction with time-lapse imaging, we are investigating the cellular roles of pcdhs that contribute to the altered network phenotypes we observe. Additionally, using proteomics, we have identified interactomes for pcdhs that have suggested relevant molecular pathways for future exploration. Ultimately, we theorize that pcdh function influences brain architecture by locally regulating and coordinating developmental processes, such as neurogenesis and axon outgrowth.

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

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 548.02/A2

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

Title: Altered cortical development and neural excitability in the medial prefrontal cortex of B-cell CLL/lymphoma 9 mutant mice

Authors: *Y. KUANG[1], B. YANG[2], S. CHEN[3], W. LI[4];
[1]Shanghai Jiaotong Univ., Shanghai, China; [2]Bio-X Inst., Shanghai, China; [3]Bio-X Institutes, Shanghai Jiao Tong Univ., Shanghai, China; [4]Shanghai Jiao Tong Univ., Shanghai City, China

Abstract: B-cell CLL/lymphoma 9 (*BCL9*), located on the human chromosome locus 1q21.1, has been implicated in tumor progression through the Wnt signaling pathway. Human genetic studies have suggested that common *BCL9* variants confer a risk of schizophrenia, bipolar disorder, and autism development. However, the function of BCL9 in central nervous system remains poorly understood. We used in utero electroporation mice and BCL9 mutant mice in our study. Here, we demonstrated BCL9 is highly expressed in mouse brain during the embryonic and early postnatal period. Knockdown BCL9 in E13.5 could severely disturb the migration of cortical neurons and down regulation of Wnt target genes. Knockdown of BCL9 increased ultrasonic vocalization in pups. Interestingly, we identify BCL9 expression level change voltage-dependent sodium channels expression, leading to abnormal neuronal excitability. We also noted that the common BCL9 variants regulate the brain structural volume and psychotic-like symptoms in adolescents. In conclusion, our findings indicate a possible role of BCL9 in the pathogenesis of neurodevelopmental disorders.

Disclosures: Y. Kuang: None. **B. Yang:** None. **S. Chen:** None. **W. Li:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 548.03/A3

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

Support: ERC-2015-CoG 681577
Ha 4466/10-1

SPP 1665
SFB 936 B5

Title: Early fast frequency activity sculpts functional and behavioral maturation of prefrontal networks

Authors: *J. A. PÖPPLAU[1], S. H. BITZENHOFER[2], M. CHINI[1], A. MARQUARDT[1], I. L. HANGANU-OPATZ[1];
[1]Developmental Neurophysiology, Inst. of Neuroanatomy, Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany; [2]Dept. of Neurosciences, Univ. of California San Diego, San Diego, CA

Abstract: Rhythmic fast frequency oscillations in prefrontal cortex (PFC) are the neural network attribute of cognitive processing. Recently we showed that they already emerge at neonatal age entrained by local synchronized firing of layer 2/3 pyramidal neurons. However, the contribution of early rhythmic activity to cortical circuit formation and their maturation across development is still largely unknown. To fill this knowledge gap we combine in vivo and in vitro electrophysiology with chronic and acute optogenetic stimulations of prefrontal neurons during awake and anesthetized state, as well as morphological and behavioral investigations of postnatal day (P) 5-40 mice. First, we show that layer 2/3 pyramidal neurons in the prelimbic subdivision of PFC entrain local circuits in fast oscillatory rhythms with increasing frequency and amplitude that relate to the progressive embedding of parvalbumin-positive interneurons into developing networks. Next, we directly test the functional engagement of early activity in shaping cortical network refinement by manipulating neonatal oscillations. Mild chronic optogenetic boosting of fast rhythmic activity in PFC during a defined period of neonatal development results in reversible neuronal morphological alterations, such as premature dendritic growth of layer 2/3 pyramidal neurons and reduced interneuronal density. These transient morphological changes are accompanied by permanent circuit dysfunction, reflected by abnormal gamma entrainment at adult age. Mice with manipulated neonatal activity show impaired social interactions and poorer recognition and working memory at juvenile and adult age. Our results indicate that early patterns of coordinated oscillatory activity are relevant for network function and behavioral performance of adults.

Disclosures: J.A. Pöpplau: None. **S.H. Bitzenhofer:** None. **M. Chini:** None. **A. Marquardt:** None. **I.L. Hanganu-Opatz:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

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

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DA021696 to KM
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Title: Chronic exposure to delta9-THC during adolescence alters muscarinic M2 receptor distribution in adult prefrontal cortical neurons contacted by CB1 terminals

Authors: M. GARZON[1], K. MACKIE[2], *V. M. PICKEL[3];
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Abstract: Chronic intermittent administration of marijuana's major psychoactive compound, Δ9-tetrahydro-cannabinol (THC) results in adaptive changes in adult social and cognitive functions that are dependent on activity of output neurons in the prelimbic prefrontal cortex (PL-PFC). Memory and learning processes in PL-PFC neurons can be regulated by cholinergic transmission through muscarinic-2 -like receptors (M2R) and modulated by activation of cannabinoid-1 receptors (CB1Rs) that are targeted by THC. This learning is a key contributor to the experience-dependent plasticity ongoing in the PL-PFC during the vulnerable stage of adolescence, which suggests that chronic exposure to THC during adolescence may alter the expression and/or distribution of M2Rs in PL-PFC neurons receptive to CB1R terminals. We used high resolution electron microscopic dual CB1R and M2R immunolabeling in adult C57BL/6J male mice (postnatal day, PD70) that had received vehicle or escalating dose (2.5-10mg/kg/ip) of THC through adolescence (PD 29-43) to test this hypothesis. In **vehicle controls** CB1R-immunolabeling was mainly localized to small unmyelinated axons and axon terminals almost none of which contained M2R but often apposed M2R-immunoreactive profiles. M2-labeling was also localized to axons, but it was more often seen in the cytoplasm or on extrasynaptic plasma membrane of varying sized dendrites and dendritic spines. The dendritic profiles receive input from CB1R-labeled or unlabeled terminals, whereas the dendritic spines received asymmetric synapses exclusively from axon terminals lacking CB1Rs. **Adolescent THC** produced a significant increase in M2R-immunogold density exclusively in large dendrites receiving input from CB1R-labeled terminals. In contrast, the cytoplasmic M2R-immunogold density was decreased in small spines of the THC-treated adult mice. We conclude that THC occupancy of presynaptic CB1R receptors during adolescence produces increased plasmalemmal accumulation of M2R in large proximal dendrites and decreased cytoplasmic expression in small spines influenced by CB1R regulated modulators in PL-PFC. They have implications for understanding and treating psychiatric disorders worsened by teenage marijuana use.

Disclosures: M. Garzon: None. **K. Mackie:** None. **V.M. Pickel:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

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Program #/Poster #: 548.05/A5

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

Support: ERC Advanced Grant 694829 "neuroXscales"

Title: Connectivity profiling and single-cell RNA sequencing to study homeostatic plasticity in hippocampal neuronal networks *in vitro*

Authors: *T. KIM, J. BARTRAM, M. SCHROETER, A. HIERLEMANN;
D-BSSE Bioengineering Lab., ETH Zurich, Basel, Switzerland

Abstract: Homeostatic plasticity represents an important set of regulatory mechanism to help maintaining stable neuronal circuit function and to flexibly adapt firing rates to changes in external drive (Turrigiano and Nelson 2004; Turrigiano 2008). Moreover, deficits in the ability to homeostatically regulate neuronal activity have been linked to a series of neurological and neuropsychiatric diseases (Frere and Slutsky 2018; Roselli and Caroni 2015). Although the intrinsic and synaptic mechanisms underlying homeostatic responses have been an area of active research (Turrigiano 2012), only few studies have attempted to link the electrophysiological properties of individual neurons to their gene-expression profiles following up- or down regulation of activity (Schanzenbächer et al. 2018; Schanzenbächer et al. 2016; Schaukowitch et al. 2017).
We sought to gain a more integrated understanding of how the homeostatic firing-rate regulation of single neurons correlates to their functional connectivity in the network and their transcriptomic changes, respectively. To track the development and spontaneous activity of primary rodent hippocampal networks *in vitro*, we used high-density microelectrode arrays (HD-MEAs) (Müller et al. 2015). HD-MEAs enable studying of neuronal function both at the network and subcellular scale (Obien et al. 2014) and, futhermore, provide the means for tracking extracellular multi-channel footprints of single neurons over extended developmental periods (Gong et al. 2016). Finally, combined with simultaneous patch clamp recordings, HD-MEAs are a suitable tool to map the synaptic connectivity of individual neurons (Jäckel et al., 2017).
Here, we tracked the emerging spontaneous activity of hippocampal neuronal networks across development and inferred their functional connectivity. Once the network had reached a mature devlopmental stage, we applied bicuculline and followed the homeostatic response of the full network and a subset of pre-selected neurons at high resolution. In a second step, we applied the Patch-seq protocol (Cadwell et al. 2017) to extract cellular content from cells of interest and to combine the identification of the electrophysiological phenotype of neurons with post-hoc single-cell RNA sequencing. We demonstrate that the response dynamics of individual neurons

to perturbation are heterogeneous, which is also reflected in the mRNA extracted from these neurons. We propose that a combined analysis of neuronal activity, synaptic connectivity and gene expression patterns is a promising approach to study the mechanisms underlying neuronal homeostasis.

Disclosures: **T. Kim:** None. **J. Bartram:** None. **M. Schroeter:** None. **A. Hierlemann:** 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.; ERC Advanced Grant 694829 "neuroXscales".

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 548.06/A6

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

Support: FRM

Title: A synaptic switch gates developmentally-regulated homeostatic plasticity in parvalbumin interneurons of the visual cortex

Authors: ***M. DRUART**[1,2], M. SOIZA-REILLY[3], M. QUAGGETTO[1,2], M. GARCIA[1,2], I. MOUTKINE[1,2], C. LE MAGUERESSE[1,2];
[1]INSERM U1270, Inst. Du Fer À Moulin, Paris, France; [2]Sorbonne Univ., Paris, France; [3]IFIBYNE (UBA-CONICET), Buenos Aires, Argentina

Abstract: Brain development is shaped by synaptic plasticity, which contributes to the formation of mature neuronal networks. Critical periods (CP) of brain development are specific time windows characterized by high plasticity in neural networks in response to environmental perturbations. A specific CP has been well characterized in the developing visual cortex where permanent changes in ocular dominance (OD) occur after monocular deprivation (MD) during CP. Converging evidence implicates glutamatergic inputs onto parvalbumin-expressing (PV) interneurons in the onset of the CP for OD plasticity. However, the underlying molecular and synaptic mechanisms remain largely unknown. Using patch-clamp recordings in acute slices from mice at different developmental stages, we studied the development of the glutamatergic input onto PV interneurons. Our results revealed a transient decrease in the AMPA-receptor (AMPAR) rectification index during CP. This suggests a transient loss of AMPAR subunit GluA2 at excitatory synapses onto PV interneurons during CP. Interestingly expression of GRIP1, a protein involved in GluA2 trafficking, has been shown to be transiently downregulated in cortical PV interneurons at P25. Furthermore, the interaction between GRIP1 and GluA2

mediates homeostatic plasticity at glutamatergic synapses. To assess homeostatic plasticity in PV neurons, we sutured one eye for 3 days before recording miniature excitatory postsynaptic currents (mEPSCs) in PV neurons of the contralateral visual cortex. We observed an increase in mEPSC frequency before and after CP but not during CP. This result suggests an absence of homeostatic plasticity at excitatory synapses onto PV interneurons selectively during CP, thus potentially allowing profound changes in visual cortex connectivity at this crucial developmental stage. We hypothesized that the downregulation of GRIP1 during CP prevents the trafficking of GluA2 subunit to the synapse and homeostatic plasticity in PV interneurons during CP. To test this hypothesis, we generated PV-Cre::GRIP1lox/lox mice in which GRIP1 is ablated specifically in PV neurons and then recorded PV neurons in the visual cortex of adult (P50) mice after MD. The rectification index of AMPAR was decreased in adult mice lacking GRIP1 in PV neurons. In addition, MD in KO mice did not elicit the increase in mEPSC frequency observed in WT mice, indicating that GRIP1 is necessary for homeostatic synaptic plasticity in PV neurons. Taken together, our results suggest that the transient downregulation of GRIP1 prevents the homeostatic plasticity of glutamatergic inputs onto PV interneurons in visual cortex selectively during CP.

Disclosures: **M. Druart:** None. **M. Soiza-Reilly:** None. **M. Quaggetto:** None. **M. Garcia:** None. **I. Moutkine:** None. **C. Le Magueresse:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

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

Support: Israel Science Foundation (ISF) grant number 300/16

Title: Multiplexing rhythmic information by spike timing dependent plasticity

Authors: *M. SHAMIR[1], N. SHERF[2];
[1]Ben-Gurion Univ., Be'er Sheva, Israel; [2]Ben-Gurion Univ. of the Negev, Be'er-Sheva, Israel

Abstract: Rhythmic activity has been associated with a wide range of cognitive processes including the encoding of sensory information, navigation, the transfer of emotional information and more. Past studies have shown that spike timing dependent plasticity (STDP) can facilitate the transfer of rhythmic activity downstream along the information processing pathway. However, STDP has also been known to generate strong winner-take-all like competition between subgroups of correlated synaptic inputs. Consequently, one might expect that STDP will induce strong competition between different rhythmicity channels; thus, preventing the multiplexing of information across the different frequency channels. Here we ask: **Can STDP**

facilitate the multiplexing of information across different frequency channels, and if so, under what conditions? This question was addressed using the framework of a modelling study. We investigated the STDP dynamics of two competing sub-populations of neurons that synapse in a feedforward manner into a single post-synaptic neuron. Each sub-population was assumed to oscillate in an independent manner and in a different frequency band. To investigate the STDP dynamics, a mean field Fokker-Planck theory was developed in the limit of slow learning rate. Surprisingly, our theory predicted limited interaction between the different sub-groups. Our analysis further reveals that the interaction between those channels is mainly mediated by the shared component of mean (DC) activity. Next, we generalized our results beyond the simplistic model using numerical simulations. We found that, for a wide range of parameters, the system converges to a dynamic solution, in which the post-synaptic neuron responds to both rhythms. However, all of the synaptic weights remain dynamic and do not converge to a fixed point. Thus, we find that STDP can support multiplexing of rhythmic information, depending on the temporal structure of the STDP rule. This work demonstrates how functionality (multiplexing of information) is retained in the face of continuous remodelling of all of the synaptic weights.

Disclosures: M. Shamir: None. **N. Sherf:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

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

Support: HKRGC-GRF 17125115
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Title: Mechanism by which perineuronal nets promote hardwiring of vestibular circuits for sensori-motor behaviors

Authors: *Y.-S. CHAN, T. KWAN, A. TAM, C.-W. MA, K. WU, D. SHUM;
Sch. of Biomedic. Sci., Fac. Med., Univ. Hong Kong, Hong Kong, China

Abstract: Chondroitin sulphate (CS)-rich perineuronal nets (PN) have emerged as a powerful regulator of plasticity. We asked how PN governs early brain development. Consolidation of PN around GABAergic neurons in the VN coincides with emergence of vestibular-dependent negative geotaxis behavior at P9 in rats. Treatment of the VN at P6 with chondroitinase ABC (ChABC) to delay consolidation of PN resulted in shift of negative geotaxis to P13. To elucidate the effect of ChABC treatment at the cellular level, we performed whole-cell patch-clamp recordings on VN interneurons in brainstem slice preparations at P9 and P14 when PN-CS underwent consolidation. Pre-treatment of the VN with ChABC decreased inhibition but

promoted excitatory neurotransmission in VN neurons. We found that ChABC treatment increased excitability of VN neurons due to increase in membrane potential. Apart from this direct effect, we further showed that the PN-CS associated plasticity-inducing factor semaphorin 3A (Sema3A) was liberated with treatment of ChABC. In vitro tests confirmed that Sema3A promoted neurite growth and branching of VN neurons. To reveal the behavioral consequence, we compared Sema3a treatment alone with combined ChABC and Sema3A delivery to the VN at P6. Sema3A delayed the emergence of another graviceptive reflex air-righting from P15 to P16, while combined treatment further delayed it to P18. Taken together, our results suggest that retention of Sema3A by PN-CS moieties limits dendritic/synaptic plasticity of VN interneurons, thereby contributing to developmental hardwiring of the central circuitry for vestibular behavior.

Disclosures: Y. Chan: None. **D. Shum:** None. **T. Kwan:** None. **A. Tam:** None. **C. Ma:** None. **K. Wu:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

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

Support: PHS NRSA T32GM007270

Title: Genetic disruption of DCC and Ntn1 expression in adult midbrain dopamine neurons produces significant behavioral changes

Authors: *M. M. CLINE[1], A. HUNKER[2], B. JUAREZ[2], L. S. ZWEIFEL[2];
[1]Psychiatry and Behavioral Sci., [2]Pharmacol., Univ. of Washington, Seattle, WA

Abstract: Netrin1 signaling through the netrin receptor deleted in colorectal cancer (DCC) promotes growth cone attraction, axon elongation and branching, and synaptic development during embryogenesis. Emerging evidence suggests DCC and secreted netrins may play an additional role in maintaining excitatory synaptic connections in the adult brain. Both netrin1 and DCC are highly expressed in the adult ventral tegmental area (VTA) and substantia nigra (SN), and co-label with TH expression, but their function in these cells remains unclear. To explore the function of netrin1 and DCC in adult dopamine neurons, we used a combination of viral-mediated, cre-inducible CRISPR/Cas9 technologies and transgenic mice to selectively disrupt *Ntn1* and *Dcc* expression exclusively in midbrain dopamine neurons of adult mice. Eight-week old DAT-IRES$^{Cre/+}$ mice were injected bilaterally into the VTA with AAV-FLEX-SaCas9-HA-sg*Ntn1*, or -sg*Dcc*, and AAV-FLEX-YFP. Control DAT-IRES$^{Cre/+}$ mice received bilateral injections of AAV-FLEX-YFP. Four weeks following viral injections, mice were screened for alterations in dopamine-mediated behaviors. Open field testing revealed *Ntn1* and *Dcc*

conditional knockout (cKO) mice spent significantly less time in the arena center (Mean±SEM; *Ntn1* cKO 34.58s ± 4.375, *Dcc* cKO 30.21s ± 6.117) compared to YFP controls (66.67s ± 8.030, $p<0.001$), and significantly more time on the arena edge ($p=0.0015$, *Ntn1* cKO 425.8s ± 13.15, *Dcc* cKO 427.6s ± 12.65, YFP 360.2s ± 14.41). Locomotion measured across three nights and two days showed significantly reduced day distance traveled in *Ntn1* and *Dcc* cKOs compared to controls ($p<0.05$, *Ntn1* cKO 1867cm ± 152.3, *Dcc* cKO 1416cm ± 142.5, YFP 2635cm ± 383.8) on day one. Curiously, *Dcc* cKO, but not *Ntn1* cKO, mice displayed significant impairment in novel object recognition and social recognition. These data suggest that both *Ntn1* and *Dcc* play an important role in regulating specific aspects of dopamine-regulated behaviors through their actions in dopamine neurons of the adult midbrain. Future experiments will be aimed at establishing a role for these proteins in maintaining excitatory synaptic connectivity in dopaminergic midbrain neurons in the adult brain.

Disclosures: **M.M. Cline:** None. **A. Hunker:** None. **B. Juarez:** None. **L.S. Zweifel:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

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Program #/Poster #: 548.10/DP01/A10

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Title: Humanization of SRGAP2C expression increases cortico-cortical connectivity and alters cortical neural responses in the mouse brain

Authors: *E. SCHMIDT[1], H. T. ZHAO[2], C. KIM[2], E. HILLMAN[2], F. POLLEUX[1];
[1]Neurosci., [2]Biomed. Engin. and Radiology, Columbia University, Mortimer B. Zuckerman Mind Brain Behavior Inst., New York, NY

Abstract: Little is known about the molecular changes that have led to the emergence of human-specific traits of brain development and function. Recently, we have focused our attention on human-specific gene duplications as potential genetic modifiers of human brain development.

One such gene is SRGAP2: the ancestral copy SRGAP2A, which is present in all mammals, promotes maturation and limits the density of both excitatory (E) and inhibitory (I) synapses received by cortical pyramidal neurons (PNs). Partial duplication of SRGAP2A resulted in a human-specific paralog, SRGAP2C, which inhibits all known functions of SRGAP2A. Expression of SRGAP2C in mouse PNs leads to the emergence of phenotypic traits characterizing human cortical PNs, including increased E and I synapse density and delayed synapse maturation. However, how these changes in synapse number and maturation affect the structure and function of cortical circuits remains unknown. We explored how humanization of SRGAP2C expression affects the structural organization of mouse cortical circuits by using monosynaptic rabies tracing from sparse populations of cortical layer 2/3 PNs in the primary somatosensory cortex (S1). Using a novel method for reconstruction and mapping of traced neurons, we found that humanization of SRGAP2C expression causes a significant increase in local connectivity, as well as long-range feedback connections from other cortical areas, including M2 and contralateral S1. Interestingly, we did not detect any quantitative changes in inputs for subcortical neurons, showing humanization of SRGAP2C expression selectively increases cortico-cortical connectivity of layer 2/3 PNs. These results suggest that developmental mechanisms that control synaptic connectivity, like SRGAP2, represent suitable evolutionary substrates through which increased complexity of cortical circuit wiring has emerged during human brain evolution. We now investigate how this increased cortico-cortical connectivity impacts circuit performance related to sensory processing and behavior. Using multiple *in vivo* imaging approaches, including wide-field optical imaging, we are testing how SRGAP2C expression alters cortical circuit function and modifies sensory evoked neuronal responses across the entire dorsal cortex. Our work aims to uncover the mechanisms whereby human-specific genetic modifiers altered synaptic development and neuronal connectivity and how these changes in circuit architecture affected cortical function and might have allowed the emergence of human-specific features of brain function during evolution.

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Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

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Program #/Poster #: 548.11/A11

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

Support: CIHR FDN-14323
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Molson Neuroengineering Studentship

Title: Distinct roles of TrkB and p75NTR signaling in neural circuit refinement in the developing visual system

Authors: *E. KUTSAROVA[1], A. SCHOHL[1], M. MUNZ[2], O. BILASH[3], Y. ZHANG[1], A. WANG[4], E. S. RUTHAZER[1];
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Abstract: Building a brain which contains properly connected neurons is essential for the survival of an animal in the surrounding world. Sensory experience translated into patterned neuronal activity instructs various aspects of topographic map refinement, crucial for orderly representation in the brain of the outside world. Forming and refining proper brain connectivity relies on the communication between a projecting neuron and its future postsynaptic partners. Brain-derived neurotrophic factor (BDNF) was identified as one of the prominent molecular candidates that underlies activity-dependent neural circuit refinement. BDNF is synthesized as a precursor protein proBDNF which has been shown to play a role in facilitating synaptic weakening through p75 neurotrophin receptor (p75NTR) signaling, whereas the post-cleavage mature form (mBDNF) signals through p75NTR and tropomyosin-related kinase B (TrkB) and is crucial for synaptic strengthening. Overall, BDNF signaling is crucial for structural remodeling of dendrites and axons during development. We used multiphoton imaging of retinal ganglion cells (RGCs) projecting into the optic tectum in the albino Xenopus laevis tadpole to observe their structural remodeling in vivo. A single ectopic ipsilaterally projecting RGC axon was visually stimulated either synchronously or asynchronously with its neighboring inputs, while blocking BDNF signaling with TrkB-Fc, or knocking down its receptors TrkB or p75NTR in RGCs. We showed that acute BDNF signaling is necessary for suppression of axonal branch addition in response to correlated firing. p75NTR in RGCs is required for asynchrony-induced branch addition, while TrkB signaling in RGCs acts as an activity-dependent suppressor of branch elimination. p75NTR in the RGCs is crucial for exploratory growth over days. p75NTR and TrkB appear to have distinct signaling in darkness compared to during visually evoked activity. These results provide cellular structural details for BDNF, TrkB and p75NTR signaling as mechanisms underlying specific aspects of activity-dependent structural remodeling during development.

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Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

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

Support: Einhorn Family Charitable Trust
Deki Stephenson
Fleur Fairman

Title: Family nurture intervention (FNI) which increases EEG power of preterm infants at term age does so through mechanisms other than FNI effects on delta brushes, effectors of early brain development

Authors: P. G. GRIEVE[1], M. M. MYERS[1], J. L. BARONE[1], R. J. LUDWIG[1], R. I. STARK[1], J. R. ISLER[1], ***M. G. WELCH**[2];
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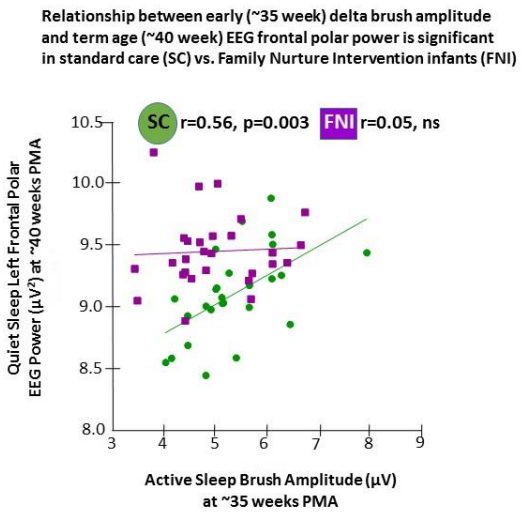
Abstract: The Nurture Science Program (NSP) at Columbia University (nurturescienceprogram.org) conducted an RCT of Family Nurture Intervention (FNI) in the NICU. Prior results showed that FNI, which facilitates emotional connection (EC) and physiological co-regulation between preterm infants and their mothers, has positive physiological and neurobehavioral effects including robust increases in frontal brain activity (EEG power, 19-21Hz) at term age. Prominent features of preterm EEG activity are bursts known as delta brushes (DB) which appear at 28-30 wks and which are largely gone by 42 wks. It is thought that early bursting activity plays a key role in shaping brain development. Here we characterize FNI effects on early EEG bursting activity and ask if they mediate effects of FNI on term EEG activity. Results from 31 SC and 33 FNI infants (~30 wks GA at birth) show that FNI alters two aspects of DBs: 1) FNI infants have more rapid increases in amplitudes of the brush component of DBs from ~35 to ~40wks, and 2) DBs in FNI infants have longer durations, especially during quiet sleep (QS). Consistent with the hypothesis that DBs shape subsequent brain activity we found, pooling data from both SC and FNI, four parameters of DBs at ~35 weeks were correlated with term power: active sleep (AS) rate, $r=0.30$, $p<0.05$; AS brush amplitude, $r=0.32$, $p<0.05$; QS brush amplitude, $r=0.28$, $p<0.05$; QS brush oscillation frequency, $r=0.36$, $p<0.05$. However, results from mediator analyses found no evidence that effects of FNI on early burst parameters mediate effects of FNI on term power. This finding is also illustrated in the figure. Thus, while early bursting activity can have important effects on shaping later brain activity, facilitating EC through FNI results in maturation of brain activity being less dependent on early bursting activity. Mechanisms underlying how co-regulation and EC embedded in FNI alter brain development are not clear but ongoing NSP research in human infants and animal models are exploring autonomic conditioning as key to understanding these important effects of nurture.



Disclosures: **P.G. Grieve:** None. **M.M. Myers:** None. **J.L. Barone:** None. **R.J. Ludwig:** None. **R.I. Stark:** None. **J.R. Isler:** None. **M.G. Welch:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 548.13/A13

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

Support: NIH R01MH086507
NIH R01MH105488
CIHR 201811MFE-415573-64156

Title: Maturation of prefrontal cortex responses to basolateral amygdala inputs during adolescence: Frequency-dependent regulation by local excitatory & inhibitory signaling

Authors: *M. AUGER[1], K.-Y. TSENG[2];
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Abstract: Basolateral amygdala (BLA) inputs to the prefrontal cortex (PFC) are involved in the regulation of decision-making, impulse control and affective processing. Past research has suggested that BLA innervation of the PFC is remodeled during adolescence, which may

contribute to the adolescent maturation of these cognitive faculties. If so, the functional refinement of BLA-PFC circuitry is expected to occur during adolescence to impact how the PFC processes inputs from the BLA. To address this issue, we conducted local field potential recordings in the PFC and changes in the pattern of responses elicited from the BLA using different frequencies of train stimulation were compared across 4 age groups of rats (postnatal day): P30-37, P40-47, P50-57, and P65-80. Reduced facilitation of PFC responses to 15 Hz BLA stimulation was observed during adolescence in comparison to adults, an effect that was most prevalent within the P30-37 and P40-47 age groups. In contrast, adolescents showed blunted suppression of responses to 30-40 Hz BLA stimulation, an effect that was most obvious in the P50-57 age group. These results suggest BLA recruitment of excitatory and inhibitory components in the PFC mature over adolescence, which may display distinct developmental trajectories in a frequency-dependent manner. Future studies will elucidate how variations in BLA output transmission and local PFC signaling regulate the distinct frequency-dependent responses observed during the transition from adolescence to adulthood. Collectively, these findings point to a novel feature of PFC development during adolescence that may support the dynamic cognitive and emotional changes that occur during this time.

Disclosures: **M. Auger:** None. **K. Tseng:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 548.14/A14

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

Support: NIH Grant R01 EY022730

Title: Maturation of cFos expression in cortical circuits

Authors: *M. POMPEIANO, M. T. COLONNESE;
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Abstract: Wakefulness in cortical circuits is accompanied by robust expression of the activity-induced gene cFos, which is driven by a combination of neuronal activity and noradrenergic release (Pompeiano et al 1994). During development, circuit formation in the cerebral cortex is accompanied by unique patterns of activity whose similarities with adult cortical activities are not fully understood (Colonnese and Phillips 2018). Early background activity is discontinuous (long silent periods) and poorly modulated by arousal state. The switch to adult-like patterns of background activity occurs, with some regional heterogeneity, during the second week postnatally in mice, first in somatosensory cortex and last in visual cortex. Here we investigated when cFos expression matures in the cerebral cortex in order to determine its relationship with

the maturation of cortical activity patterns and potentially validate its use as a marker to predict developmental activity patterns throughout the brain. C57BL/6 mouse pups were killed at 5 (P5), 9, 13, and 17 days of age or as adults (n=4, 2 males and 2 females for each age) after manual stimulation to keep them awake for 1-2 hours. At P5, cFos staining was limited to layer 6b in somatosensory, motor and auditory cortex. These cells co-labeled with Nurr1 indicating they are subplate neurons. The only structure with adult-like, widespread staining at this age was the piriform cortex, consistent the early development of olfaction to cue suckling (Al Aïn et al 2013). Dense, multi-layer adult-like staining was observed in somatosensory, motor, and auditory cortex by P13 and in visual cortex by P17 in line with the timing of whisking, ear-opening and eye-opening respectively (Colonnese and Phillips 2018). cFos staining was very low or absent in sleeping animals of the same ages. These observations show that immature spontaneous activity bursts do not drive cFos expression beyond the subplate. Robust cFos expression is instead correlated with the onset of mature, continuous, background activity. cFos is therefore a potential marker for the maturation of cortical activity patterns.

Disclosures: M. Pompeiano: None. **M.T. Colonnese:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 548.15/A15

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

Title: Microglia-mediated remodelling of the medial pulvinar connectivity: New insights for schizophrenia

Authors: *J. HOMMAN-LUDIYE, J. A. BOURNE;
Australian Regenerative Med. Inst., Monash Univ., Clayton, Australia

Abstract: Uniquely evolved in primates, the medial pulvinar (PM) is a multimodal thalamic nucleus, responsible for coordinating the simultaneous processing of many elements of information and the modulation of selective directed attention. Anatomical and structural evidence of abnormal PM architecture and activity in patients suggest that the cognitive and behavioural symptoms associated with schizophrenia result from abnormal PM connectivity. To address this hypothesis, we mapped the extensive connectivity between the PM and neocortex in the adult marmoset monkey (*Callithrix jacchus*) using MRI-guided bidirectional tracer injections (n=3; > 2yo; sex was not a selection criterion). Whilst we confirmed previous connections with the temporal, parietal and prefrontal cortices, we identified 20 additional cortices connected with the PM. Based on our previous evidence that connectivity between the inferior pulvinar and neocortex is profoundly remodelled during development, we investigated if this principle is conserved in the PM. Using the same tracing paradigm applied to neonatal (postnatal day (PD)

14); juvenile (PD90) and adolescent (PD300; n=2/ stage) monkeys, we observed a more extensive PM connectivity in the juvenile brain, in terms of both density and spatial distribution, which is refined during adolescence to make place for the adult profile. Co-labelling with the microglial marker Iba1 enabled the identification of tracer-labelled PM terminals internalised within the phagocytic cells, suggesting that the microglia participate in sculpting PM efferents in the neocortex. Dysregulation of the microglia-mediated synapse elimination has been associated with the excessive pruning and loss of grey matter characteristic of schizophrenia. Therefore, abnormal PM connectivity in patients is potentially a consequence of dysfunctional developmental processes. To further investigate the role of PM in neocortical maturation, we performed chemical lesions of PM in neonatal animals (n=2, PD14). Analysis in adulthood revealed abnormal expression of maturation markers in neocortical areas connected to PM, akin to observations in schizophrenia patients. Therefore, we conclude that the PM plays an instructive role on cortical development and is central in the aetiology of schizophrenia.

Disclosures: J. Homman-Ludiye: None. **J.A. Bourne:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 548.16/A16

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

Support: ANR-15-CE16-0003-01
Equipe FRM DEQ20130326521
ANR-10-IAHU-01
Equipe FRM DEQ20150331681
ARSEP
ED BioSPC

Title: Death of Cajal-Retzius cells regulates the wiring of upper cortical layers

Authors: *M. RIVA[1,2,3], I. GENESCU[4], C. HABERMACHER[1], D. ORDUZ[5], F. LEDONNE[3], F. RIJLI[6], G. LOPEZ BENDITO[7], E. COPPOLA[1,2,3], S. GAREL[4], M. C. ANGULO[1,5], A. PIERANI[1,2,3];
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Abstract: Programmed cell death (PCD) is emerging as a key player in the wiring of cortical circuits.

Cajal-Retzius cells (CRs) are among the first born cortical neurons and reside in the most superficial layer of the developing cerebral cortex from where they coordinate multiple crucial steps in the construction of functional circuits. At embryonic stages CRs comprise at least three distinct subtypes which differ for their generation site (septum, ventral pallium and hem), molecular signature, distribution at the cortical surface and function. The vast majority of CRs are thought to be transient as they disappear during early postnatal life in mice as well as in primates and their abnormal persistence is associated with pathological conditions in humans. Here we show that subtype-specific features persist at postnatal stages. Using genetic fate mapping our work revealed that CR subtype-specific differences exist in the distribution and timing of disappearance in the postnatal mouse brain. We showed that all CR subtypes undergo cell death although, surprisingly, through at least two molecularly distinct pathways. Conditional inactivation of the pro-apoptotic factor *Bax* prevented death of septum but not hem-derived CRs. Surviving CRs are integrated in neural circuits and keep the electrophysiological properties of immature CRs. Furthermore, we found that CRs survival promotes exuberance of dendrites and spine density in upper layers pyramidal neurons. This results in imbalanced Excitatory/Inhibitory (E/I) ratio due to an increase in excitatory drive in the network. These changes are activity-dependent as hyperpolarization of CRs by Kir2.1-dependent expression promoted their survival in the absence of any differences in pyramidal neuron morphology, number of spines or electrophysiological properties.
These results strongly suggest that CRs demise is a novel player in developmental remodeling and maturation of dendrites and synapses and provide the first mouse model to test the relevance of altered PCD in human pathologies. We will discuss the effects of maintaining immature neurons in the mature cortex, the role of a subtype-specific control of CR programmed cell death in the construction of cortical functional and dysfunctional circuits.

Disclosures: **M. Riva:** None. **I. Genescu:** None. **C. Habermacher:** None. **D. Orduz:** None. **F. Ledonne:** None. **F. Rijli:** None. **G. Lopez Bendito:** None. **E. Coppola:** None. **S. Garel:** None. **M.C. Angulo:** None. **A. Pierani:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 548.17/A17

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

Support: NIH grant MH106757
discovery pilot award from CTSI-Children's National

Title: Early life adversity and maturation of dorsal raphe synapses

Authors: *A. KISNER, C. GOMEZ, M. CAMACHO, A. M. POLTER;
Pharmacol. and Physiol., The George Washington Univ., Washington, DC

Abstract: Early life is a critical period in the development and refinement of the central nervous system. Experience during this early life period plays an important role in shaping the maturation of the brain. Exposure to early life adversity is implicated in increased susceptibility to many neuropsychiatric disorders such as depression, anxiety and addiction. These processes are themselves linked to dysfunction of neuromodulatory systems. In particular, the serotonergic neurons of the dorsal raphe nucleus (DRN) exert widespread and complex neuromodulatory effects that are necessary for fine-tuning neural circuit formation. While it is known that serotonin regulates a wide range of brain functions and behavior, it is not clear how their circuits regulating serotonergic function are modulated by development and early-life experience. Here, we used slice electrophysiology to characterize the maturation of synaptic inputs received by serotonergic and GABAergic neurons in the DRN from juvenile to adult developmental stages in mice. We found that the strength of excitatory transmission increased over the course of the juvenile and adolescent period and was maintained through early adulthood. Additionally, we determined that within the juvenile (PND15) and adolescent (PND35) developmental stages the AMPA/NMDA receptor-mediated current ratio in serotonergic neurons is higher than that found in GABAergic neurons, suggesting differential patterns of synaptic maturation in DRN serotonergic and GABAergic neurons. To better understand the impact of early life experience on maturation of DRN synapses, we implemented a limited bedding model to induce early life stress (ELS) from PND4 to PND11. We then used slice electrophysiology to assess the maturation of DRN synaptic inputs. Our results indicate a decrease in excitatory neurotransmission (mean spontaneous excitatory postsynaptic current frequency ELS 1.11 Hz ± 0.1, n = 3 cells vs control 2.43 Hz ± 0.1, n = 3 cells) onto DR serotonergic neurons immediately following stress that persists into adulthood. Thus, our results demonstrate that adverse experience during early life can cause persistent alterations in the synaptic architecture of the DRN. We anticipate that our findings will be a starting point to understand the impact of adverse experiences on synaptic maturation of the DRN highlight targets for novel treatments for stress-related disorders.

Disclosures: **A. Kisner:** None. **C. Gomez:** None. **M. Camacho:** None. **A.M. Polter:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 548.18/A18

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

Support: ERC starting grant 679175

SNSF grant 31003A_170037

Title: Developmental divergence of sensory stimulus representation in cortical VIP and SST interneurons

Authors: *R. KASTLI[1], R. VIGHAGEN[1], A. VAN DER BOURG[2], A. ARGUNSAH[1], A. IQBAL[1], F. F. VOIGT[3], D. KIRSCHENBAUM[4], A. AGUZZI[4], F. HELMCHEN[5], T. KARAYANNIS[6];
[1]Univ. of Zurich, Zurich, Switzerland; [2]Brain Res. Inst., Zürich, Switzerland; [3]Brain Res. Inst., Zurich, Switzerland; [4]Univ. Hosp. Zurich, Zurich, Switzerland; [5]Brain Res. Inst. / Univ. of Zurich, Zurich, Switzerland; [6]Brain Res. Institute/University of Zurich, Zurich, Switzerland

Abstract: Inhibitory interneurons play an important role in sensory processing in the rodent whisker somatosensory cortex (wS1). In wS1 of adult mice the VIP^+ and SST^+ interneurons have been shown to be critically involved in modulating network activity during active whisking. However, little is known about the activity of these cells in the early post-natal brain before the mouse pup starts to actively whisk. Using *in vivo* two-photon calcium imaging, we investigated the activation of VIP^+ and SST^+ interneurons in response to two different whisker stimulation paradigms (single- and multi-whisker), before and after the onset of active whisking (P14). We found that before P14 both interneuron types respond stronger to the multi- compared to the single-whisker stimulation. In contrast, after the onset of active whisking the activation profiles diverge and only the SST^+ interneurons retain the ability to differentiate between the two stimuli while the VIP^+ cells do not. In order to get at the potential circuit mechanisms underlying the diverging response profiles we used monosynaptic rabies virus tracings followed by CLARITY based tissue-clearing, as well as photostimulation-coupled electrophysiology to investigate the cortico-cortical and thalamo-cortical inputs onto the two interneuron types. We found that, both before and after P14, SST^+ interneurons receive cortical inputs from further away within wS1 compared to VIP^+ cells, pointing at one route for cross-whisker sampling by SST^+ cells. In addition, we also found that a second route for SST^+ cells to sample multiple whiskers before P14 was the robust inputs from the somatosensory thalamus, which was also true for VIP^+ cells of that age. Nevertheless, the thalamic inputs onto the two cell types significantly re-arrange after P14, with those onto SST^+ interneurons shifting to nuclei associated with the motor thalamus. These results show that wS1 VIP^+ and SST^+ interneurons undergo impactful changes around the time the animal starts actively whisking, potentially to diversify their role and allow the refined processing of multiple aspects of the environment.

Disclosures: **R. Kastli:** None. **R. Vighagen:** None. **A. Van Der Bourg:** None. **A. Argunsah:** None. **A. Iqbal:** None. **F.F. Voigt:** None. **D. Kirschenbaum:** None. **A. Aguzzi:** None. **F. Helmchen:** None. **T. Karayannis:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 548.19/A19

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

Support: NIH Grant R01DC009607

Title: Development of cortical AMPA and GABA-A receptor mediated connections in the absence of NMDA receptors

Authors: *R. DENG, P. O. KANOLD;
Biol., Univ. of Maryland, College Park, MD

Abstract: Fast neurotransmissions mediated by ionotropic receptors are essential for interneuronal communication and neural computation. Our understanding of the mechanisms underlying the development of synaptic connections in the brain is still incomplete. Synaptic inputs to developing cortical neurons are mostly supplied via glutamatergic and GABAergic synapses. In early development glutamatergic synapses are mostly composed of NMDA receptors while AMPA receptors emerge later. NMDA receptors are thought to play a crucial role in the development of AMPA receptor mediated connections. Since GABA can be depolarizing in immature neurons it has been hypothesized that GABAergic signaling activates NMDA receptors to facilitate the maturation of AMPA receptor containing glutamatergic synapses during early development. This scenario suggests that activation of NMDA receptors is required for the development of glutamatergic connections. However, in the hippocampus NMDA receptors are not required for the formation of AMPA and GABA-A receptors mediated connections received by excitatory neurons, raising the question if indeed NMDA receptors are required for the maturation of synaptic connections in the cerebral cortex. Moreover, it is unknown if the development of spatially specific inter- and intra-laminar cortical synaptic connections depend on NMDA receptors. To test if the development of synaptic connections to cortical excitatory neurons requires NMDA receptors, we sparsely eliminated NMDA receptors in cortical neurons through *in utero* electroporation of *Cre* plasmid driven by *Cdk5r* gene promoter in *Grin1*$^{fl/fl}$ mice at embryonic day 12.5 or 13.5. Consequently, in post-mitotic neurons expressing the electroporated plasmid the obligatory NMDA-R1 subunit was eliminated and NMDA currents were absent. The development of AMPA and GABA-A connections in the cortex was subsequently investigated through *in vitro* whole-cell patch clamp recordings coupled with laser-scanning photostimulation via glutamate uncaging at the end of the second postnatal week. We found that the amount and the spatial distribution of AMPA and GABA-A receptor mediated connections received by neurons lacking NMDA receptors are comparable to those received by control neurons. We thus conclude that NMDA receptors are not required for the

formation of AMPA and GABA-A receptors mediated neurotransmission in cortical excitatory neurons.

Disclosures: **R. Deng:** None. **P.O. Kanold:** None.

Poster

548. Molecular Mechanisms of Synaptogenesis and Circuit Refinement

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 548.20/A20

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

Title: Establishment of clustered protocadherin-regulated high reciprocal connectivity between clonal cortical neurons requires sensory experience in mouse barrel cortex

Authors: *E. TARUSAWA[1,2], M. SANBO[2], M. HIRABAYASHI[2], T. YAGI[1], Y. YOSHIMURA[2];
[1]Osaka university, Suita, Japan; [2]NIPS, Okazaki, Japan

Abstract: The specificity of neural connections in the sensory cortex is fundamental for the proper processing of sensory information. We previously have shown that high reciprocal connectivity is established between clonal cortical neurons and the establishment is regulated by clustered protocadherins in mouse barrel cortex. In this study, we analyzed the effect of sensory deprivation on the establishment of the cell-lineage-dependent reciprocal connectivity. To visualize clonal neurons, we generated chimeric mice by injecting a small number of induced pluripotent stem cells (iPS cells) marked with GFP into blastocysts. We conducted dual whole-cell recordings from GFP-positive excitatory neuron pairs (presumed clonal pairs) or GFP-positive and negative excitatory neuron pairs (non-clonal pairs) within a layer 4 barrel in acute cortical slices prepared from the chimeric mice. In naïve chimeric mice at postnatal day 9 (P9) to P11, almost all connected neuron pairs showed one-way connections in both clonal and non-clonal neuron pairs. After that, high reciprocal connectivity in clonal neuron pairs was established by two sequential processes, an initial formation of reciprocal connections from P9-11 to P13-16, and a selective elimination of one-way connections from P13-16 to P18-20. As a result, 83% of connected neuron pairs showed reciprocal connections. This high reciprocity was not observed in non-clonal neuron pairs.To reveal the influence of sensory deprivation on the development of high reciprocal connectivity, whisker trimming was performed on the chimeric mice from P13 to the day before recording. In clonal neuron pairs after whisker-trimming, the formation of reciprocal connections at P15-16 was strongly suppressed and the lower reciprocity was kept at P18-20. The elimination of one-way connections from P15-16 to P18-20 was also prevented by the whisker trimming. Consequently, only 20% of connected neuron pairs showed reciprocal connections after deprivation. Surprisingly, the effect of sensory deprivation on the neural connections was not observed in non-clonal neuron pairs, suggesting that cell-lineage-

specific neural connections are selectively modified by sensory experience. Our previous and current findings suggest that the sensory inputs and clustered protocadherins are required for the establishment of reciprocal connections between clonal neurons, and further investigations into the signaling pathways to link neural activity and clustered protocadherins may shed light on the mechanisms underlying cell-lineage-dependent connection specificity in neocortex.

Disclosures: E. Tarusawa: None. **M. Sanbo:** None. **M. Hirabayashi:** None. **T. Yagi:** None. **Y. Yoshimura:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.01/A21

Topic: A.07. Developmental Disorders

Support: Jim and Betty Ann Rodgers Chair Fund
NIH Grant R15DA043848

Title: Transgenerational transmission of behavioral phenotypes in a paternal aspartame exposure mouse model

Authors: *S. K. JONES, D. M. MC CARTHY, P. G. BHIDE;
Biomed. Sci., Florida State Univ. Col. of Med., Tallahassee, FL

Abstract: The use of low-calorie sweeteners as weight loss tools is highly prevalent. In the US, 25% of children and 41% of adults report using low-calorie sweeteners, which represents a 54% increase since 1999. Aspartame is among the most widely used low-calorie sweeteners worldwide. We examined whether aspartame exposure results in adverse behavioral consequences for male mice, and if offspring derived from the aspartame-exposed males display behavioral alterations. We exposed adult (6-8 week) male C57BL/6 mice to aspartame in drinking water (0.03% or 0.015% - doses equivalent to 50% and 25%, respectively, of FDA's acceptable daily intake). We used a two-bottle choice paradigm in which mice had continuous access to aspartame containing or plain drinking water. Following 12 weeks of such exposure, we analyzed spontaneous locomotor activity (home-cage activity), anxiety-like behavior (elevated zero maze), and spatial working memory (Y-maze). The mice exposed to 0.015% aspartame did not show significant changes in any of the behavioral measurements. However, mice exposed to 0.03% aspartame displayed significant reduction in spontaneous locomotor activity, as well as significant anxiety-like behavior, and spatial working memory deficit (ANOVA, $p < 0.05$; followed by Dunnett's multiple comparisons test). The aspartame-exposed and control mice were bred with drug-naïve females. Male offspring derived from the aspartame-exposed males displayed anxiety-like behavior and spatial working memory deficit whereas the

female offspring displayed anxiety-like behavior only (ANOVA, $p < 0.05$; followed by Bonferroni multiple comparisons test). These data suggest that aspartame exposure produces significant behavioral changes in male mice and their offspring. Thus, aspartame exposure at levels equivalent to 50% of the FDA recommended human daily intake, carries the risk of adverse behavioral outcomes not only in individuals exposed to the aspartame but also their descendants. The molecular mechanisms underlying the "transgenerational transmission" are not known. We suggest that aspartame-induced epigenetic modification of spermatozoa is a likely mechanism.

Disclosures: S.K. Jones: None. **D.M. Mc Carthy:** None. **P.G. Bhide:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.02/A22

Topic: A.07. Developmental Disorders

Support: NSF DGE 1752814

Title: Distraction processing in adults with ADHD: An ERP study

Authors: *E. T. MARCELLE, Y. ZHAO, N. KARIMI, J. W. KAM, S. P. HINSHAW; Univ. of California, Berkeley, Berkeley, CA

Abstract: Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most commonly occurring and impairing neurodevelopmental disorders across the lifespan. Although ADHD has traditionally been conceptualized as a deficit in one's ability to sustain attention, replicated evidence of ability to sustain attention in reduced distraction environments for such individuals has challenged this accepted framework. That is, ADHD may be best viewed as a disorder of attention regulation. Furthermore, as conceptualization moves toward a focus on distractibility as a key feature of the disorder, examining neural differences in distraction processing between adults with and without ADHD is an important area of focus. Although preliminary studies have begun to investigate associated neural processes in children, adult investigations are warranted. Therefore, the present study seeks to examine the neural correlates of distraction processing in adults with ADHD using EEG. To accomplish this goal, adults with and without ADHD completed a three-stimulus auditory oddball task using Standard (500Hz tone, probability P = 0.80); Target (1000Hz tone, P = 0.10); or Distractor (e.g., bell, whistle, tone sweep, P = 0.10) sounds. Participants were instructed to respond by (green) button press to target sounds, vs. (red) button press to standard and distractor sounds. A button press for each tone, as opposed to only target tones, was required to minimize motor-related confounds between target, distractor, and standard sounds. EEG data were collected by a 128-channel BioSemi ActiveTwo system with a

sampling rate of 250 Hz. Participants were recruited from a larger pool of 70 subjects with and without ADHD participating in a completed study of sustained attention in ADHD at UC Berkeley. Event-related potentials (ERPs) examined included Mismatch Negativity (MMN), P3a, P3b, and Reorienting Negativity (RON). Behavioral measures included response time and discrimination/accuracy. Preliminary behavioral findings in pilot testing were consistent with existing literature: response times to distractor sounds were significantly longer than response times to target and standard tones, indicating the attentional cost of distraction processing. Implications of behavioral and EEG findings for future conceptualization of adult ADHD are discussed.

Disclosures: E.T. Marcelle: None. **Y. Zhao:** None. **N. Karimi:** None. **J.W. Kam:** None. **S.P. Hinshaw:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.03/A23

Topic: A.07. Developmental Disorders

Title: Memory consolidation in children with ADHD is improved by the exploration of an unrelated novel virtual environment

Authors: *V. BAUMANN[1], T. BIRNBAUM[1], C. BREITLING[1], J. TEGELBECKERS[3], E. EDELMANN[4], J. BERGADO-ACOSTA[2], H.-H. FLECHTNER[1], K. KRAUEL[5];
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Abstract: Recent experiments have shown that weak learning can be enhanced by unrelated salient events like reward, stress or novelty, if those events occur during a vulnerable phase of consolidation. According to the Behavioral Tagging theory (Moncada & Viola, 2007), this memory mechanism is associated with an interaction between a synaptic tag set by the learning event and the synthesis of plasticity related proteins (PRPs) triggered by the salient event. In animal research, Behavioral Tagging is often operationalized by letting animals explore a novel open field before or after learning a certain task. In this case, memory modulation is supposedly mediated by an enhanced release of dopamine in the hippocampus triggered by the novel experience. Translating from animal to human research, the novelty induced surplus of dopamine could be potentially used to tackle the learning difficulties observed in children with attention deficit hyperactivity disorder (ADHD), who often exhibit a hypofunction of the dopaminergic system.

In the current experiment, we asked 30 children with ADHD and 30 healthy control children (age 9-15) to explore either a previously familiarized or a novel virtual environment 45 minutes after they had learned a list of 20 words. During immediate free recall, patients with ADHD remembered significantly less words than healthy control children. When measured 24 hours later, the ADHD patients who explored a novel environment showed a free recall performance similar to the level of healthy control children, while ADHD patients who explored a familiar environment did not show any improvement. Contrary to previous studies, this beneficial effect of novelty was only present for patients and not for healthy control children, indicating that Behavioral Tagging with novel virtual environments might be especially useful to promote memory consolidation in children with ADHD.

Disclosures: V. Baumann: None. **T. Birnbaum:** None. **C. Breitling:** None. **J. Tegelbeckers:** None. **E. Edelmann:** None. **J. Bergado-Acosta:** None. **H. Flechtner:** None. **K. Krauel:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.04/A24

Topic: A.07. Developmental Disorders

Support: 2016R1D1A1B02010387
2017M3A9G2077568

Title: Overexpression of the ataxin 7 gene in the prefrontal cortex and striatum leads to the development of hyperactive phenotype in mice: Involvement of the noradrenergic and dopaminergic systems

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Abstract: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder marked by excessive levels of hyperactivity, impulsivity, and/or inattention. To identify the potential genetic underpinnings of ADHD, we previously identified a number of common differentially expressed genes in the prefrontal cortex of the hyperactive spontaneously hypertensive rat (SHR), the most validated animal model for ADHD. This included Ataxin 7 (Atxn7), a gene that codes the Atxn7 protein, which is implicated in gene transcription. Then, we established a line of mice overexpressing the Atxn7 gene (Atxn7 OE) and found them to be hyperactive and impulsive. Treatment with atomoxetine (ATO), a common drug for ADHD, normalized their behaviors and the Atxn7 gene expression in the prefrontal cortex and striatum. However, there is still a need to elucidate the underlying mechanism of the observed behaviors

of the Atxn7 OE mice. Thus, in this study, we determined the involvement of the noradrenergic and dopaminergic systems in the ADHD symptoms of the Atxn7 OE mice, considering the effects of ATO, by measuring the mRNA expressions of noradrenergic and dopaminergic-related genes in the prefrontal cortex. We also examined the brain electrical activity of the Atxn7 OE mice. Furthermore, protein levels of ubiquitinated histone H2B (Ub-H2B) in the prefrontal cortex of the Atxn7 OE mice were measured. Atxn7 has been suggested to affect H2B ubiquitination, a necessary process for gene transcription. Our results show that the Atxn7 OE mice have altered noradrenergic and dopaminergic-related gene expressions in the prefrontal cortex. Atxn7 OE mice showed decreased delta, theta, alpha, and beta waves, and were normalized by ATO treatment. Furthermore, Ub-H2B protein levels were decreased in the Atxn7 OE mice. Taken together, we suggest that the noradrenergic and dopaminergic systems are involved in the ADHD-like symptoms exhibited by the Atxn7 OE mice.

Disclosures: L.L. Sayson: None. **C. Botanas:** None. **R. Custodio:** None. **A. Abiero:** None. **M. Kim:** None. **H. Lee:** None. **H. Kim:** None. **J. Cheong:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.05/A25

Topic: A.07. Developmental Disorders

Title: Brain-derived neurotrophic factor improves neurite development and mitochondrial activity of dopaminergic neurons differentiated from exfoliated deciduous tooth-derived pulp stem cells of children with ADHD

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Abstract: Attention deficit hyperactivity disorder (ADHD)—the most common neurodevelopmental disorder—is characterized by impaired attention, hyperactivity, and impulsivity. While multiple factors have been implicated in the pathogenesis of ADHD, the underlying mechanism remains unclear. Dysregulation of dopaminergic signals, mitochondria, or brain-derived neurotrophic factor (BDNF) have been hypothesized to explain the mechanism of ADHD pathogenesis in children; however, only a few reports have demonstrated these associations. Stem cells from human exfoliated deciduous teeth (SHED) are neural crest-derived mesenchymal stem cells, and they are present in the dental pulp of exfoliated deciduous teeth; these cells can efficiently differentiate into dopaminergic neurons (DNs). SHED are associated with few ethical limitations in research; they can be obtained using minimally invasive methods. Thus, SHED are useful as a disease-specific cellular model for studying a neurodevelopmental

disorder associated with DN dysfunction. The purpose of this study was to elucidate the association between DNs, mitochondria, and BDNF in ADHD by analyzing DNs differentiated from SHED obtained from three boys with ADHD compared with those from three typically developing boys. Without exogenous BDNF, the DNs derived from the boys with ADHD (ADHD-DNs) showed impaired neurite outgrowth and branching, which is associated with decreased mitochondrial activity, i.e., reductions in mitochondrial membrane potential, number of mitochondria within the neurites, number of mitochondria/cell area, and ATP production. In addition, we found that BDNF mRNA expression was significantly lower in ADHD-DNs. Exogenous BDNF supplementation significantly enhanced neurite outgrowth and branching and mitochondrial function in ADHD-DNs. In conclusion, ADHD-DNs may show impaired neurite development and mitochondrial function associated with an impaired BDNF expression, and the consequent BDNF deficiency can be improved by exogenous BDNF supplementation. This ADHD-derived SHED-based study may contribute to the development of treatment strategies for aberrant dopaminergic signaling, mitochondrial function, and BDNF levels in patients with ADHD, in future.

Disclosures: H.T. Nguyen: None. **H. Kato:** None. **H. Sato:** None. **H. Yamaza:** None. **K. Masuda:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.06/A26

Topic: A.07. Developmental Disorders

Title: Hand performance asymmetry as a motor phenotype of children with fetal alcohol spectrum disorder

Authors: *D. E. LIDSTONE[1], *F. Z. MIAH[2], J. F. BEASLEY[2], J. S. DUFEK[1];
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Abstract: Fetal Alcohol Spectrum Disorder (FASD) is a common neurodevelopmental disorder characterized by neurological, developmental, and neurobehavioral deficits caused by prenatal alcohol exposure. Neuroimaging studies of children with FASD have identified hypoplasia of the Corpus Callosum (CC) as the most frequently observed structural abnormality. Reduced size of the CC is a neurophenotype of FASD and the size of the CC is associated with the strength of handedness. Therefore, reduced hand performance asymmetry may be a motor phenotype of FASD. In the current study, we examined whether hand performance asymmetry could differentiate a group of children (7-17 years old) with a clinical diagnosis of FASD (N = 16; 15 right-handed; 6 males; age = 12.6±3.0 years; full-scale intelligence quotient (FSIQ) = 90.6±11.3)

from a clinical control group with a diagnosis of Autism Spectrum Disorder (ASD) (N = 23; 21 right-handed; 18 males; age = 12.2±2.8 years; FSIQ = 93.7±13.8) and a typically developing (TD) control group (N = 12; 12 right-handed; 5 males; age = 11.6±2.8 years; FSIQ = 116.7±7.5). To examine manual dexterity performance, the 9-hole pegboard test was completed on the dominant and non-dominant hand with the order of hand assessed randomized. Manual dexterity performance for the dominant-hand and non-dominant hand was assessed as the fastest time (in sec) of three attempts. Hand performance asymmetry was defined as the percent difference between dominant and non-dominant hand manual dexterity performance. Results showed that hand performance asymmetry was significantly greater in the ASD group (-15.70±19.76%) compared to the FASD group (-3.77±8.31%; p=0.02). Hand performance asymmetry was also significantly greater in the TD group (-14.78±15.89%) compared to the FASD group (p=0.02). In conclusion, our results show that hand performance asymmetry differentiated a group of children with FASD from children with ASD and TD controls. Therefore, reduced hand performance asymmetry may be a motor phenotype of FASD and an indirect measure of CC hypoplasia. A larger sample of children should be examined to determine the robustness of our findings. Discovery of motor phenotypes in children with FASD may improve diagnostic practices in clinical settings.

Disclosures: **D.E. Lidstone:** None. **F.Z. Miah:** None. **J.F. Beasley:** None. **J.S. Dufek:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

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Program #/Poster #: 549.07/A27

Topic: A.07. Developmental Disorders

Support: Research Innovation and Pilot Grant, Cincinnati Children's Hospital Medical Center

Title: Altered anatomic and functional connectivity in Tourette syndrome

Authors: *S. W. WU[1], H. S. JACKSON[1], D. A. HUDDLESTON[1], W. YUAN[2];
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Abstract: OBJECTIVE Tics are the hallmark symptoms in Tourette Syndrome (TS). Prior diffusion tensor imaging (DTI) studies have revealed white matter alterations in the cortico-striato-thalamo-cortical (CSTC) circuit. In adult controls, dual-site Transcranial Magnetic Stimulation (TMS) has shown that right frontal stimulation can reduce primary motor cortex (M1) excitability. Here we used DTI and TMS to examine CSTC network connectivity in Tourette Syndrome children and controls.
METHOD Twenty-three right handed subjects (12 controls, 11 TS; average ages 11.5, 12.6 years

respectively, p=0.7) participated in the study. Brain MRI was obtained using 3T Phillips MR scanner. DTI indices, including fractional anisotropy (FA), mean, axial, and radial diffusivity (MD, AD, and RD, respectively), were calculated and analyzed using the Tract Based Spatial Statistics approach in FSL software. DTI group difference was tested using 2-sample t-test with age adjusted as a covariate and Threshold Free Cluster Enhancement method to correct for multiple comparison. DTI data in the region with significant group difference was extracted and fitted with age with a linear model. These residual values that are free of age effect was used in correlation analysis. Left M1 resting motor thresholds (RMT) were measured using the right 1st dorsal interosseous muscle. Figure-8 coil was navigated to the right pre-supplementary motor area (pre-SMA), identified as the gyrus anterior to the Vertical Commissure Anterior line, using BrainSight to perform dual-site TMS. The pre-SMA conditioning pulse (110%*RMT) preceded the M1 pulse (120%*RMT) by 6, 8 and 10ms. A mixed, repeated-measures regression model (age included as a covariate) was used to analyze motor-evoked potential (MEP) amplitudes, using False Discovery Rate to correct for multiple comparison.
RESULT DTI analysis showed TS participants had increased FA and decreased RD in the right superior corona radiata when compared to controls ($p<0.05$). Diagnosis*pulse condition interaction was significant ($p=0.02$), with post-hoc analysis showing that controls had ~20% inhibition while this inhibition was not present in TS children. FA residual ($\rho = -0.68$, $p = 0.04$) and 6ms TMS data ($\rho = -0.78$, $p = 0.008$) correlated with clinical rating of tic suppressibility, suggesting that those who are more efficient at suppressing tics had DTI/TMS data more similar to controls.
CONCLUSION Using DTI and dual-site TMS, we showed that anatomic and functional connectivity within the right frontal region in TS children are different from typically-developing children. This multi-modal approach may help to further understand TS pathophysiology.

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Poster

549. Neural Mechanisms for Developmental Disorders II

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Topic: A.07. Developmental Disorders

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NWO grant agreement no. 057-14-005
Grant no. 016-130-669 (Vici Barbara Franke)
NeuroLabNL project grant agreement no. 400 17 602

Title: Brain and behavioural changes in mice colonized with human ADHD gut microbiota

Authors: *S. DAM[1], A. TENGELER[2], M. WIESMANN[2], C. BELZER[3], B. FRANKE[1], T. KOZICZ[2], A. KILIAAN[2], A. ARIAS VASQUEZ[1];
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Abstract: Microbes inhabiting our gastrointestinal tracts, the gut microbiota, are involved in regulation of the gastrointestinal system, modulation of the immune, endocrine as well as nervous systems by influencing the brain, mood and stress regulation. The microbiota can stimulate the release of serotonin from specific cells located in the gastrointestinal tract. Some members of the microbiota can also independently synthesize neurotransmitters or precursors of neurotransmitters, that can communicate bidirectionally with the brain (gut-brain axis). A growing body of research recognizes the role of gut microbiota in behaviour and neurodevelopment in which an imbalance in microbiota has been observed in patients and animal models of several neurodevelopmental disorders, especially in attention-deficit /hyperactivity disorder (ADHD). Therefore, the current study was designed in which we implanted gut microbiota of anonymous human donors of the NeuroIMAGE cohort with and without ADHD into germ-free mice. We hypothesized that the microbiota from humans with ADHD would differentially affect mouse behaviour and brain structure and function compared to that from controls. To test our hypothesis, we performed behavioural tests (Open Field, Marble Burying and Novel Object Recognition), did brain scanning with an 11.7 T MR scanner (DTI and resting-state fMRI) and collected fecal samples after colonization and sequenced the 16s rRNA genes to measure bacterial composition (α & β-diversity and relative abundance). Mice colonized with ADHD microbiota (i) were more anxious in the open field test, (ii) showed decreased resting-state fMRI-based functional connectivity between right motor and visual cortices and (iii) showed gray and white matter integrity loss in hippocampus and right internal capsule. Structural brain changes found in mice colonized with ADHD microbiota occurred in regions corresponding to those reported to be altered in human ADHD. Mice colonized with ADHD and control microbiota showed a global difference in microbiome composition (β-diversity). Moreover, we found 22 genera overlapping with the microbiota in our human cohort, predominantly from *Ruminococcaceae* family, showing different relative abundance between the mice groups. Similar changes in this family have been observed in multiple psychiatric and neurodevelopmental disorders including ADHD, which highlights the relevance the gut microbiome plays at the brain level, through the gut-brain-axis. While further research is needed, our findings might open a window of opportunity for potential treatment strategies targeting the microbiota in disorders such as ADHD.

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Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.09/A29

Topic: A.07. Developmental Disorders

Title: Motivation is deficient in the spontaneously hypertensive rat (SHR), a rodent model of ADHD: Evidence from an operant breakpoint paradigm

Authors: *A. S. NAZARIO, M. E. STEVENSON, Y. S. GREENBERG, B. S. LARSON, C. C. MILLER, R. A. SWAIN;
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Abstract: Attention Deficit Hyperactivity Disorder (ADHD) is one of the most commonly diagnosed childhood neurobehavioral disorders. ADHD is characterized by three core behavioral deficits (hyperactivity, inattention, and impulsivity) that significantly hinder the daily functioning of those diagnosed. Furthermore, children with ADHD have problems with motivation and often require larger, more frequent rewards in order to complete a task. While the etiology of the disorder is largely unknown, we do know that various areas of the brain, including the cerebellum, have abnormalities and warrant further investigation. In this study, we used the Spontaneously Hypertensive Rat (SHR), a rodent model of ADHD that exhibits all of the core deficits of the disorder. The goal of the current study was to further validate the SHR as a model of ADHD by training rats in an operant conditioning breakpoint paradigm, which is commonly used to assess motivation. Twelve male SHR and 12 male Wistar Kyoto (WKY) control rats were trained on a Progressive Ratio (PR-20) schedule that increased in difficulty until the rats reached their breakpoint, which was defined as the point at which the animals stopped working. The breakpoint served as a measure of motivation and the higher the breakpoint, the more motivated the animal was. Results show that the SHR animals display a significantly lower breakpoint compared to the control animals, indicating that the SHR animals gave up working on the task much sooner. Furthermore, we found that during the operant session, the SHR animals spent significantly more time off task, engaged in significantly more off-task behaviors, and pressed the lever significantly less times consecutively in a row compared to the WKY. Open field analyses indicated that the SHR animals crossed significantly more squares and spent significantly more time in the inner zone. Elevated plus maze results indicated that the SHR animals appeared to be less anxious compared to the controls as the SHR animals entered into and spent significantly more time in the open arms of the maze. Future analyses include an examination of cerebellar anatomy that may provide an explanation for why the motivational behavior is altered in the SHR model. Together, our behavioral findings from the operant chamber, open field, and elevated plus maze indicate that the SHR rat displays

motivational deficits in addition to the core ADHD symptoms of hyperactivity, inattention, and impulsivity.

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Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.10/A30

Topic: A.07. Developmental Disorders

Title: The cerebello-thalamo-prefrontal pathway in ADHD

Authors: *E. M. ALLISON, T. IKUTA;
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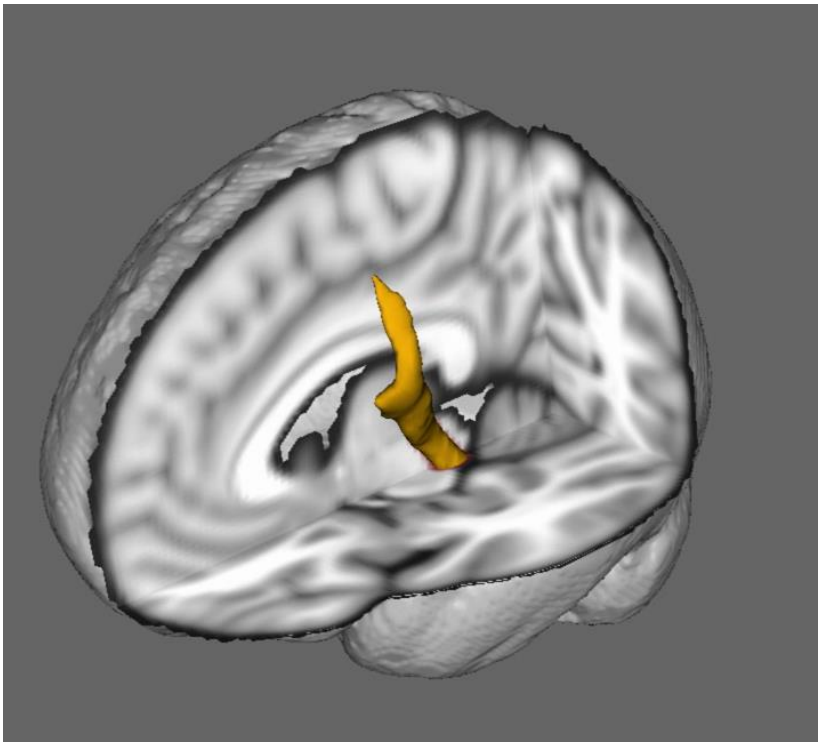
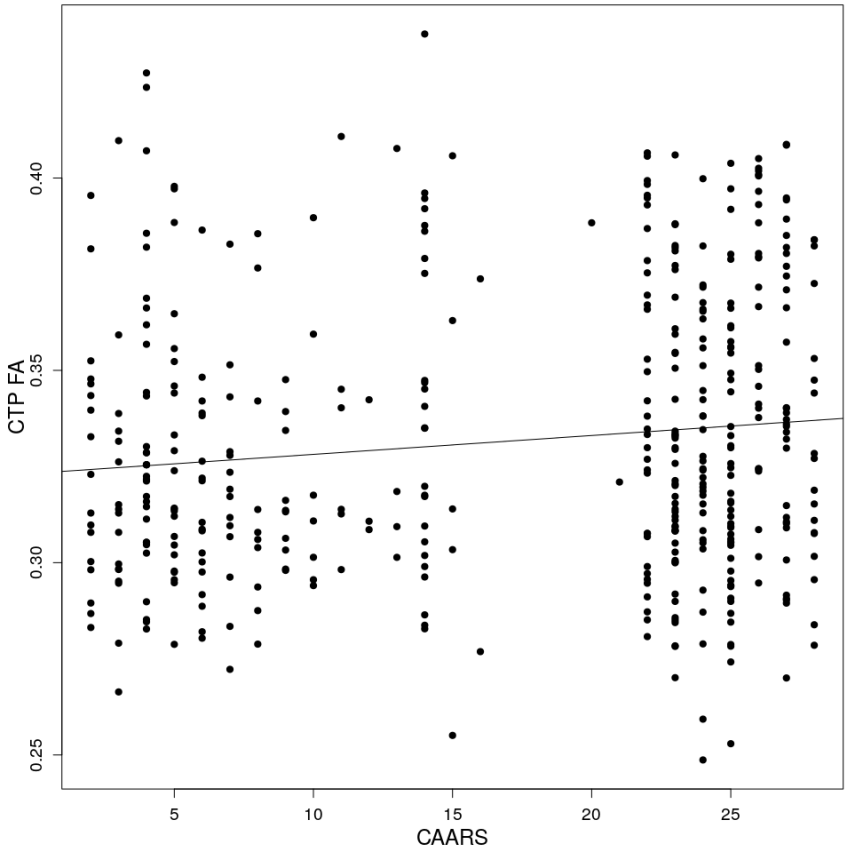
Abstract: The cerebellum has been repeatedly implicated in ADHD. Smaller cerebellar volume has long been known and white matter reduction has also been found in ADHD. However, it is not quite well understood how cerebellar deficits relate to attentional functions that are considered to be prefrontal. In this study, we isolated the cerebello-thalamo-prefrontal (CTP) white matter pathway and tested the association between its integrity and Conners Adult ADHD Rating Scale (CAARS) total score in 440 individuals. There was significant association between the white matter integrity of the CTP pathway and CAARS total score. A significant regression equation was found ($F(2,438)=7.07$, $p=0.00096$) with an $R2$ of 0.027. The predicted CAARS total score is equal to 5.47 + 26.19 (CTP FA) – 0.062 (age). The CTP FA significantly predicted the CAARS total score ($p=0.028$). Our results suggest that the integrity of the CTP pathway is positively associated with ADHD spectrum, suggesting that the CTP pathway may contribute to ADHD. This may not be consistent with previous findings. Volume reductions in cerebellar white matter has been repeatedly reported (van Ewijk et al 2012). It has been reported that disrupted functional connectivity is found between the cerebellum and default mode network in ADHD (Kucyi et al 2015).




CTP FA
0.25
0.30
0.35
0.40
5
10
15
20
25
CAARS

Disclosures: **E.M. Allison:** None. **T. Ikuta:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

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Topic: A.07. Developmental Disorders

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Title: Shared and unique neural correlates of reading and attention

Authors: ***M. E. MARKO**[1], R. F. SLOMOWITZ[2], B. C. DRURY[1], L. M. MCGRATH[2], C. J. STOODLEY[1];
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Abstract: Neurodevelopmental disorders of reading (i.e. developmental dyslexia) and attention (i.e. ADHD) are highly prevalent (5-10%) with a high rate of comorbidity (25-40%). While prior studies have found overlapping risk factors at the cognitive and genetic levels, little is known about the neural underpinnings of this comorbidity. To identify potential neural correlates of comorbid reading and attention problems, we used voxel based morphometry (VBM) to investigate the shared and unique brain regions associated with reading and attention in 330 children (156 males, 174 females; age=8-18 years, M=13.4, SD=3.1) drawn from a publicly-available, population-based sample, the Philadelphia Neurodevelopmental Cohort (PNC). For inclusion, participants were required to have a T1-weighted MRI scan that passed quality control and behavioral measures of both reading and attention. Participants were excluded if they had any genetic or major health condition that would impact the CNS. Word reading was assessed with the Wide Range Achievement Test-4 (WRAT-4) and attention was measured by clinical interview of parents using 6 inattention symptoms from the DSM-IV ADHD criteria. Data were preprocessed using the CAT12 toolbox, and SPM12 multiple regression analyses were used to determine regions of the brain where grey matter (GM) volume was related to reading or attention scores ($p<0.001$, cluster FDR<0.05). Covariates included age, age^2, sex, handedness, and total intracranial volume. Better attention scores correlated with increased GM in the left precuneus. Higher reading scores were associated with increased GM in the bilateral thalamus. A conjunction analysis ($p<0.05$, $k>100$, uncorrected) was performed to determine regions associated with both reading and attention, and revealed overlap in the bilateral caudate and bilateral precuneus. These results are consistent with a recent meta-analysis of VBM studies of developmental dyslexia and ADHD which found shared GM reductions in the caudate. It is possible that caudate dysfunction may contribute to the shared deficits in executive dysfunction

in both disorders and partially explain their high rates of comorbidity. Future work will investigate the roles of the caudate and precuneus in dyslexia and ADHD.

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Poster

549. Neural Mechanisms for Developmental Disorders II

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Program #/Poster #: 549.12/A32

Topic: A.07. Developmental Disorders

Support: NIH Grant P50 NS22343
NIH Grant T32DC7361

Title: Differences in social behaviors as reflected by parental judgement in school age children with perinatal stroke and school age children with high functioning autism

Authors: *E. M. BEAVER, M. MEYER, S. EDWARDS, P. LAI;
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Abstract: Social behavior affects all aspects of one's life. Lacking the ability to process and effectively convey social information can lead to deficits in maintaining peer and family relationships, in addition to academic failure in school. Individuals with neurodevelopmental disorders often have significant impairments in social communication that impact their relationships with others. In this study, two groups of children were assessed, children with High Functioning Autism (HFA) and children with Perinatal Stroke (PS). This study included 43 children in total between 7 to 14 years of age, 23 children with HFA, 20 children with PS. Individuals with HFA are characterized by deficits in core areas such as: social interaction, social communication, and restricted repetitive and stereotyped patterns of behavior, interests, and activities. This disorder affects an estimated 1 in 68 children in the United States. Children with PS experience a cerebrovascular event around the perinatal period. The estimated prevalence rate is 1 in 4,000 births. In this study, the Social Responsiveness Scale (SRS) was distributed to caregivers to complete. The SRS assesses children's social and affective impairments. The results of these items on the SRS questionnaire allows us to analyze the similarities and differences between these groups to gain a deeper understanding of each group's social phenotype from the caretaker's perspective. Results from the one-way analysis of variance (ANOVA) showed a significant difference between the two groups when it came to the item of "staring off into space" (SRS #65). The HFA group was rated as producing more of this particular behavior and this was rarely observed in children with PS ($p=0.004$). There was also a trend ($p=0.13$) for children with HFA not matching their expressed emotions on their face (SRS

#2). Once again, this behavior was not observed in children with PS. Taken together, even at school age, children with HFA are continuing to show social deficits, while, children with PS are not displaying these behaviors. These results in school age children provide clinical value as strengths and weaknesses of social behavior can be observed with the goal of constructing more targeted treatment methods for the future.

Disclosures: E.M. Beaver: None. **M. Meyer:** None. **S. Edwards:** None. **P. Lai:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

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Program #/Poster #: 549.13/A33

Topic: A.07. Developmental Disorders

Support: Investigator Sponsored Trial from BioMarin Pharmaceutical Inc.
University of Missouri Life Sciences Fellowship

Title: The progression of white matter abnormalities in phenylketonuria

Authors: *H. E. CLOCKSIN[1], D. A. WHITE[2], Z. HAWKS[2], S. E. CHRIST[1];
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Abstract: Phenylketonuria (PKU) is a rare autosomal recessive disorder characterized by an inability to metabolize phenylalanine (phe) to tyrosine, a precursor for dopamine and other catecholamines. Despite early and continuous treatment, individuals with PKU experience cognitive and neurological sequelae. The most common neurological finding is abnormalities of the cortical white matter (WM). Past findings suggest that generally posterior regions may be more affected than anterior regions, but little is known regarding the potential impact on individual WM tracts. The aim of the present study is to further characterize the progression of WM abnormalities in early-treated PKU (ETPKU) by investigating the interaction between spatial locations along established WM tracts using Automated Fiber-Tract Quantification (AFQ). DTI neuroimaging data from a group of 22 individuals with ETPKU between the ages of 9 to 35 (*M*=23.8, *SD*=7.0) and 22 individuals without PKU between the ages of 9 to 33 (*M*=23, *SD*=6.9) was analyzed using AFQ. Results revealed significant reductions in mean diffusivity (MD) in our ETPKU group compared to our non-PKU group in several WM tracts including the callosum forceps minor (p=.001) and the left arcuate fasciculus (p =.013). Among those with ETPKU, higher plasma phe levels (associated with poorer treatment adherence) was associated with greater reductions in MD. Additionally, the within-tract pattern of disruptions appeared to differ based on the orientation of the tracts. For tracts (e.g., arcuate fasciculus) with a primary anterior-to-posterior orientation, PKU-related differences were more apparent in the posterior as compared to anterior aspects of the pathway. For other tracts (e.g., callosum forceps minor) with

a more dorsal-ventral or left-right orientation, PKU-related differences were relatively equivalent across the spatial extent of the tracts. Overall, these findings can be taken to suggest that WM integrity worsens overall as individuals with ETPKU age and their phe levels increase. Furthermore, the progression of WM disruptions in ETPKU seems to vary along the spatial location of WM tracts such that tracts extending in an anterior-to-posterior direction are differentially affected while tracts with different directionality experience a main effect of phe.

Disclosures: H.E. Clocksin: None. **Z. Hawks:** None. **S.E. Christ:** 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.; BioMarin Pharmaceutical Inc. F. Consulting Fees (e.g., advisory boards); BioMarin Pharmaceutical Inc. **D.A. White:** 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.; BioMarin Pharmaceutical Inc. F. Consulting Fees (e.g., advisory boards); BioMarin Pharmaceutical Inc.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.14/A34

Topic: A.07. Developmental Disorders

Support: CNPq
CAPES
FAPERGS

Title: Caffeine via adenosine A2A receptors recovers neuronal outgrowth in attention deficit and hyperactivity disorder (ADHD) rat model

Authors: C. B. ALVES, A. S. ALMEIDA, D. M. MARQUES, A. FAÉ, A. L. MACHADO, **L. O. PORCIÚNCULA**;
Biochem., Univ. Federal do Rio Grande do Sul, Porto Alegre, Brazil

Abstract: Attention deficit and hyperactivity disorder (ADHD) is the most prevalent psychiatric disorder in children and adolescent, which is characterized primarily by a triad of symptoms that include hyperactivity, inattention and impulsivity. Experimental studies have evidenced the potential of caffeine in counteracting cognitive and inattention deficits in Spontaneoulsy hypertensive rats (SHR, the most validated ADHD rat model). Studies about the development *in vitro* of cortical neurons from this ADHD model were not performed yet; the effects of caffeine at cellular levels were not investigated. In this study, we sought to find morphological

differences between in cultured frontal cortical neurons from SHR and Wistar-Kyoto rats (WKY, control strain). In addition, we investigated the effects of caffeine and adenosine receptors signaling in these morphological alterations. The percentage of neurons with less branch points was higher in SHR neurons (76 ±3.83% vs 57.86 ±5.29, n=7), while it was decreased for neurons with more branch points (17.75 ±2.85 vs 29.61 ±4.21, n=7). The maximal neurite length was also decreased in SHR neurons (21 %, $P < 0.05$, n=7). Tau immunoreactivity was also decreased in SHR neurons (117.4 ±11.03 vs 206.7 ±31.67 a.u., n = 9). The percentage of neurons with less branch points decreased after 24 h of exposure to 30 μM caffeine [$F_{(1, 20)}= 11.77$; $P = 0.0026$, n=6]and the selective adenosine A_{2A} receptors ($A_{2A}R$) antagonist [$F_{(1,20)}= 8.560$; $P = 0.0084$, n= 6]. A trend toward recovering Tau immunoreactivity was observed after 24 h of incubation with $A_{2A}R$ antagonist[$F_{(1, 25)}= 3.639$; $P = 0.0680$, n = 7-8], which was further confirmed when PI3K inhibitor blocked its effects in recovering Tau immunoreactivity [$F_{(1,30)}= 5.32$, $P = 0.0281$, n = 8-9]. Likewise, PI3K inhibitor blocked the effects of caffeine in increasing the number of branch points [$F_{(1,12)}= 7.159$; $P = 0.0202$, n = 4], maximal neurite length [$F_{(1,12)}= 18.35$; $P = 0.0011$, n = 4]. Similar findings were found for PKA inhibitor, which also blocked the effects of caffeine in recovering total [$F_{(1,12)}= 31.17$; $P = 0.0001$, n = 4]and maximal neurite length [$F_{(1, 12)}= 16.45$; $P = 0.0016$, n = 4]from SHR neurons. Our findings showed for the first time impaired neuronal differentiation in cultured frontal cortical neurons from ADHD model. In addition, our data revealed that the benefits of caffeine against memory and attentional disturbances in ADHD model may involve its ability in recover neuronal outgrowth.

Disclosures: C.B. Alves: None. **A.S. Almeida:** None. **D.M. Marques:** None. **A. Faé:** None. **A.L. Machado:** None. **L.O. Porciúncula:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.15/A35

Topic: A.07. Developmental Disorders

Support: European Union‘s Horizon 2020 research and innovation programme (grant agreement number 731827)

Title: Effects of repeated tDCS over the right IFG in children and adolescents with ADHD

Authors: *C. BREITLING[1], T. ZAEHLE[2,3], V. BAUMANN[1], J. TEGELBECKERS[1,4], H.-H. FLECHTNER[1], K. KRAUEL[1,3];
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Abstract: ADHD related deficits in response inhibition and working memory are associated with an underactivation of the right inferior frontal gyrus (IFG). Repeated applications of tDCS could induce long-lasting increase in activity of this area and therefore enhance cognitive functions. 33 ADHD patients in the age between 10 and 16 years underwent five sessions of HD-tDCS over the right IFG on consecutive days. Participants received either sham (n=13), 500 µA or 250 µA stimulation depending on individual dermal sensitivity. During tDCS patients solved a combined working memory and response inhibition paradigm (n-back/Go-Nogo). Pre, post and in a 3-months follow up EEG was recorded during the task and performance in transfer tasks of visuo-spatial working memory (span board task) and interference control (flanker task) was assessed. ADHD patients who received 500 µA tDCS showed no change in performance of the n-back/Go-Nogo task from pre to post tDCS. But amplitudes of P2, N2 and P3 were increased at frontal sites post tDCS during nogo trials compared to the sham group. Furthermore, accuracy in the flanker task was improved post tDCS. In contrast, patients who received 250 µA tDCS made more nogo commission errors post tDCS than patients who received sham stimulation. This effect occurred not in the first session, but started from the second tDCS session and increased throughout the course of the five-day stimulation. P3 was reduced at frontal sites and accuracy in the flanker task was reduced post tDCS. In both groups, effects of tDCS were not significant in the 3-month follow up. The increase of nogo related ERP amplitudes and enhanced flanker task accuracy indicates that consecutive tDCS sessions of the right IFG with 500 µA are suitable for modulating inhibitory processes. It is therefore a promising approach for inducing cognitive improvement in ADHD patients. This study demonstrated the outstanding importance of current intensity for the success of stimulation. Furthermore, it is remarkable that performance decline manifested only from the second tDCS session showing the importance of studies investigating of not only one but several applications of tDCS.

Disclosures: C. Breitling: None. **T. Zaehle:** None. **V. Baumann:** None. **J. Tegelbeckers:** None. **H. Flechtner:** None. **K. Krauel:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.16/A36

Topic: A.07. Developmental Disorders

Support: CIHR, IDRC, ISF and Azrieli Foundation Grant 2425/15
ISF Grant 1650/17

Title: Reduced sensitivity to auditory statistics in dyslexia is associated with a reversed activation pattern in the default mode network

Authors: *A. GERTSOVSKI, M. AHISSAR;
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Abstract: Developmental dyslexia is an impairment in the acquisition of expert reading skills. It is associated with a difficulty in efficient use of long-term statistics of both speech and simple sounds (the 'anchoring deficit' hypothesis; Ahissar et. al, 2006; Lieder et al., 2019), which can reduce load from online processing. We now asked how these deficits in utilizing sound statistics are manifested in the pattern of brain activity during performance of a 2-tone pitch discrimination task. We administered two conditions, with and without a fixed cross-trial reference tone, which differ in the advantage afforded by efficient utilization of tone repetition. For good readers the reference condition enables much better discrimination, whereas individuals with dyslexia do not use this regularity efficiently. Thus, to create equal levels of difficulty across conditions (for the good readers), the acoustic distance between the two tones was smaller in the reference condition. Adult participants with and without dyslexia (N=21,20) performed the task during fMRI scanning (protocol of Daikhin & Ahissar, 2015). As expected, good readers benefited more than individuals with dyslexia from stimulus repetition. This successful fast learning was associated with reduced activity in the primary auditory cortex, suggesting that repetition was detected there. No such reduction was observed in the primary auditory cortex of individuals with dyslexia. Importantly, individuals with dyslexia had higher activation in the reference compared with the no-reference condition in a network of higher-level cortical areas, including the inferior frontal gyrus, medial prefrontal cortex, posterior cingulate cortex, angular gyrus and middle temporal gyrus. This network is similar to the previously identified default mode network. Contrasting the conditions between the two groups, we found an opposite pattern of activation in the temporo-parietal areas of the network, and in the hippocampus, where individuals with dyslexia activated the high-level network more in the easier-by-regularity reference condition. We propose that controls' auditory-cortex based improved ability to utilize stimulus repetition allows them to perform the reference condition as a lower-level task compared to the no-reference condition, increasing their task signal to noise ratio. In contrast, for the dyslexia group the reference condition is substantially more difficult perceptually, hence it is noisier. This results in the two groups using different and even opposite strategies for the two task conditions. Surprisingly, this also determines the relative activation of the default mode network.

Disclosures: A. Gertsovski: None. **M. Ahissar:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.17/A37

Topic: A.07. Developmental Disorders

Support: CAPES
CNPq

Title: Delayed neuronal outgrowth and alterations in synaptic proteins in cultured cortical neurons from attention deficit and hyperactivity disorder (ADHD) rat model

Authors: *D. M. MARQUES, A. S. ALMEIDA, C. B. ALVES, L. O. PORCIÚNCULA; Biochem., Federal Univ. of Rio Grande Do Sul, Porto Alegre, Brazil

Abstract: Attention deficit hyperactivity disorder (ADHD) is a heterogeneous and phenotypically complex neurobehavioral disorder with unknown etiology, characterized by symptoms of inattention, hyperactivity and impulsivity. Spontaneously hypertensive rats (SHR) are considered the most validated model for ADHD studies. However, cultured neurons from this animal model and alterations in synaptic proteins at neuronal level were not assessed yet. In this study, we sought to characterize neuronal course development of cortical neurons from SHR and whether these neurons could present alterations in synaptic proteins over time. Based on polymorphisms found in ADHD patients whose genes encode synaptosomal-associated protein 25 (SNAP-25), synaptophysin and brain-derived neurotrophic factor (BDNF), we also evaluated the immunocontent of these proteins in primary cortical neuron culture from SHR and Wistar-Kyoto rats (WKY, control strain). As revealed by MAP-2 staining, SHR neurons presented decreased maximal neurite length over days *in vitro* (DIV) ($n = 5$; $F_{(3, 12)} = 12.21$; $p = 0.0006$). Percentage of WKY neurons with zero branch points was different from 1 and 5 DIV and from 1 and 8 DIV within subjects ($n = 5$; $F_{(3, 24)} = 10.82$; $p = 0.0001$). SHR presented a lower percentage of neurons with one branch point at 2 DIV in relation to WKY ($n = 5$; $p < 0.05$). WKY presented different percentage of neurons with two branch points from 1 and 5 DIV, from 1 and 8 DIV and from 2 and 5 DIV within subjects ($n = 5$; $F_{(3, 24)} = 8.831$; $p = 0.0004$). Percentage of WKY neurons three branch points was different from 1 and 5 DIV and from 5 and 8 DIV within subjects ($n = 5$; $F_{(3, 24)} = 6.958$; $p = 0.0016$). Percentage of SHR neurons with zero and four branch points was different from 1 and 5 DIV within subjects ($n = 5$; $F_{(3, 24)} = 10.82$; $p = 0.0001$; $F_{(3, 24)} = 3.633$; $p = 0.0272$). Compared to WKY neurons, SHR neurons presented increased synaptophysin immunocontent at 1 DIV ($n = 6$; $p = 0.0313$), decreased both SNAP-25 at 5 DIV ($n = 8$; $p = 0.0078$) and CREB at 1 DIV ($n = 7$; $p = 0.0169$). While BDNF and phospho-TrkB and TrkB immunocontent were not altered over time, a trend towards decreasing proBDNF was detected at 5 DIV ($n = 7$; $p = 0.06$). Cortical neurons from both strains did not change their morphology after 24 h of BDNF treatment ($n = 6$). Altogether, our findings suggest that changes at protein level may be associated to the alterations in neuronal development of SHR neurons. These changes found in the neuronal outgrowth and dendritic arborization from ADHD model may contribute to understand the neurobiological basis of ADHD. Ethical committed CEUA/UFRGS (Proc. 29196).

Disclosures: D.M. Marques: None. **A.S. Almeida:** None. **C.B. Alves:** None. **L.O. Porciúncula:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.18/A38

Topic: A.07. Developmental Disorders

Support: CAPES
CNPq

Title: Sex differences in impulsivity, cognition, proteins involved in brain maturation and response to caffeine in a rat model of attention deficit and hyperactivity disorder (ADHD)

Authors: *A. S. ALMEIDA, F. NUNES, D. M. MARQUES, L. O. PORCIÚNCULA;
Biochem., Federal Univ. of Rio Grande Do Sul, Porto Alegre, Brazil

Abstract: Attention Deficit and Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by hyperactivity, inattention and impulsivity, whose symptomatology varies according to sex. We aimed at investigating the influence of sex differences on behavioral outcomes and on proteins involved in brain maturation of Spontaneous Hypertensive Rats (SHR, the most validated rat model of ADHD). Our data revealed that infant SHR females showed recognition [$t = 1.733$; $p = 0.1138$, $n = 7$ litters] and olfactory [$t = 1.214$; $p = 0.2423$, $n = 7$ litters] memory impairment, when compared to control strain (Wistar Kyoto rats) and to their male counterparts. In the delay discounting task (a learning and impulse control task), adolescent SHR from both sexes required more sessions in order to complete the training phase, but females presented a worse performance [$F_{(1, 26)} = 28.42$; $p < 0.05$, $n = 4$ litters]. Impulsivity was observed in male SHR, which chose larger food rewards (to which they had to wait longer) less often than the smaller ones compared to the control strain [$F_{(1, 28)} = 7.622$; $p < 0.05$ $n = 4$ litters]. When we evaluated Growth Associated Protein 43 (GAP-43) and Sonic Hedhehog (SHH) immunocontent, SHH equally increased over time (from 8º to 22º postnatal day) in both strains and sexes in the hippocampus [$F_{(1,48)} = 19.50$; $p < 0.05$, $n = 7$ litters]. Although GAP-43 increased over time in the frontal cortex (FC) and in the olfactory bulb (OB), this increase was more pronounced in SHR from both sexes in FC [$F_{(1,48)} = 235.1$; $p < 0.05$, FC; $F_{(1,23)} = 4.527$; $P < 0,05$, OB. $n= 7$ litters]. Based on previous findings, caffeine has been able to improve cognitive and attention deficits in ADHD model, we also investigated the effects of caffeine in the delay discounting task. Our data revealed that both sexes of SHR treated with caffeine improved their performance in the task, as evidenced by the decrease in the number of sessions required to finish the training phase [$F_{(1, 22)} = 2,998$; $p = 0.09$, $n = 2$ litters]. Besides, an attenuation in the impulsivity was observed in male SHR treated with caffeine [$F_{(1, 25)} = 0,9252$; $p = 0.3453$, $n = 2$ litters]. Our findings revealed significant sex differences in ADHD model, with females presenting more cognitive deficits while male SHR showed evident signs of impulsivity. GAP-43 remained

increased over time in SHR frontal cortex, which might suggest impairments in neural networks. These data may contribute for better understanding of the neurobiological basis of ADHD**.** Moreover, caffeine was able to attenuate impulsivity, a characteristic symptom of ADHD, and thus such results extend its potential as an alternative for ADHD treatment. Ethical committed CEUA/UFRGS (Proc. nº29196).

Disclosures: A.S. Almeida: None. **F. Nunes:** None. **D.M. Marques:** None. **L.O. Porciúncula:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.19/A39

Topic: A.07. Developmental Disorders

Support: MOST105-2320-B-004-001, Taiwan
MOST107-2320-B-004-001-MY3, Taiwan
International Foundation of CDKL5 Research, USA (2015~2019)

Title: Methylphenidate ameliorates hyperlocomotion in CDKL5 deficient mice

Authors: *W.-L. LIAO[1,2], Y. LUO[1], C.-L. JHANG[1];
[1]Inst. of Neuroscience, Natl. Cheng-Chi Univ., Taipei, Taiwan; [2]Res. Ctr. for Mind, Brain and Learning, Natl. Cheng-Chi Univ., Taipei, Taiwan

Abstract: Cyclin-dependent kinase-like 5 (CDKL5), a serine-threonine kinase encoded by an X-linked gene, is highly expressed in mammalian forebrain. Mutations in this gene cause CDKL5 deficiency disorder (CDD), a neurodevelopmental encephalopathy characterized by early-onset seizures, motor dysfunction and intellectual disability. We previously found that mice lacking CDKL5 exhibit hyperlocomotion and increased impulsivity, resembling the core symptoms present in attention-deficit hyperactivity disorder (ADHD). The underlying neuronal mechanisms remain poorly understood. Here, we report that hyperlocomotion in *Cdkl5* null mice was recapitulated in mice carrying *Cdkl5* deletion selectively in dopaminergic neurons those express dopamine transporters (DAT). The phosphorylation of DAT and extracellular dopamine levels were altered in the striatum differently along the rostocaudal axis in hyperactive *Cdkl5* null mice. Moreover, administration of methylphenidate (MPH), a DAT inhibitor commonly used for treating ADHD, significantly alleviated hyperlocomotion in *Cdkl5* null mice. The behavioral effects of MPH were accompanied by region-specific normalization of phosphorylation of dopamine- and cAMP-regulated phosphoprotein Mr 32 kDa, a phosphoprotein enriched in the striatal neurons. Together, our findings uncover the CDKL5-mediated motor control through

region-specific regulation of dopamine transmission proteins that may serve as potential therapeutic targets to ameliorate the shared symptoms in CDD and ADHD.

Disclosures: **Y. Luo:** None. **W. Liao:** None. **C. Jhang:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

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Program #/Poster #: 549.20/A40

Topic: A.07. Developmental Disorders

Support: NICHD 1R15HD087937
Alan & Wendy Pesky Resesarch award

Title: Decoding dyslexia: Early identification of reading impairment

Authors: ***L. A. GABEL**[1], E. JOHNSON[3], D. T. TRUONG[5], S. PANIAGUA[5], B. E. SHELTON[4], J.-L. HUNG[4], E. MURRAY[2], K. VOSS[2], O. GRIGAUX[2], M. SCHIAZZA[2], M. DENBLEYKER[2], W. DUNCAN[2], J. R. GRUEN[6];
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Abstract: Reading disorder (RD, a.k.a. Dyslexia) is a specific learning disability affecting children across language orthographies, despite adequate intelligence and educational opportunity. If learning disabilities remain untreated, a child may experience long-term social and emotional problems, which may influence future success in all aspects of their lives. Early detection and intervention will help to close the gap between typically developing and reading impaired children in acquiring reading skills. Recently we demonstrated that animal models of dyslexia (i.e. genetic models based on candidate dyslexia susceptibility genes) and children with specific reading impairment show a common deficit on a virtual Hebb-Williams maze. In addition, we have demonstrated that this deficit is consistent across language orthographies (i.e. transparent and non-transparent languages). In this study we examined phonological awareness, genetic risk factors and virtual Hebb-Willimas maze performance in pre-school (4-5 years of age) and school-aged (5-6 years of age) children to determine if maze performance correlated with risk of future reading impairment. In addition, a subset of children were re-examined on maze performance and reading measures in second grade, in order to determine if their ability to complete the task was a strong predictor of future reading ability. Since virtual maze task does not require oral reporting (i.e. rapid access to phonological processing), or rely on text, performance is not influenced by a potential difference in reading experience between groups. Using computational modeling of students' actions using maze locations and latency values,

prediction results can be integrated into the test for real-time feedback of the performance in the form of at-risk percentages for reading. Initial computational modeling exceeded 80% accuracy in identifying known reading outcomes based on these predictors. New modeling techniques that include auto-encoding, a deep learning framework, holds promise for even higher identification successes. If performance on the maze task is a strong predictor of future reading ability, then the maze task may be effective in the early identification of children at risk for reading impairment.

Disclosures: **L.A. Gabel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Provisional Patent. **E. Johnson:** F. Consulting Fees (e.g., advisory boards); CEO, Lee Pesky Learning Center. **D.T. Truong:** None. **S. Paniagua:** None. **B.E. Shelton:** None. **J. Hung:** None. **E. Murray:** None. **K. Voss:** None. **O. Grigaux:** None. **M. Schiazza:** None. **M. DenBleyker:** None. **W. Duncan:** None. **J.R. Gruen:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.21/A41

Topic: A.07. Developmental Disorders

Support: Northeastern University Honors Early Research Award

Title: Chronic exposure to the psychostimulants Ritalin and Adderall during adolescence alters brainstructure and function

Authors: ***J. L. DEMAREE**[1], D. AGGARWAL[1], I. SENTHILKUMAR[1], C. LAWSON[1], X. CAI[2], P. P. KULKARNI[3], C. F. FERRIS[4];
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Abstract: Attention Deficient Hyperactivity Disorder (ADHD), commonly diagnosed in children and adolescence, is routinely treated with the psychostimulants Ritalin and Adderall. It has been argued, ADHD is over diagnosed resulting in “normal” individuals being exposed to psychostimulants for prolonged periods of time during adolescence, a critical development period in brain maturation. This study used non-invasive multimodal magnetic resonance imaging (MRI) to examine the changes in brain structure and function in healthy rats following chronic exposure to d-amphetamine (Adderall ®) and methylphenidate (Ritalin®) during adolescence. On postnatal day 21 (PND 21), 30 male rats were divided into three groups of 10 animal each. At the same time each day, for three weeks, rats were given intraperitoneal injections of either saline vehicle, Ritalin (10mg/kg) or Adderall (5 mg/kg) assigned to one of the

three groups. At the cessation of treatment on PND 45, rats were imaged for changes in brain volumes, gray matter microarchitecture and function connectivity. Images were acquired using a 7.0T MRI scanner.The imaging modalities included T1 weighted voxel-based morphology, diffusion weighted imaging with quantitative anisotropy and resting state BOLD functional connectivity. All images for each modality were registered to a 3D MRI Rat Atlas with 171 segmented and annotated brain areas used to generate an unbiased computational analysis of all data. Changes in measures of anisotropy, often used in clinical studies to identify areas of potential inflammation or injury, were not significantly different between experimental groups. There were only 14/171 brain areas that showed a significant increase in brain volume between treatments and only in response to Ritalin. Interestingly, Ritalin's effect on brain volume was primarily localized to the cerebellum, particularly the deep cerebellar nuclei. These same cerebellar nuclei showed a significant increase in connectivity to the rest of the cerebellum and the brainstem that was not observed with vehicle or Adderall treatments. Ritalin treatment also showed a significant increase in functional connectivity across the midbrain dopaminergic system but not the anticipated connectivity between the prefrontal cortex and striatum. These data suggest a reorganization of neural circuitry around the brainstem/cerebellum and midbrain dopaminergic system in response to chronic exposure to psychostimulants during adolescence. Behavioral studies assessingchanges in cognition, motivation and emotion in these animals were ongoing at the time of this submission.

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Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.22/A42

Topic: A.07. Developmental Disorders

Title: A retroviral twist to Angelman syndrome

Authors: *N. J. PANDYA[1], P. LOPATTA[1], V. COSTA[2], B. BANFAI[3], M. T. MILLER[1], M. EBELING[3], M. TZOUROS[3], T. DUNKLEY[3], R. JAGASIA[1];
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Abstract: Angelman syndrome (AS) is a neuro-developmental disorder caused by neuronal loss of E3 Ubiquitin ligase UBE3A leading to a plethora of severe intellectual disabilities. Although neuronal loss of UBE3A causes AS, there is a paucity of knowledge of downstream molecular and cellular dysfunction, ultimately hampering drug discovery. To this end, protein and RNA

expression profiling was performed on AS patient and healthy control human induced pluripotent stem cell (iPSC)-derived neurons. UBE3A and proteins and pathways were deregulated across patient lines. Using RNAi molecules, reducing UBE3A protein in control lines or restoring it in patient lines, by knocking down the sense or anti-sense transcript respectively, reciprocally modulated a subset of these proteins. This included a subset of LTR retrotransposon-derived genes containing GAG capsid domains. UBE3A formed a complex with these Gag proteins and regulated its ubiquitination to modulate proteosomal degradation. These proteins share similarities to retroviruses and by virtue of their expression in AS cells, modulate extracellular vesicle content and RNA granule assembly. Thus, we identify a novel proteins modulated by UBE3A and demonstrate their role in regulating extracellular vesicle content and RNA granules. This work is expected to ultimately lead to a better understanding of Angelman pathophysiology and potentially enable target engagement biomarker discovery for therapies currently under development for Angelman syndrome.

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Poster

549. Neural Mechanisms for Developmental Disorders II

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Topic: A.07. Developmental Disorders

Support: JSPS KAKENHI 16K09965
JSPS KAKENHI 19K08251

Title: Integrative DNA methylation and gene expression analysis of Williams syndrome

Authors: *R. KIMURA[1], R. LARDENOIJE[4], K. TOMIWA[5], Y. FUNABIKI[2], M. NAKATA[1], S. SUZUKI[1], T. AWAYA[1], T. KATO[6], T. MURAI[3], T. HEIKE[6], B. P. F. RUTTEN[4], M. HAGIWARA[1];
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Abstract: Williams Syndrome (WS) is a genetic neurodevelopmental disorder with a wide spectrum of symptoms, including hypersociability. Although the disorder is known to be caused by 7q11.23 deletions, the molecular basis of phenotypic variability remains unclear. Thus, we systematically investigated the relationship between DNA methylation and WS phenotypes. Genome-wide DNA methylation analysis was performed using Illumina DNA methylation arrays with blood samples. WS-associated modules were identified at the systems level by weighted

gene co-methylation network analysis. DNA methylation profiles were validated by pyrosequencing and integrated with gene expression profiles. The effects of age on methylation of the most promising candidate gene were examined in 90 WS patients. Differential DNA methylation associated with WS was detected throughout the genome. Systems-level network analysis revealed that multiple co-methylation modules were significantly correlated with intermediate phenotypes of WS, with the top-scoring module linked to neurogenesis and development of the central nervous system. Notably, *ANKRD30B*, a promising hub gene, was found to be significantly hypermethylated in WS patients, regardless of age. Furthermore, potential master regulator transcription factors associated with WS, including *BCL11A*, were identified by the integration of methylome and transcriptome profiles. To our knowledge, this is the largest epigenetic study of WS, as assessed at the systems-level, providing a possible explanation for complex phenotypes among patients. Our findings could help to further understand not only WS but other neuropsychiatric disorders.

Disclosures: **R. Kimura:** None. **R. Lardenoije:** None. **K. Tomiwa:** None. **Y. Funabiki:** None. **M. Nakata:** None. **S. Suzuki:** None. **T. Awaya:** None. **T. Kato:** None. **T. Murai:** None. **T. Heike:** None. **B.P.F. Rutten:** None. **M. Hagiwara:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.24/A44

Topic: A.07. Developmental Disorders

Support: R01GM112715

Title: Magnetic resonance assessment of learning deficiency induced by neonatal exposure to isoflurane

Authors: *D. P. AKSENOV, P. VENKATASUBRAMANIAN, C. DIXON, L. LI, M. MILLER, A. WYRWICZ;
NorthShore Univ. HealthSystem, Evanston, IL

Abstract: Each year approximately 6 million children in the USA alone undergo anesthesia in the course of surgeries, imaging and other diagnostic procedures. Multiple studies have indicated that early exposure to general anesthesia can affect neuronal development, leading to deficits in learning and memory. It was found, for example, that children who underwent anesthesia were more than twice as likely to exhibit behavioral/developmental deficits in young adulthood. Animal studies provide a more well-controlled analysis of anesthesia-related effects and allow for more precise comparisons between anesthetized subjects and controls. A variety of animal models have been used to study the effects of inhaled anesthetics and have revealed associations

between early anesthesia exposure and developmental pathologies including increased cell apoptosis, defects in myelination, hippocampal and cortical cell loss and disruption of associative learning in adult subjects. Changes in the brain associated with such impairments have not been directly characterized using MRI. Previously, we have used blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) to examine the learning-related functional changes that occur during eyeblink classical conditioning (ECC) in awake rabbits. fMRI allowed us to evaluate the functional state of the sensory system before learning, and together with ECC provided a non-invasive, easily quantifiable approach for characterizing the impact of anesthesia on learning. Our findings demonstrated learning impairment fore trace ECC and changes in BOLD activation induced by the CS after training in anesthesia-exposed subjects. In this study we evaluated the effects of anesthesia exposure during infancy with and without supplemental oxygen using MR volumetry, spectroscopy (MRS), and diffusion tensor imaging (DTI) during young adulthood. Infant rabbits were exposed to isoflurane anesthesia using a common surgical protocol and then received training with a trace ECC paradigm at three months of age. MRI experiments were performed in adolescent rabbits to measure the BOLD response to the whisker vibration CS as well as the hippocampal volume before and after learning. The awake rabbit model allowed us to compare directly the results in anesthesia-exposed animals versus controls. MRS and DTI data were also acquired from anesthesia-exposed rabbits as well as controls during final stage of the experiments. Our MRI findings revealed a variety of significant changes in the brain associated with learning impairment on the trace ECC paradigm.

Disclosures: D.P. Aksenov: None. **C. Dixon:** None. **M. Miller:** None. **L. Li:** None. **A. Wyrwicz:** None. **P. Venkatasubramanian:** None.

Poster

549. Neural Mechanisms for Developmental Disorders II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 549.25/A45

Topic: A.07. Developmental Disorders

Support: NIH Grant R01GM112715

Title: Chronic metabolic effects of anesthesia on the developing brain

Authors: *P. N. VENKATASUBRAMANIAN, L. LI, A. M. WYRWICZ, D. P. AKSENOV; Ctr. for Basic MR Res., NorthShore Univ. HealthSystem, Evanston, IL

Abstract: Millions of children undergo general anesthesia each year and a growing body of literature suggests that exposure to anesthesia at an early age can impact neuronal development, leading to learning and memory impairments later in childhood. Although behavioural and structural effects of anesthesia exposure during infancy have been reported, long-term metabolic

effects of anesthesia have not been examined. In this study we have investigated metabolic changes in the dentate gyrus (DG) of rabbits exposed to volatile anesthetics when they were pups. Dutch-belted rabbits were anesthetized at postnatal days 8, 11, and 14. Kits were anesthetized with either sevoflurane (SVF) or isoflurane (ISF) in air or in 80% O_2. At 3 months of age, animals were given eyeblink classical conditioning. After the learning sessions, localized proton MR spectra were acquired from voxels located in the left and right DG of awake rabbits on a 9.4T imager. N-Acetyl aspartate (NAA), glutamate (Glu), glutamine (Gln), GABA, creatine/phosphocreatine (Cr/PCr), choline (Cho), taurine (Tau), and myo-Inositol (Ins) were seen in the DG. In the left DG of the *SVF+air* group, NAA, Glu+Gln, and GABA were significantly lower than controls. In the left DG of *SVF+O_2* group GABA and Tau were lower than controls. ISF treated groups did not show many differences from the control group, with only Ins being elevated in the left DG of *ISF+air* group. Metabolite levels in the right DG revealed a different pattern. The *SVF+O_2* group showed significant decreases in Glu and Cho, which were also significantly lower in the *SVF+air* group. In contrast, no significant changes in metabolite levels were detected in the *ISF+air* and *ISF+O_2* groups. MR spectroscopy of the DG showed differential effects of exposure to sevoflurane and isoflurane in rabbit pups nearly 4 months after anesthesia. Decreases in NAA, Glu+Gln, GABA and Tau in the pups exposed to SVF mixed with air or O_2 suggest that SVF has long-term effects on neurons, both excitatory and inhibitory neurotransmitters, and brain osmolyte. In contrast, ISF causes minimal long-term neuronal effects in the DG. Increases in Ins in the *ISF+air* group indicates glial metabolic effect of anesthesia. The difference in the metabolic patterns between left and right DG in anesthetic-exposed animals suggests that the effects of anesthesia might be modulated by behavioural training, with the side involved in learning showing changes in fewer metabolites. Exposure to volatile anesthetics in infancy has chronic adverse effects on the metabolism of the developing brain. SVF causes greater metabolic impairment than ISF. The metabolic effects of anesthesia may be modulated by behavioural training.

Disclosures: P.N. Venkatasubramanian: None. **L. Li:** None. **A.M. Wyrwicz:** None. **D.P. Aksenov:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.01/A46

Topic: A.09. Adolescent Development

Support: NSERC (RGPIN-2014-05570)

Title: Sex differences in blood-brain barrier permeability during lipopolysaccharide-induced sickness

Authors: *D. KOLMOGOROVA[1], E. AH-YEN[1], K. B. SMITH[2], B. C. TAYLOR[4], R. CHANDRASEGARAM[4], N. ISMAIL[3];
[2]Sch. of Psychology, [3]Dept. of Psychology, [1]Univ. of Ottawa, Ottawa, ON, Canada; [4]Cardiff Univ., Cardiff, United Kingdom

Abstract: Puberty is a critical period with extensive neurodevelopmental changes that render it vulnerable to immune challenges. In CD-1 mice, a peripheral immune challenge during the stress-sensitive period of puberty (i.e., 6 weeks of age) alters various brain processes and behaviours in a sex-specific manner. For example, six-week-old CD-1 mice show a female-biased increase in neuroinflammation and neuronal cell death during sickness induced by intraperitoneal (*ip*) lipopolysaccharide (LPS) exposure. However, the mechanisms underlying such sex differences in how peripheral immune events influence the central nervous system is unclear. One promising explanation lies in how systemic pathogens affect substance exchange at the blood-brain barrier (BBB) in males and females. This study examined sex differences in the effects of a systemic immune challenge on BBB permeability during puberty. Male and female CD-1 mice were treated with either LPS (1.5 mg/kg body weight, *ip*) or .9% sterile saline (LPS-matched volume, *ip*) at six weeks of age (i.e., stress-sensitive pubertal period). BBB disruption (whole brain) was measured using ^{14}C-sucrose (1 x 10^6 *dpm*) at 24 hours (i.e., during sickness) post-treatment. Regional differences in BBB permeability during sickness were also examined in the prefrontal cortex, hippocampus, hypothalamus, and the cerebellum. Treatment and sex differences in BBB permeability were assessed with a 2x2 analysis of variance. As expected, systemic LPS induced more sickness behaviours and body weight loss than saline treatment in all mice, with LPS-treated females showing a quicker symptomatic recovery than LPS-treated males (all $p < .05$). BBB disruption was present among females but not males treated systemically with LPS during puberty (all $p < .05$). Sex differences in BBB permeability were not observed among the saline-treated mice. These BBB-mediated sex differences during sickness may explain some sex differences in brain and behaviour outcomes of a systemic immune challenge during puberty.

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Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.02/A47

Topic: A.09. Adolescent Development

Title: Enriching experiences during adolescence affect enrichment evoked activity in entorhinal cortex in late adolescence and early adulthood

Authors: *H. GODFREY, C. H. GODFREY, D. E. DRURY, D. D. WRIGHT, E. M. BUNCICK-ROAKES, M. C. ZRULL;
Appalachian State Univ., Boone, NC

Abstract: Environmental enrichment (EE) provides opportunity for stimulation with and learning about spatial, object, and social cues within some environment and can have both immediate and lasting impact on brain structures and circuits. With its role in processing spatial information, we examined neural activity in medial and lateral entorhinal cortex (MEC, LEC) neurons evoked by a single enriching experience in rats with and without a history of EE during adolescence (EE+EE, No+EE, respectively) in two experiments. Control groups with and without EE history did not have a final EE experience (EE+No, No+No), and EE+EE and EE+No groups of Long-Evans rats experienced periodic EE sessions through adolescence in both experiments. For Experiment 1 (groups of 5), EE+EE and No+EE rats experienced a final EE session immediately following periodic EE on postnatal day (pnd) 49 and were then sacrificed; however, for Experiment 2 (groups of 7), the final EE session for EE+EE and No+EE occurred about 20 days after periodic EE ended. Periodic and final EE sessions occurred in the same environment but objects, object locations, and rats varied session-to-session. In both experiments, controls were sacrificed on the same schedule as evoked activity rats, and neural activity was quantified using tissue processed for c-FOS and digital light microscopy with stereological techniques. Experiment 1 provided insight about the immediate effects of an EE history, and Experiment 2 showed persisting effects of EE history. When the final EE session was novel (No+EE), superficial MEC (sMEC) exhibited more c-FOS+ neurons than for all other groups (EE+EE, EE+No, No+No) tested at pnd 49 (+334%, $p<.030$) and at pnd 75 (+382%, $p<.001$) suggesting enhanced neural activity reflecting novelty of the EE space for only the No+EE rats. In contrast, deep MEC (dMEC) and superficial and deep LEC (sLEC, dLEC) of EE+EE and No+EE rats showed more c-FOS+ neurons than rats not experiencing a final EE session at pnd 49 (dMEC, +215%, $p<.001$; sLEC, +89%, $p<.002$; dLEC, +272%, $p<.001$) and pnd 75 (dMEC, +200%, $p<.001$; sLEC, +119%, $p<.010$; dLEC, +142%, $p<.003$) suggesting enhanced neural activity evoked by being in a novel or familiar space with new or newly located objects. Our results support the idea that MEC neurons represent information about global cues or the overall spatial scene of an organism's environment, and LEC neurons respond to more local cues within a space or, perhaps, what is where in an environment. Further, enriching experiences during adolescence seem to influence, at least to some degree, how MEC and LEC neurons respond to some aspects of novelty at least until early adulthood.

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Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.03/A48

Topic: A.09. Adolescent Development

Support: DFG BR 3479/11-1
Neurocure

Title: Constant innervation despite pubertal growth of the mouse constant innervation despite pubertal growth of the mouse constant innervation despite pubertal growth of the mouse penis

Authors: *L. PURKART, J. SIGL-GLÖCKNER, M. BRECHT;
Bernstein Ctr. for Computat. Neurroscience, Humboldt-Universität Zu Berlin, Berlin, Germany

Abstract: It has long been recognized that the sexual characteristics of the vertebrate body change under the control of sex hormones (Berthold, 1849). Hence, in mammals the genitals undergo major changes in puberty. While such bodily changes have been well documented, the associated changes in the nervous system are still poorly understood. To address this issue we studied the growth and innervation of the mouse penis throughout puberty. To this end we measured length and thickness of the mouse penis in prepubertal (P21) and adult (P56-77) mice and performed fiber counts of the dorsal penile nerve. We obtained dorsal penile nerve fiber counts by confocal microscopy of thin proximal sections of the mouse penis after paraffin embedding, antibody staining with antibody Neurofilament H in combination with antigen retrieval procedures. We find that the mouse penis grows roughly 1,4 times in both, thickness and length. Fiber counts in the dorsal penile nerve were not different in prepubertal (1596 ± 188 fibers per penis) and adult (1569 ± 384 fibers per penis) mice, however. The number of nerve fibers on the left and right side of the penis was bilaterally symmetric. The constant innervation of mouse penis through puberty suggests that changes in central representation of the rodent penis (Lauer, Lenschow, & Brecht, 2017; Lenschow, Sigl-Glöckner, & Brecht, 2017) are probably not simply a reflection of peripheral change.

References

Berthold, A. A. 1849. Transplantation der hoden. ***Arch Anat Physiol***, 42-46.
Lauer, S. M., Lenschow, C., & Brecht, M. 2017. Sexually selected size differences and conserved sexual monomorphism of genital cortex. ***Journal of Comparative Neurology***. https://doi.org/10.1002/cne.24237.
Lenschow, C., Sigl-Glöckner, J., & Brecht, M. 2017. Development of rat female genital cortex and control of female puberty by sexual touch. ***PLoS Biology***, 15(9). https://doi.org/10.1371/journal.pbio.2001283.

Disclosures: L. Purkart: None. **J. Sigl-Glöckner:** None. **M. Brecht:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.04/A49

Topic: A.09. Adolescent Development

Title: Treatment with the PDE9 inhibitor BI409306 during adolescence mitigates social interaction and dopaminergic deficits in adult offspring of the poly(I:C) based maternal immune activation neurodevelopmental mouse model

Authors: J. RICETTO[1], J. SCARBOROUGH[1], R. ARBAN[2], ***C. DORNER-CIOSSEK**[2], H. ROSENBROCK[2], U. MEYER[1];
[1]Inst. of Pharmacol. and Toxicology, Univ. of Zurich-Vetsuisse, Zurich, Switzerland; [2]CNS-DR, Boehringer Ingelheim Pharma GmbH & Co KG, Biberach an der Riss, Germany

Abstract: Rodent models of maternal immune activation (MIA) are used to study neurodevelopmental disorders such as schizophrenia by analyzing the neuronal and behavioral dysfunctions of the offspring. Injection of the viral mimic poly(I:C) in pregnant mice causes disruption of neuronal development of the offspring leading in adulthood in particular to deficits in social behavior and the dopaminergic system. BI 409306 is a selective phosphodiesterase-9 (PDE9) inhibitor [1] currently investigated for intervention in patients with Attenuated Psychosis Syndrome (APS) (NCT03230097). PDE9 inhibition is hypothesized to improve the NMDA-receptor signaling cascade by increasing cGMP levels which subsequently leads to strengthening of synaptic plasticity. Abnormalities in the excitatory/inhibitory network related to NMDA-receptor hypofunction at adolescent age, along with dopaminergic dysfunction, are hypothesized to occur in individuals with APS. In this study, we have investigated the effect of BI 409306 administered during adolescent age on the behavioral deficits of the adult offspring from the poly(I:C)-based MIA mouse model. Pregnant C57BL6/N mice were treated with poly(I:C) (5 mg/kg, i.v.) or control (saline, i.v.) solution on gestation day 12. All offspring (n=21-22/group) were administered orally once daily with BI 409306 (1 mg/kg) or vehicle starting at post-natal day (PND) 30 for 4 weeks or until subjected to a battery of consecutive behavioral tests social interaction to assess social behavior, pre-pulse inhibition (PPI) for sensorimotor processing and amphetamine-induced hyperlocomotion to assess the dopaminergic system at PND 72-114. Statistical analyses used one-way ANOVA followed by Fisher's LSD post-hoc. Maternal poly(I:C)-induced immune challenge led to a significant decrease in social interaction ($p<0.01$) in the adolescent and adult offspring, and to a significant potentiation of amphetamine-induced hyperlocomotion at adulthood. PPI was not affected. Treatment with BI 409306 during adolescence significantly mitigated the social interaction deficits ($p<0.005$) and amphetamine hyper-responsiveness ($p<0.05$) at adult age of the offspring. Plasma exposure of BI 409306 determined in satellite mice was in the range as expected for the doses used in the clinical trial.

For the first time, we could show that treatment with the PDE9 inhibitor BI 409306 during adolescence offsets social behavior and dopaminergic deficits observed in adult offspring in this model. Therefore, our findings support the test of BI 409306 for early intervention in patients with APS. [1] Moschetti et al. (2017), Br. J. Clin. Pharmacol., 82(5):1315-1324.

Disclosures: **J. Ricetto:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Boehringer Ingelheim Pharma. **J. Scarborough:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Boehringer Ingelheim Pharma. **R. Arban:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma. **C. Dorner-Ciossek:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma. **H. Rosenbrock:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma. **U. Meyer:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Boehringer Ingelheim Pharma.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.05/A50

Topic: A.09. Adolescent Development

Title: Dosage sensitivity intolerance of VIPR2 duplication is causative in manifestation of schizophrenia-like striatal dopamine abnormality, cognitive, social, and developmental deficits in a novel bacterial artificial chromosome transgenic mouse model

Authors: *X. TIAN[1], M. REN[1], A. D. RICHARD[1], M. ELSAADI[1], D. S. DWYER[2], R. L. KLEIN[1], N. E. GOEDERS[1], X. W. YANG[3], X.-H. LU[1];
[1]Dept. of Pharmacology, Toxicology & Neurosci., [2]Psychiatry, Louisiana State Univ. Hlth. Sci. Ctr., Shreveport, LA; [3]Dept Psych, UCLA, Los Angeles, CA

Abstract: Recent genome-wide association studies (GWAS) have identified copy number variations (CNVs) at chromosomal locus 7q36.3 that significantly contribute to the risk of schizophrenia, with all of the microduplications occurring within a single gene: Vasoactive intestinal peptide receptor 2 (VIPR2). To confirm disease causality and translate such a genetic vulnerability into mechanistic and pathophysiological insights, we have developed a series of conditional VIPR2 Bacterial Artificial Chromosome (BAC) transgenic mouse models of VIPR2 CNV with one extra copy (microduplication) or four extra copies of human VIPR2, and one fully

humanized model in the murine Vipr2 null background. The conditional design of the BAC allows switching-off the transgene expression in desired spatiotemporal patterns, thus facilitating the dissection of the inflicted neurocircuits. VIPR2 CNV mouse model recapitulates gene expression and signaling deficits seen in human CNV carriers. VIPR2 duplication in mice elicits prominent dorsal striatal dopamine dysfunction, consistent with recent human neuroimaging reporting dopamine abnormalities in schizophrenia are the greatest within dorsal striatum. VIPR2 CNV mice manifest cognitive, sensorimotor gating and social behavioral deficits preceded by an increase of striatal cAMP/PKA signaling and the disrupted early postnatal striatal development. Genetic removal of VIPR2 transgene expression via crossing with Drd1a-Cre BAC transgenic mice rescued the dopamine dysfunction and multiple behavioral deficits, implicating a pathogenic role of VPAC2 overexpression in dopaminoceptive neurons. Thus, our results provide further evidence to support the GWAS studies that the dosage sensitivity intolerance of VIPR2 is causative in the manifestation of schizophrenia-like dopamine, cognitive, and social behavioral deficits. The conditional BAC transgenesis offers a novel strategy to model CNVs with a gain-of -copies and facilitate the genetic dissection of when/where/how the genetic vulnerabilities affect development, structure, and function of neural circuits. Our findings have important implications for therapeutic development, and the etiology-relevant mouse model provides a useful preclinical platform for drug discovery.

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Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.06/A51

Topic: A.09. Adolescent Development

Title: Feminized digit ratios in androgen insensitive rats

Authors: *V. DI RITA, S. M. BREEDLOVE, C. L. JORDAN;
Neurosci. Program, Michigan State Univ., East Lansing, MI

Abstract: The ratio of the length of the second digit to the fourth digit (2D:4D) is often used as a statistical indicator of prenatal androgen exposure in both human and non-human subjects. The ratio is sexually dimorphic in humans beginning before birth; males - on average - have lower ratios than females. Additionally, masculinized ratios have been identified in both men and women with congenital adrenal hyperplasia (CAH), in self-identified “butch” lesbians, and in male and female rats whose mothers received testosterone enhancements during gestation. Prior to this study, the 2D:4D had not been investigated in the testicular feminized (Tfm) rat, which expresses a dysfunctional androgen receptor (AR) gene on the X chromosome, giving rise to a

female external phenotype in XY rats. Because testosterone plays essentially no role in the development of these animals in utero, they offer a unique model to study the relationship between fetal testosterone and 2D:4D. We hypothesized that male Sprague Dawley Tfm rats would show feminine digit ratios compared to their wildtype (wt) brothers. Examining the hind paws of 21 male Tfm rats and 13 wt male rats at six weeks of age revealed a more feminine (larger) 2D:4D in the Tfm group, with an average ratio of 0.997 (SEM = 0.010) in the right hind paw, compared to male wt rats which showed an average 2D:4D of 0.951 (SEM = 0.014) in the right hind paw ($p = 0.01$, $d' = 0.95$). We did not find a significant difference between the mean digit ratios of wt male and female (N =13) rats, perhaps due to greater variance among females. Nevertheless, the more feminine digit ratio in Tfm males compared to males with a wt AR demonstrates that androgen activity plays a role in the development masculine digit ratios in rats, as has been shown in mice with limb AR deletions. Our study supports the theory that 2D:4D is inversely related to prenatal androgen stimulation in both human and non-human animals, validating efforts to link statistical trends in human behavior to digit ratios as a proxy of prenatal hormone influence.

Disclosures: V. Di Rita: None. **S.M. Breedlove:** None. **C.L. Jordan:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.07/A52

Topic: A.09. Adolescent Development

Support: ETSU Graduate Student Grant

Title: The effects of an adenosine A(2a) agonist on the rewarding associative properties of nicotine and neural plasticity in a rodent model of schizophrenia

Authors: *W. D. GILL, H. W. SHELTON, K. C. BURGESS, R. W. BROWN;
Dept. of Biomed. Sci., East Tennessee State Univ., Johnson City, TN

Abstract: A neurobiological hallmark of schizophrenia (SZ) is increased dopamine D_2 receptor sensitivity. Additionally, nicotine abuse is greatly increased in individuals diagnosed with SZ compared to the normal population. The adenosine system has been identified as a potential novel target for both SZ treatment and nicotine abuse, because adenosine A_{2a} receptors form a heteromeric complex with dopamine D_2 receptors that is mutually inhibitory. This relationship means each receptor exhibits lower sensitivity to its agonist after the opposing receptor agonist is bound, thus, adenosine A_{2a} agonists have been suggested to treat both psychosis and nicotine abuse. This study investigated the efficacy of an adenosine A_{2a} agonist, CGS 21680, in alleviating the rewarding aspects of nicotine in the neonatal quinpirole rodent model of SZ. Rats

were treated neonatally from postnatal (P)day 1 through 21 with the dopamine D_2/D_3 agonist quinpirole, raised to P41, and tested on conditioned place preference (CPP). Rats were conditioned to saline or nicotine (0.6 mg/kg base) from P43-51. Groups receiving CGS 21680 (0.03 or 0.09 mg/kg) were given the agonist 15 min before nicotine was administered. A drug-free post-conditioning test was administered on P52 to determine preference. The following day, brain tissue was analyzed for brain-derived neurotrophic factor (BDNF) and glial cell-lined neurotrophic factor (GDNF). Results revealed that neonatal quinpirole enhanced nicotine CPP, replicating previous work, and both doses of CGS 21680 alleviated this enhancement. Nicotine resulted in a CPP in controls, and both doses of CGS 21680 also alleviated this preference. BDNF analyses in the nucleus accumbens (Nacc) revealed that CGS 21680 alleviated the enhancement in Nacc BDNF in neonatal quinpirole-treated animals, and eliminated the increase in Nacc BDNF produced by nicotine in controls, much like CPP results. GDNF analyses revealed that neonatal quinpirole animals conditioned to nicotine resulted in an increase of GDNF in the NAacc, but this was eliminated by CGS 21680. This project revealed that an adenosine agonist with antispsychotic properties may have utility towards decreasing the rewarding aspects of nicotine and its accompanying neural plasticity changes in a model of SZ.

Disclosures: W.D. Gill: None. **H.W. Shelton:** None. **K.C. Burgess:** None. **R.W. Brown:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.08/A53

Topic: A.09. Adolescent Development

Support: NIH 5UL1GM118979
NIH 5TL4GM118980
NIH 5RL5GM118978

Title: The effect of early-life fluoxetine administration on binge eating behavior in adulthood in male and female rats

Authors: *A. L. CASTRO[1], Y. TREESUKOSOL[2];
[2]Dept. of Psychology, [1]California State Univ. Long Beach, Long Beach, CA

Abstract: Fluoxetine (Prozac), a selective serotonin reuptake inhibitor (SSRI) is a commonly prescribed antidepressant for adolescents. Recommendations for adolescent-use are based on findings from data collected from adult samples which raises the question of how SSRIs affect the developing brain. Fluoxetine administration in adolescent rats has been shown to affect responses to reward and aversive stimuli in adulthood (Iñiguez et al., 2010). In the current study,

male and female rats (n=46) were treated daily (i.p.) with 20 mg/kg fluoxetine (FLX) or saline (control) during adolescence (postnatal day PND 35-49). In adulthood (from PND 72) rats were exposed to a binge access eating paradigm twice a week for six consecutive weeks. Each session began with 23-h food restriction followed by a 30-minute presentation of chow (3.43 kcal/g) and sweetened fat (8.6 kcal/g). This experimental design allows us to ask whether fluoxetine treatment in early life will lead to increased response to sweetened fat compared to controls. Here, FLX and control rats did not significantly differ in preference for sweetened fat versus chow or total caloric intake across the test session. Whereas juvenile fluoxetine administration results in enduring changes in mood-related measures, here, no long-term changes in preference for a palatable stimulus are observed. Both males and females preferred sweetened fat during the first 2 sessions but whereas females maintained this preference, preference in male rats decreased over time thus providing evidence for sex differences.

Disclosures: A.L. Castro: None. **Y. Treesukosol:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.09/A54

Topic: A.09. Adolescent Development

Support: NSERC Individual Discovery Grant RGPIN-2018-05307

Title: Investigation of GLuR1 and GLuR2 AMPA receptor subtype distribution in the hippocampus of long evans rats during a sensitive developmental period

Authors: *N. TZAKIS, M. R. HOLAHAN;
Neurosci., Carleton Univ., Ottawa, ON, Canada

Abstract: Understanding the development of spatial memory abilities requires insight about the development of cellular underpinnings that mediate the transition from juvenile-like to adult-like spatial processing capabilities. We reported that the hippocampus shows morphological adjustments from postnatal days 18 - 24 (p18 - p24) that predicted the emergence of spatial memory function. Examination of axonal and dendritic processes (structural changes) and c-Fos labeling (functional changes) in the hippocampus revealed improved connectivity patterns and developmentally-dependent increases in c-Fos positive cells that predicted the emergence of spatial behavior. From this, we hypothesized that p16 - p24 (pre-adolescent) represented a sensitive period for hippocampal development and modification. The effect of AMPAr blockade during this time revealed an important role of AMPA receptor-mediated function in the organization and long-term storage of spatial memories acquired during the juvenile period. AMPAr are made up of 4 subunits, of which GluR1 and GluR2 have been shown to play the

most prominent role in cognitive processes. While their function in adults has been well documented, their developmental expression in juveniles is less understood. To study this, Western blotting and immunohistochemistry were performed on the hippocampus in preadolescent rats (P18-30) and compared to postadolescent rats (P50) to determine the quantitative and cellular distribution of GluR1 and GluR2 through development. Western blot results showed that both GluR1 and GluR2 expression peaked during late hippocampal modification then reached adult levels after P30. Immunohistochemical staining of the GluR1 subunit showed a pattern of cellular labeling that peaked in the CA3 and dentate gyrus at p20 and declined thereafter. Further studies will be carried out to determine if these cells are immature neurons or interneurons. Within all hippocampal regions, immunohistochemical localization of GluR2 stained cells remained constant. These results indicate that this period of hippocampal modification is a crucial transitionary period, whereby the cellular processes that mediate spatial memory capabilities shift from juvenile- to adult-like.

Disclosures: N. Tzakis: None. **M.R. Holahan:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.10/A55

Topic: A.09. Adolescent Development

Title: Stress in adolescence enhances the use of dorsolateral striatum-dependent habit learning in adulthood

Authors: *T. M. GADBERRY, C. A. BOLANOS-GUZMAN, M. G. PACKARD; Psychological and Brain Sci., Texas A&M Univ., College Station, TX

Abstract: Previous research indicates that anxiety and stress can influence the relative use of hippocampal-dependent cognitive and dorsolateral striatal-dependent habit memory systems. Specifically, stress/anxiety biases both lower animals and humans towards the use of habit memory. These results have been observed primarily in adult organisms. Early life stress in humans has been associated with predisposition to various psychopathologies that involve the development and expression of maladaptive habitual behaviors (e.g. OCD, addiction, PTSD). However, the effect of early life stress during adolescence on the later use of DLS-dependent habit memory in adulthood has not been extensively investigated. Accordingly, in the present study adolescent male Long-Evans rats were injected with either 5mg/kg corticosterone (CORT) or sesame oil vehicle (VEH) once daily for 5 days beginning PND 37(±4) and then allowed to mature into adulthood (>PND 60) undisturbed. Subjects were then trained over 7 days (6 trials/day) in a single-solution water plus-maze task that requires the use of DLS-dependent response learning. In this task, rats were released from different starting positions (i.e. north or

south) and were required to make a consistently reinforced body turn response (i.e. always turn right) at the maze choice point to mount a hidden escape platform. Relative to VEH-subjects, adolescent animals injected with CORT were significantly enhanced in the later acquisition of response learning in the plus-maze during adulthood. These findings suggest that activation of stress pathways in adolescence may have a long-term effect on the use of memory systems in adulthood. The present findings suggest that an enhancing effect on habit memory functions may potentially be part of the mechanism by which early life stress influences later habitual behavior.

Disclosures: T.M. Gadberry: None. **C.A. Bolanos-Guzman:** None. **M.G. Packard:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.11/A56

Topic: A.09. Adolescent Development

Support: Veteran Affairs Career Development Award
Brain and Behavior Foundation NARSAD Young Investigator Award

Title: Age-dependent voluntary ethanol consumption and escalation in a rat model using alcohol vapor self-administration

Authors: *M.-L. RISHER[1,2], H. G. SEXTON[1];
[1]Joan C. Edwards Sch. of Medicine, Marshall Univ., Huntington, WV; [2]Duke Univ. Med. Ctr., Durham, NC

Abstract: Introduction: Binge drinking typically begins in adolescence and is associated with increased risk of developing an alcohol use disorder later in life. The adolescent alcohol research field models binge drinking using number of rat involuntary ethanol (EtOH) administration techniques. However, these methods not provide an opportunity to assess self-initiated EtOH consumption, subsequent escalation, and dependence. Rat self-administration models typically use methods such as sucrose fading to mask the aversive taste of EtOH, however very few result in binge-level consumption within the adolescent timeframe. To address this, we used nose-poke initiated, EtOH inhalation vapor chambers to elucidate how age influences voluntary consumption and escalation. Methods: Adult (PND70) and adolescent (PND30) male Sprague Dawley rats were placed in the vapor chambers every other day for 30 sessions and had the choice of water (H2O) and/or ethanol (EtOH) vapor for 8 HR/day. Blood alcohol levels and general signs of withdrawal were assessed. Anxiety was assessed in the light/dark box after the final EtOH exposure. Results: Across the first 3 sessions, adolescent rats showed equal preference for H2O and EtOH. Throughout the following sessions, adolescent rats showed repeated, self-initiated escalation and de-escalation of EtOH consumption, indicative of binge-

like drinking behavior followed by bouts of withdrawal. Adult rats demonstrated a 70% preference for H2O across the first 4 sessions. Beginning on session 5, adult rats showed a gradual escalation in EtOH preference, plateauing at 70% EtOH preference. Data from the following 20 sessions, impulsivity, anxiety, and withdrawal will also be presented. Conclusion: These data demonstrate that by eliminating the aversive taste of ethanol, adolescent and adult male Sprague Dawely rats will self-administer ethanol. Adolescent rats demonstrate bouts of heavy drinking that may be reminiscent of drinking patterns commonly observed in adolescent and college-age students. Adult rats demonstrate a slower initiation of EtOH consumption and progressive escalation. Ongoing work will continue to dissect the nuances of age-dependent patterns of EtOH consumption and consequences on brain function.

Disclosures: M. Risher: None. **H.G. Sexton:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.12/A57

Topic: A.09. Adolescent Development

Support: AA020024
AA020023
AA011605
AA019767
AA025713

Title: Galantamine prevents adolescent binge ethanol-induced loss of cholinergic neurons, neuroimmune activation, and epigenetic modifications in the adult basal forebrain

Authors: *R. P. VETRENO, F. T. CREWS;
Dept. of Psychiatry, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Binge drinking and alcohol abuse are common during adolescence, and cause lasting cholinergic pathology. Using the preclinical adolescent intermittent ethanol (AIE; 5.0 g/kg, i.g., 2-day on/2-day off from postnatal day [P]25 to P55) model of human adolescent binge drinking, we tested the hypothesis that treatment with the acetylcholinesterase inhibitor galantamine (4.0 mg/kg, i.p. 30-min prior to each EtOH administration) would prevent AIE-induced cholinergic pathology. We report that galantamine treatment from P25-P55 prevented the loss of cholinergic neuron markers (i.e., ChAT, TrkA, and NGFR) and cholinergic neuron shrinkage in the adult (P70) basal forebrain. Recent studies from our laboratory link AIE-induced neuroimmune activation and epigenetic histone methylation modifications to the persistent cholinergic pathology. In the present study, we found increased expression of the proinflammatory nuclear

transcription factor pNF-kB p65 in the adult AIE-treated basal forebrain, which colocalized with ChAT+IR cells, an effect that was prevented in galantamine-treated AIE animals. Further, AIE is associated with increased histone 3 lysine 9 dimethylation (H3K9me2) and trimethylation in the adult basal forebrain, which was prevented with galantamine treatment. Together, these data suggest AIE-induced neuroimmune and epigenetic mechanisms may contribute to the loss of cholinergic neurons in the adult basal forebrain. Galantamine prevention of the persistent AIE-induced loss of cholinergic neurons is a novel therapeutic intervention to ameliorate the persistent adolescent binge ethanol-induced cholinergic pathology. Supported by the NADIA of the NIAAA.

Disclosures: R.P. Vetreno: None. **F.T. Crews:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.13/A58

Topic: A.09. Adolescent Development

Support: Shippensburg University Graduate Research Grant

Title: Effects of WIN 55,212-2 on inhibitory control in adolescent mice

Authors: A. LAUER, ***T. K. LAFFERTY**, R. HALE;
Shippensburg Univ., Shippensburg, PA

Abstract: The purpose of this research was to examine the effect of the synthetic cannabinoid receptor agonist WIN 55,212-2 (WIN) exposure during adolescence on the development of inhibitory control among mice (*Mus musculus*). A total of 40 CD-1 IGS outbred mice were included in the study. Mice in the experimental group received a solution containing 3 mg of WIN per kg of body weight through subcutaneous injection each day, from postnatal day 30 to postnatal day 50. Mice in the control group received a saline solution of a comparable volume. Mice in both the experimental and control conditions were examined on the detour paradigm of animal cognition starting at postnatal day 70. The results revealed a significant difference in weight between groups, with those exposed to WIN weighing less than the control group. On the detour paradigm, the group exposed to WIN performed significantly worse on the habituation phase of the paradigm. During testing of the paradigm, no significant differences were noted between groups on either measures of latency and perseveration. However, significant differences in body weight were present which suggests appropriate dosage techniques.

Disclosures: A. Lauer: None. **T.K. Lafferty:** None. **R. Hale:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.14/A59

Topic: A.09. Adolescent Development

Support: NSERC Discovery Grant
NSERC-CGS M

Title: The behavioural effects of early adolescent lipopolysaccharide administration on adolescent and adult male and female rats

Authors: *I. BISHNOI, M. KAVALIERS, K.-P. OSSENKOPP;
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Abstract: There is accumulating evidence for sex differences in the behavioural, physiological, and immunological effects of infection. Lipopolysaccharide (LPS), a cell wall component of Gram-negative bacteria, has been effectively used to examine these differences. Generally, males are more susceptible to infection than females. However, age-related changes are a contributing factor to the sex differences. As such, it is important to examine sex differences in the susceptibility to infection within the context of various developmental periods. A number of rodent studies have found several behavioural effects upon prenatal and neonatal administration of LPS, particularly in males. Yet, there have been limited investigations of: (1) the impact of adolescent infection, (2) the long-term effects in later adolescence compared to adulthood, and (3) whether or not there are sex differences in these long-term effects. The present exploratory study was designed to examine sex differences in the long-term behavioural effects of LPS measured in late adolescence and adulthood following early adolescent LPS exposure. Thus far, a standard sample size of eight male Charles River rats were assigned to each of the LPS (0.2 mg/kg dissolved in 0.9% NaCl) and vehicle control (0.9% NaCl) groups. The rats received early adolescent intraperitoneal injections on postnatal days 30 and 32. After a five-day washout period, (1) general locomotor activity; (2) anxiety; (3) social behavior; (4) memory; (5) acoustic startle response (ASR); and (6) sensorimotor gating were examined in late adolescence and adulthood. The behavioural tasks were organized from least to most stressful and a single day gap between each task was used to buffer against the stressful effects of the previous behavioural task(s). Physiological tolerance to LPS was established. Early adolescent LPS administration increased locomotor activity in adolescence, decreased anxiety and social initiations in adolescence and adulthood, and had no significant effects on memory, ASR, and sensorimotor gating in male rats. Upon completion of this project through early adolescent LPS exposure in female rats, variations in age and sex will be accounted for to better our understanding of differences in the behavioural effects of LPS in late adolescence and adulthood.

Disclosures: **I. Bishnoi:** None. **M. Kavaliers:** None. **K. Ossenkopp:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.15/A60

Topic: A.09. Adolescent Development

Title: High-sucrose intake in post-weaned rats is associated with morphological and functional changes in the pubococcygeus muscle

Authors: *Y. M. DE LEON RAMIREZ[1], P. PACHECO[2], O. LARA GARCÍA[3], M. A. LARA GARCIA[4], J. ANTOLIN[3], M. MARTINEZ-GOMEZ[5,3], L. NICOLÁS TOLEDO[3];
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Abstract: In humans, obesity is one of the most important health problems due to its considerable increase and tends to remain from childhood to adulthood, producing alterations in metabolism, mainly carbohydrates. Diet rich in carbohydrates, induces endocrine disorders and metabolic syndrome. For instance, leptin levels increase with sucrose consumption in rats and are inversely correlated with testosterone levels. In contrast, increase of lactate levels favors increase of testosterone, this has been poorly studied in reproduction. Obese animals present a deterioration of sexual behavior associated with infertility. It has been described that the pubococcygeus muscle (Pcm) participates in sexual function. In male rats, Pcm participates in micturition and ejaculation. This muscle has a heterogeneous proportion of slow oxidative fibers (type I), rapid oxidative-glycolytic (type IIa/d) and rapid glycolytic (type IIb) fibers. It has been shown that androgens affect muscle weight, muscle fibers size and cross-sectional area of their fibers. These morphological changes correlate with an increase in speed of contraction of the muscle fibers. Moreover, it has been said that this muscle can change its metabolism, since it stores a large amount of testosterone-dependent glycogen. In the present study we explore sugared water consumption effect in early age animals concerning morphological changes through basic ATPase and NADH-TR techniques, and also determine expression of LDH in male rats Pcm. Wistar rats of 21 days-old were divided into 2 experimental groups: Control and experimental (S30). The S30 animals showed an increase in glycolytic fibers but a decrease the oxidative fibers, associated with an increase in leptin levels without affecting testosterone concentration. In addition, they showed a higher expression of LDH. A sucrose rich diet, at young age, has a greater impact on the Pcm, affecting the number of both oxidative and glycolytic fibers. This, may have an impact on male sexual behavior.

Disclosures: **Y.M. De Leon Ramirez:** None. **J. Antolin:** None. **P. Pacheco:** None. **O. Lara García:** None. **M. Martinez-Gomez:** None. **L. Nicolás Toledo:** None. **M.A. Lara Garcia:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.16/A61

Topic: A.09. Adolescent Development

Title: Gestational diabetes mellitus results in cerebral vascular remodeling in the developing brain of offspring

Authors: T. ROGERS, Q. LIU, K. RARICK, *S. S. COHEN;
Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Background Diabetes mellitus during pregnancy (GDM) results in fetal exposure to hyperglycemia and a subsequent relative hypoxia. The cerebral cortex undergoes vascular remodeling to support neuronal function in response to hypoxia. There appear to be two major pathways by which brain angiogenesis occurs: hypoxia-inducible factor-1α (HIF-1α) dependent upregulation of vascular endothelial growth factor (VEGF) and a HIF-1α independent process with upregulation of angiopoietin (Ang)-1 and 2 and tyrosine-protein kinase receptor (TIE)-2. **Objective** To investigate the cortical vascular development in offspring of GDM mothers at infancy and adolescence and measure key proteins that regulate brain angiogenesis. **Design/Methods** Sprague Dawley rats were injected with citrate buffer or streptozotocin (STZ) to induce GDM on gestational day 14. Subsequent maternal glucose was monitored to maintain serum glucose of diabetic rats within 200-400 mg/dl resulting in offspring exposed to hyperglycemic or control conditions. All pups were naturally born and raised by control foster dams. Offspring were sacrificed at postnatal day (P)1 (infancy) and 21 (adolescence). Cerebral cortexes were collected for histology and protein quantification. Frozen sections were processed with lectin to evaluate cerebral vasculature. Protein expression of HIF-1α, VEGF, Ang-1, Ang-2, TIE-2 proteins were measured by Western blot in cortical tissue lysates. Results were compared using student's T-test with significance set at $p < 0.05$. **Results** GDM-exposed offspring rats had higher quantified number of vessels within the cerebral cortex, smaller average size of visualized vessels, yet equivalent total area of vessels compared to controls at P1 (n=1 slide per 8 litters, $p<0.05$). GDM-exposed offspring rats had less number of vessels within the cortex, comparable average size of visualized vessels, and smaller total area of vessels compared to the controls at P21 (n=1 slide per 3 litters, $p<0.05$). Western blot results from P1 show no significant difference in HIF-1α dependent or independent pathway proteins for angiogenesis, but at P21 there were significant decreases in HIF-1α and VEGF protein levels in whole cell lysate from cerebral

cortex (n=8, per age, p<0.05). **Conclusions** This study is among the first to demonstrate that GDM can affect the cortical vascular development of the developing infant brain and suggests that alterations in angiogenesis may persist into adolescence. It also demonstrated these changes are associated with decrease of key angiogenic proteins at adolescence.

Disclosures: T. Rogers: None. **Q. Liu:** None. **K. Rarick:** None. **S.S. Cohen:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.17/A62

Topic: A.09. Adolescent Development

Support: R01 HD090925
Yerkes National Primate Research Center Base Grant (OD P51OD011132)

Title: Emotional reactivity in adolescent male rhesus macaques: The role of puberty on brain and behavioral development

Authors: J. RAPER[1,2], F. KAZI[1,3], A. RATLIFF[1], R. RICHARDSON[1], R. HONG[6], E. MORIN[1], M. PINCUS[1], L. LI[2,7], E. J. FECZKO[8,9], E. EARL[8], D. FAIR[8], ***M. SANCHEZ**[1,4], J. BACHEVALIER[1,5], Z. KOVACS-BALINT[1];
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Abstract: Studies investigating the drastic social, emotional, hormonal and neural changes during adolescence are crucial to understand the emergence of psychopathology during this developmental phase. Increases in pubertal hormones may be responsible for neural remodeling and maturation during adolescence, including reports of increased amygdala (AMY) activity and changes in its connectivity with the prefrontal cortex (PFC). The goal of this study was to investigate changes in emotional responses toward stressors from pre- to peri-puberty, and underlying changes in PFC-AMY circuitry in a translational non-human primate model.Data were collected from 3 male macaques during pre-puberty (~24 months) and early adolescence (~32 months). Testicular volume was used to establish pubertal stage, while the Human Intruder Task (HIT) was used as an acute stressor to measure emotional reactivity. Structural and resting-state functional MRI (rsfMRI) scans were acquired at both ages using a 3T MRI scanner to examine developmental changes in functional connectivity (FC) between AMY and medial PFC across pubertal stage. We hypothesized that pubertal status would be associated with the

developmental changes in emotional reactivity and in underlying PFC-AMY FC.Testicular volumes increased from pre- to peri-puberty, but the magnitude of increase showed high individual variability. The results showed that increased testicular volumes from pre- to peri-puberty were associated with (1) enhanced fear (freezing) and declined hostile behaviors, and (2) increased FC between medial PFC and AMY and between right and left AMY. Thus, despite individual variability in behavioral reactivity and PFC-AMY FC at each age, pubertal status seemed to better account for the individual differences than chronological age. As our sample size increases with the addition of a second cohort of 7 animals, and more longitudinal timepoints are collected from peri-puberty to adulthood, stronger statistical power will allow to formally test the effect of pubertal maturation on emotional regulation and neural development. We expect that as neural circuits critical for emotional and stress regulation (PFC-AMY) become more mature and show stronger connectivity during late adolescence, behavioral reactivity (e.g. freezing) will be reduced due to top-down modulation of AMY reactivity by the PFC. To further understand the role of pubertal stage on stress reactivity and emotion regulation, future studies will also examine the relationship between gonadal hormone concentration (Testosterone) and cortisol release during HIT.

Disclosures: **J. Raper:** None. **F. Kazi:** None. **A. Ratliff:** None. **R. Richardson:** None. **E. Morin:** None. **M. Pincus:** None. **L. Li:** None. **E.J. Feczko:** None. **E. Earl:** None. **D. Fair:** None. **M. Sanchez:** None. **J. Bachevalier:** None. **Z. Kovacs-Balint:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.18/A63

Topic: A.09. Adolescent Development

Support: R01AA026347

Title: Adolescent binge ethanol slows oligodendrocyte maturation through regulation of histone methylation in the PFC

Authors: E. BLAY, R. E. STEVENSON, A. C. PAIS, *J. T. WOLSTENHOLME;
Pharmacol. and Toxicology, Virginia Commonwealth Univ., Richmond, VA

Abstract: Alcohol use in teens primarily occurs in binges, often begins at a young age, and is associated with cognitive impairments, decreased white matter content, and structural changes in the brain. Ongoing frontal cortex myelination during this developmental period may make these adolescent drinkers particularly vulnerable to long-term consequences of binge ethanol. However, the molecular mechanisms underlying ethanol-induced myelin deficits in prefrontal cortex (PFC) development are not fully understood. Recently, we reported immediate and long-

lasting transcript changes in the PFC following adolescent binge ethanol; myelin-related genes and genes that regulate H3K9 methylation were decreased in the PFC. H3K9 tri-methylation (H3K9me3) is a stable repressive mark primarily found in heterochromatin and is associated with the development of oligodendrocyte precursors into mature, myelin-forming oligodendrocytes. Given that binge ethanol decreased lysine demethyases specific for H3K9 methylation, this may be a potential mechanism through which ethanol decreases myelin expression in the frontal cortex. To uncover the immediate adaptive and maladaptive responses during the course of adolescent binge ethanol, we dosed male and female DBA2/J mice with binge-levels of ethanol (4g/kg, i.g.) intermittently from PND 29-42. Tissue from the frontal cortex was collected at four time points during the course of binge ethanol administration: 24 hours after 1 binge at PND 30, after 4 binges at PND 35, after 8 binges at PND 43 and 3 weeks after the last binge to assess persistence of these transcriptional changes. Oligodendrocytes were enriched from frontal cortex and compared to bulk PFC for expression of oligodendrocyte maturation markers at each age by qPCR. We also tracked changes in genes responsible for depositing and removing methyl groups from H3K9me3 during the course of binge ethanol treatments. Together, these results will be the first to quantify changes in oligodendrocyte maturation during adolescent ethanol binges in male and female mice and link these changes to an epigenetic mechanism for how ethanol disrupts oligodendrocyte maturation in the frontal cortex. *Supported by NIAAA R01AA026347 to JTW.*

Disclosures: E. Blay: None. **R.E. Stevenson:** None. **A.C. Pais:** None. **J.T. Wolstenholme:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.19/A64

Topic: A.09. Adolescent Development

Support: CAPES/PROSUP 001

Title: Reduction of litter size induces overweight, depressive-like behavior, and increases IL-1β plasma levels in juvenile rats

Authors: *A. S. SAMPAIO, T. M. LIMA, P. S. RODRIGUES, N. A. SANTOS, L. M. SILVA, M. C. GALVÃO, K. E. KIATAQUI, T. M. REIS-SILVA, N. MOREIRA, I. B. SUFFREDINI, T. B. KIRSTEN, M. M. BERNARDI;
Envrn. and Exptl. Pathology, Paulista Univ., Sao Paulo, Brazil

Abstract: Overweight and obesity disorders are considered worldwide epidemics, which predispose the individual to numerous diseases. In the last three decades, its incidence has

increased intensively among the population, however, this growth has been greater among children. The objective of this study was to evaluate the effects of overnutrition during lactation on weight gain, depressive-like behavior, and immune mediators of juvenile male Wistar rats. On postnatal day (PND) 2, the experimental group (EG) litters were reduced to 3 males and 1 female, whereas the control group (CG) remain with its standard distribution of 4 males and 4 females per litters of. Body weight during the PND 2, 9, 21, and 31 was collected to calculate the weight gain. On PND 31 the rats were submitted to the forced swimming test and immediately euthanized for blood samples collection for pro-inflammatory cytokines and corticosterone evaluation. For the statistical analysis with more than two variables, a two-way ANOVA was performed followed by the Tukey post hoc test when pertinent. Student's t test was used for analysis with only one variable. The behavioral results indicate that the EG presented increased weight gain [$F(1.30) = 5.074$, $p = 0.03$] between PNDs 9 and 21, increased immobility ($p=0.0497$) and climbing time ($p=0.0319$) as well as increased latency for first immobility ($p=0.0003$) in the forced swimming test. The EG also presented increased IL-1β levels compared to CG ($p=0.0390$). In conclusion, reduction of litter size induced overweight, depressive-like behavior, and increased IL-1β plasma levels in juvenile rats. Together, these results may indicate a possible inflammatory process induced by the overnutrition during lactation, which resulted in behavioral and immune impairments in juvenile rats. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES/PROSUP) - Finance Code 001

Disclosures: **A.S. Sampaio:** None. **T.M. Lima:** None. **P.S. Rodrigues:** None. **N.A. Santos:** None. **L.M. Silva:** None. **M.C. Galvão:** None. **K.E. Kiataqui:** None. **T.M. Reis-Silva:** None. **N. Moreira:** None. **I.B. Suffredini:** None. **T.B. Kirsten:** None. **M.M. Bernardi:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.20/A65

Topic: A.09. Adolescent Development

Support: R01MH098003
RF1MH114224
R01NS085200

Title: Reorganization of dynamic connectivity patterns during brain development in awake rats

Authors: *Z. MA, Y. MA, N. ZHANG;
The Penn State Univ., University Park, PA

Abstract: Childhood and adolescence are both phases characterized by rapid social, emotional, and cognitive growth. During these transition periods, the brain undergoes a complex and dynamic maturational process that contains multiple stages. These stages are marked by notable neuronal changes such as myelination of axons, synaptic pruning. In addition, cell morphology, neural transmitter and receptor density also change drastically during early brain development. Protracted development during childhood and adolescence makes the brain particularly vulnerable to adverse early-life experience. In fact, neuropsychiatric disorders often emerge during childhood and persist across the lifespan. Therefore, understanding postnatal brain development is crucial for uncovering brain function in health and disease. Recent work and literature in our lab has demonstrated characteristics of brain functional connectivity change during development. However, brain connectivity undergoes dynamic changes during development. However, how dynamic patterns of functional connectivity links with maturation process of brain at system level remains unclear. To bridge this gap, we further investigated our resting state fMRI data.
To comprehensively trace the developmental changes of dynamic functional connectivity pattern, we longitudinally acquired rsfMRI data in awake rats during five developmental stages: juvenile (P30-P31), early adolescence (P34-P35), adolescence (P41-P42), late adolescence (P48-P49) and adulthood (P70-P90). We analyzed data using a dynamic approach that combines sliding window method and k-means clustering. We discovered that the whole brain connectivity architecture contains several patterns that occurs across several age groups. Specifically, patterns that involves stronger connections between polymodal association areas are strongly biased toward older ages, as well as patterns involves stronger within-system connections have a higher occurrence rate at younger age.

Disclosures: **Z. Ma:** None. **N. Zhang:** None.

Poster

550. Animal Models II

Location: Hall A

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Program #/Poster #: 550.21/A66

Topic: A.09. Adolescent Development

Support: RO1 Grant DA034185
RO1 Grant MH101183
F32 Grant DA043308

Title: Adolescent morphine exposure has long term, sex-specific effects on social behavior

Authors: *C. FIGUEROA[1], S. D. BILBO[2], A. M. KOPEC[1];
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Abstract: Brain regions involved with reward processing undergo sex-specific development during adolescence, which contributes to social behavior development in rats (Kopec et al. 2018). Morphine exposure during adolescence has long term effects on addiction-related behaviors in male rats (Schwarz et al. 2012), but the effects of adolescent morphine exposure on social behavior in adulthood, and whether they are sex-specific, are largely unstudied. To investigate this, we exposed male and female rats to morphine during different stages of adolescent development, early adolescence (postnatal day (P)31-35), mid-adolescence (P39-43), or late adolescence (P55-59), and then assessed social and anxiety-like behaviors in mature adulthood (~P90). In the sociability task (novel social vs. novel object stimulus), there were no differences in time spent in either the social or object chambers. However, male rats exposed to early and mid-adolescent morphine had significantly decreased exploration of the novel social stimulus compared to drug-naïve age-matched control rats. In the social novelty preference task (novel social vs. familiar social stimulus), early adolescent morphine-treated males demonstrated a trend toward ($p=0.056$) decreased exploration of the novel stimulus, but no differences in time exploring the familiar stimulus nor in time spent in either chamber. These preliminary data suggest that early adolescent morphine exposure may cause anxiety-like behaviors in male rats, but interestingly no differences were observed for these behaviors in open field. Females showed no behavioral differences in any task assessed. Altogether, our data suggest that early adolescent morphine exposure causes avoidance of novel social stimuli without affecting overall preference for social interaction, specifically in male rats. Social avoidance is a common symptom of social anxiety disorder (SAD), which is often comorbid with other anxiety and affective disorders (Toth et al. 2013). Lack of treatment effects in open field behavior indicates that anxiety may be induced specifically by novel social stimuli as opposed to generalized anxiety. In male rats, the nucleus accumbens reward region undergoes dopamine 1 receptor (D1r) pruning during early adolescence, while female D1r regulation occurs at a different developmental stage and via different mechanisms (Kopec et al. 2018). Since dopamine signaling is a key regulator of social behavior in rats (Steinman et al. 2018), in future studies we will explore the possibility that early adolescent morphine exposure alters D1r pruning in males, but not females, potentially producing SAD-related behaviors in adulthood.

Disclosures: C. Figueroa: None. **A.M. Kopec:** None. **S.D. Bilbo:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.22/A67

Topic: A.09. Adolescent Development

Title: Interactions of sex and reduced dopamine transporter expression on social play

Authors: *H. T. TRAN[1], B. DEMARCO[1], F. S. HALL[2];
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Abstract: Social isolation during adolescence leads to long-term behavioral deficits in adulthood. Many of these behavioral changes have been described as pathological in nature and include symptoms that resemble aspects of mood disorders, anxiety disorders, and autism spectrum disorders (ASD). These outcomes are neurodevelopmental in nature, resulting only from social isolation at this age, and are not reversed by later socialization. Other factors that influence social play may impact the consequences of social isolation. Dopamine has a role in social play, and the dopamine transporter (DAT) regulates extra-synaptic dopamine levels. Sex differences in social play may also influence the developmental consequences of social experiences. A 24-hr period of social isolation increases motivation for play and was used to study play in DAT +/+ and DAT +/- knockout mice. Methods: Male and female, DAT +/+ and DAT +/- mice were isolated for a 24-hr period, between 28 and 35 days of age, or remained in social housing. After this time, socially-housed mice were introduced to a novel cage for 10 min before a novel, non-sibling isolated mouse was introduced to the cage. Social and non-social behaviors were scored by an observer, and ultrasonic vocalizations (USV) were recorded. Results: Effects on Social behavior were observed to result from isolation, sex and genotype. Isolation: Grooming was increased by isolation, indicative of anxiety. Withdrawal (abrupt leap away from an approaching mouse) was observed only in isolated female WT Mice. Following was increased in isolated mice, but only in females. Rearing was reduced by isolation, except in female DAT +/- mice. Sex: Nose-to nose sniffing and anogenital sniffing was lower in females. Genotype: dorsal pins were reduced in male DAT +/- mice, but females showed a complex interaction between sex, genotype, and isolation. Increased USV was associated with social behavior. Conclusions: Social isolation increased social approach, but simultaneously induced anxiety, particularly in female mice. Distinct sex differences were particularly seen in certain behaviors as well, while other affected by reduced DAT expression in a sex dependent manner. These data suggest that sex and genotypic differences in the long-term effects of social isolation may result from alterations in social behavior tendencies, and consequent differences neural activation resulting from the altered experiences. Ongoing studies examine the initial neural responses to social experiences after a short period of isolation. It is thought that understanding of these neurodevelopmental processes will provide insight into ASD and associated conditions.

Disclosures: H.T. Tran: None. **B. Demarco:** None. **F.S. Hall:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.23/A68

Topic: A.09. Adolescent Development

Support: NIH grant P50AA017823

Title: Female adolescent Sprague Dawley rats display blunted central and peripheral cytokine responses following an acute stress challenge

Authors: *P. MARSLAND[1], A. PARRELLA[1], A. S. VORE[1], T. DEAK[2];
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Abstract: Adolescence is a unique developmental stage in which extensive physiological and cognitive development occurs, creating a critical period of developmental vulnerability. Recent studies in adolescent rodent models have demonstrated that adolescents demonstrate reduced reactivity to pharmacological challenges that evoke a substantial neuroimmune response, including acute alcohol (ethanol) and lipopolysaccharide administration (Doremus-Fitzwater et al., 2015). Furthermore, repeated ethanol administration during adolescence produced long-lasting changes in neuroimmune function, reminiscent of a “locking-in-like” effect of the adolescent neuroimmune phenotype (Vore et al., 2017; Gano et al., 2019). The goals of the present experiment were to (a) test whether reduced neuroimmune reactivity among adolescents would be observed in female rats; and (b) assess whether this neuroimmune insensitivity would generalize to a (non-pharmacological) stress challenge (footshock). To do this, female adolescent (P29-33) and adult (P70-80) Sprague Dawley rats were exposed to intermittent footshock (1 mA, 5 sec each, 90 sec variable inter-trial interval) for 1 hour, 2 hours, or 2 hours and a 2-hour recovery period to assess the kinetics of cytokine induction by stress. Cytokine gene expression was analyzed in the paraventricular nucleus of the hypothalamus (PVN), the medial amygdala (MeA), and the ventral hippocampus (vHPC) using RT-PCR. In addition, spleens were analyzed for cytokine protein expression via multiplex protein analysis. As expected, adolescent females displayed evidence for functionally reduced cytokine expression evoked by footshock. IL-1β was significantly increased in adult females following 1- and 2-hours of footshock in the PVN and MeA, but not in adolescent females. c-FOS gene expression was also elevated in both adolescent and adult females in the PVN during 1- and 2-hours of footshock, but adolescents displayed blunted expression when compared to adults. Protein analysis in the spleens revealed that adult females, but not adolescents, display increased IL-1α following 1- and 2-hours footshock. Similarly, IL-1β protein expression was elevated in adult females following 2-hours of footshock, but not in adolescents. Taken together, these results indicate that reduced

neuroimmune reactivity appears to be a common feature of adolescents that generalizes to non-pharmacological challenges such as footshock. This functionally immature immune response to stress among adolescents may contribute to later development of stress-related pathology.

Disclosures: P. Marsland: None. **A. Parrella:** None. **A.S. Vore:** None. **T. Deak:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.24/A69

Topic: A.09. Adolescent Development

Support: NIAAA Grant P50AA017823-08
NIAAA Grant AA025606

Title: Individual differences in brain activation following ethanol-induced social facilitation and inhibition among cFos-LacZ transgenic rats

Authors: *T. T. TOWNER[1], E. I. VARLINSKAYA[2], D. F. WERNER[3], L. P. SPEAR[4];
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[4]Ctr. For Develop. and Behavioral Neurosci., Binghamton, NY

Abstract: Adolescence is a developmental period during which increases in risk taking, novelty seeking, and drug experimentation occur. In adolescence, alcohol consumption typically takes place in a social setting, with the subjective feeling of alcohol's stimulant and sedative effects in such social contexts likely contributing to drinking behavior. Individual differences in both the physiological and subjective responses to alcohol impact vulnerabilities to later alcohol abuse, and have been recently assessed in animal models of social behavior. Previous work has shown that adolescent rats acutely challenged with ethanol display individual differences in their response to 0.75 g/kg ethanol ranging from marked increases in social behavior evident in some and inhibition in others. The aim of the current study was to examine ethanol-induced changes in social behavior following escalating doses of ethanol and differences in brain activation between animals that respond to ethanol via increases in social behavior versus social inhibition. Thirty-four adolescent male transgenic cFos-LacZ rats on a Sprague-Dawley background (postnatal day [P] 30 at beginning of testing) were assessed in a modified social interaction test. Social testing occurred under baseline no-injection conditions (P30), following a saline injection (P32), as well as after injection of 0.5 g/kg (P34) and 0.75 g/kg (P36) ethanol. Changes in social behavior following administration of the 0.75 g/kg ethanol dose relative to saline were calculated, and a tertile split was used to distinguish animals that responded to ethanol with social facilitation from those that were socially inhibited by the same ethanol dose. Following the final social interaction test on P36, animals were perfused and brains collected for beta-galactosidase staining. Brain

regions examined were the prefrontal and orbitofrontal cortices, nucleus accumbens, lateral septum, and amygdala. Social behavior was increased by 0.5 g/kg dose, whereas following the dose of 0.75 g/kg ethanol, some animals were socially facilitated and others were inhibited socially. Beta-galactosidase staining, a proxy for cFos activation, revealed significant increases in the nucleus accumbens shell as well as decreases in the prefrontal cortex among socially facilitated animals relative to their socially-inhibited counterparts. These findings demonstrate that individual behavioral differences in responding to ethanol indexed by the notable split between ethanol-induced social facilitation and inhibition are accompanied by differences in neural ensemble activation in the prefrontal cortex and accumbens shell.

Disclosures: T.T. Towner: None. **E.I. Varlinskaya:** None. **D.F. Werner:** None. **L.P. Spear:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.25/A70

Topic: A.09. Adolescent Development

Support: NIH NS022061

Title: Influence of developmental nicotine exposure on cholinergic circuits engaged in fear/threat memory

Authors: *J. A. WILKING[1], N. S. DESAI[4], D. A. TALMAGE[2], L. W. ROLE[3];
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[4]Circuits, Synapses, and Mol. Signaling Section, NINDS, Bethesda, MD

Abstract: Nicotine use during pregnancy is the most preventable risk factor associated with adverse fetal outcomes including cognitive deficits and later increased substance abuse. Additionally, approximately 80% of smokers initiate tobacco use during adolescence, suggesting the age of nicotine exposure plays a critical role in the developing brain and the cholinergic system. Further prior smoking history is a predictor of increased vulnerability to post traumatic stress (PTSD) and panic disorder following a traumatic event, and smoking rates increase after a trauma. 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 which 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, endogenous acetylcholine (ACh) induces synaptic plasticity in the BLA, and this effect requires nicotinic acetylcholine receptors (nAChRs). We predict nicotine exposure during

development increases fear learning which is long lasting. To test this prediction, we exposed (a) pregnant C57BL/6J dams from embryonic day 14 (E14) to postnatal day 21 (P21); (b) adolescent C57BL/6J animals from P21 - P42 to 200 µg/ml nicotine (plus Splenda in their drinking water), Splenda alone, or water. Animals were then tested for cued conditioned fear/threat learning. To date when animals are tested immediately after prenatal exposure the Splenda only animals exhibit decreased freezing compared to water controls and nicotine + Splenda treated animals. When animals were tested 21 days after cessation of nicotine and/or Splenda treatment, the nicotine + Splenda group showed a sustained increase in cue conditioned freezing. The surprising short term effects of Splenda will be explored further. Additional treatment x sex interactions are present during both training and recall. We have not seen effects of adolescent nicotine (or Splenda) exposure on threat learning. To determine potential cholinergic circuit modifications following early chronic nicotine exposure we are assessing intrinsic excitability and synaptic transmission using whole cell patch recordings from BLA principal neurons in slices following recall.

Disclosures: **J.A. Wilking:** None. **N.S. Desai:** None. **D.A. Talmage:** None. **L.W. Role:** None.

Poster

550. Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.26/A71

Topic: A.09. Adolescent Development

Support: NIH Grant R25 GM061838
NSF Grant OISE-#1545

Title: Isolation stress during adolescence on anxiety-like behavior and conditioned place preference to cocaine

Authors: *E. U. PÉREZ-CARDONA, A. C. SEGARRA;
Dept. of Physiol., Univ. of Puerto Rico, Med. Sci. Campus, San Juan, PR

Abstract: Adolescence is a sensitive developmental period in human beings characterized by sexual maturation and continuing brain development. Chronic stress during adolescence, as abandonment and social isolation, interferes with maturation of higher brain functions such as decision making, learning and memory; leading to behavioral alterations and mental illness. Rats are social animals, and thus serve as an animal model to investigate the consequences of isolation during adolescence on the development of anxiety-like behaviors and the rewarding response to cocaine. Male and female rats were either housed in groups of the same sex or single housed from weaning (postnatal day 21) until the end of the experiments. At day 34 rats were tested for anxiety-like behavior with the Elevated Plus Maze. From day 35 to day 48 their contextual

associated memory to cocaine (15 mg/kg) was assessed using the Conditioned Place Preference (CPP) paradigm. Our results indicate that male rats reared in isolation during adolescence spend more time in the closed arm than grouped housed rats. A similar trend was observed in the females. Grouped housed and isolated rats (females and males) showed CPP to cocaine when tested during days 35 to 48, however, no differences were observed between isolated and grouped housed rats. These results show that isolation increases anxiety in adolescent male rats, and that does not alter the rewarding properties of cocaine.

Disclosures: E.U. Pérez-Cardona: None. **A.C. Segarra:** None.

Poster

550. Animal Models II

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 550.27/A72

Topic: A.09. Adolescent Development

Support: NIH Conte Center P50MH112491
Dauten Family Foundation
Stanley Center/Broad Institute
HHMI

Title: Mapping prefrontal cortical development over adolescence in mouse

Authors: *K. J. MASTRO[1,3,4], C. WILLING[1], W. WANG[4], L. STANWICKS[3], B. SABATINI[4,5], B. A. STEVENS[2,5];
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Abstract: The prefrontal cortex (PFC) is critical for cognitive functions, like working memory and flexibility, and has been implicated in the pathogenesis of cognitive dysfunction in psychiatric disease. Onset for many psychiatric disorders occurs during adolescence and suggests alterations to the development of PFC, but our understanding of how PFC matures remains unclear. Unlike that of sensory cortices, data from human imaging and human post mortem tissue suggests that the development of PFC extends through adolescence, a developmental critical period that parallels the development of cognitive control. To understand how psychiatric disease risk genes and environment shape this developmental trajectory, we must first establish what is normal. Here, we employ a range of anatomic and electrophysiological techniques to map spatiotemporal changes to PFC inputs in the mouse. To track the development of excitatory synapses, we performed slice electrophysiology and recorded miniature excitatory postsynaptic currents across weeks of postnatal development. We found that the frequency and amplitude of these excitatory events undergo a prolonged change until reaching their stable state in adulthood.

To understand how different sources of excitatory inputs are changing over the same period, we used immunohistochemical approaches to track the density and localization of inputs across cortical layers. Consistent with our physiology results, we found that excitatory inputs are increasing dramatically during the early phases of postnatal prefrontal development, but greater subcircuit resolution is necessary. Currently, we are using virally delivered optogenetics to parse the distinct developmental timelines of specific prefrontal subcircuits. In doing so, we are examining how specific components of synaptic connectivity, including strength and impact on the local microcircuitry (e.g. feedforward inhibition) are changing over the course of adolescence. Together, these results provide a detailed timeline of how excitatory inputs to the PFC mature across the full adolescent window, and provide both the baseline and targets for perturbations to genes and environment.

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Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 551.01/A73

Topic: A.10. Development and Evolution

Support: UIW Office Undergraduate Research

Title: Photoreception in Lumbriculus variegatus, an aquatic annelid

Authors: *M. VARGAS[1], J. SCOTTY[2], C. L. BAER[3], C. R. FLORES[3], E. L. CAIN[3], V. G. MARTINEZ ACOSTA[1];
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Abstract: *Lumbriculus variegatus,* an aquatic annelid, is capable of complete regeneration from a few body segments (Martinez et al., 2006). In this study, we present an investigation of photoreception in Lumbriculus. In annelids, there are three different types of photoreceptors: rhabdomeric, ciliary, and phaosomous sensory cells. Photoreceptors are present in cerebral ocelli, in ectopic ocelli, and eyes situated in different places in photoreceptor-like sense organs. *Lumbriculus* is thought to possess photoreceptors within its posterior-most segments, as rapid tail withdrawals are evoked when a shadow is cast over the water column. Initial studies describe that Lumbriculus possesses large phaosomal photoreceptors that lie directly below the epithelial layer (Drewes and Fourtner 1989). Using a simple phototactic assay we set out to determine the range of wavelengths that result in a behavioral response. Preliminary data suggest that Lumbriculus negatively phototaxis away more strongly from red light when compared to that of

white, UV, green, or blue light respectively (*n=25; UV 36±15.01s, G: 43.6 ±29.3s, B: 48.4±24.6s, R: 31.2±12.1s, W: 34.3±12.07s*). Candidate sensory receptor cells identified at present include cells with low concentration pigmentation that are found adjacent to axonal connections that project to cell bodies found within the muscle wall. Further characterization of the photoreceptor system using transmission electron microscopy will elucidate more clearly the ultrastructural arrangement of the photoreceptors within the posterior-most segments that mediate the rapid escape tail responses previously detected. Candidate opsin sequences were determined using a newly synthesized Lumbriculid transcriptome. Phylogenetic analysis comparing two different r-opsin sequences from *Platynereis dumerilii* and *Homo sapien*s resulted in a predicted r-opsin sequence for Lumbriculid Opsin 4 (LumVa Opsin 4). Primers developed against the LumVa r-opsin successfully amplified a 1332 bp pcr product. TOPO-TA cloning step has been performed and colonies are currently being screened to isolate clones containing the most complete LumVa Opsin 4 product. Lastly, immunohistochemical analysis of the G-protein-alpha subunit, G-α q/11/14, previously described to be involved in phototransduction in other annelids and invertebrates, will be utilized to elucidate the structural arrangement of the receptors within the tail segments and subsequent mechanism of their phototransduction. Overall, this research will add to the body knowledge we currently understand regarding the evolution of photoreception in metazoans.

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Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 551.02/A74

Topic: A.10. Development and Evolution

Support: NSF 1656628

Title: Nervous system evolution: A molecular genetic characterization of neural cell types in S. kowalevskii

Authors: *J. M. ANDRADE LOPEZ[1], A. M. PANI[2], P. J. MINOR[1], C. J. LOWE[1];
[1]Biol., Stanford Univ., Stanford, CA; [2]Biol., Univ. of North Carolina, Chapel Hill, Chapel Hill, NC

Abstract: Hemichordates are a key deuterostome phylum for understanding the evolution of the chordate CNS. Their nervous system is organized around two elements; a pervasive nerve plexus concentrated anteriorly, and two nerve cords; one dorsal and one ventral. Despite the major organizational differences between the nervous system of hemichordates and vertebrates, they

share a well-conserved gene regulatory network for anterior-posterior patterning. It is still unclear whether any of this conserved pattern regulates fundamental similarities in neural cell type specification. I will present data on the spatiotemporal expression of neural markers, including genes involved in neurotransmitter synthesis and transport by in situ hybridization, to determine the level of regional specialization of the neural plexus and nerve cords in juvenile *S. kowalevskii*. These data also facilitate more direct neural comparisons with chordates. I will also present data using a meganuclease, a transposon-mediated approach, to generate transgenic animals expressing GPF in a subset of neurons. These experiments facilitate an analysis of the identity and location of specific neural cell bodies, and also neuronal morphology and connectivity, to better understand the structure and function of this nervous system. We have generated constructs to label neurons using pan-neural (synapsin, elaV, Syt1), cell type specific markers (GAT, TH), and an endogenous synaptic vesicle protein, synaptotagmin, to label synapses. I will present a preliminary analysis of these data and their impact on our understanding of the comparative relevance of hemichordate nervous systems to broader questions of nervous system evolution. This work will give insights into the evolution of deuterostomes and the origins of the vertebrate brain, but also the evolution of bilaterian nervous systems.

Disclosures: **J.M. Andrade Lopez:** None. **A.M. Pani:** None. **P.J. Minor:** None. **C.J. Lowe:** None.

Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 551.03/A75

Topic: A.10. Development and Evolution

Title: Radial glial cells coexpress DCX and GFAP in the adult turtle brain and early embryonic mouse brain

Authors: *A. J. NAPOLI[1], A. S. POWERS[1], S. GE[2];
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Abstract: Radial glial cells (RGCs), a population of neural stem cells, disappear from the cortex of mammals after development, enduring in adult neurogenic niches. However, in vertebrates that exhibit pervasive adult neurogenesis (AN), such as reptiles, RGCs persist in all regions of the telencephalon throughout life, providing a source of neural stem cells and a mechanism for migration and integration. As RGCs also give rise to glial progeny, the mechanism underlying the fate specification remains largely unknown.
Non-mammalian vertebrates are capable of pervasive AN, and many have demonstrated the ability to repair injury to the telencephalon. These vertebrates may retain, as adults, molecular

processes thought to be exclusively developmental in mammals, and which may allow for rebuilding of the brain. Some mechanistic studies have revealed that glial fibrillary acidic protein (GFAP) is expressed in RGCs. Doublecortin (DCX) is thought to be expressed exclusively in immature neurons. The expression profiles of GFAP and DCX in RGCs and their progeny have been mostly described based on mammalian adult neurogenic niches, in which sequential, not concurrent, expression has been shown. GFAP is expressed in RGC, followed by DCX expression in neuroblasts. However, whether the unique circumstances of adult mammalian AN are reflective of the developmental state is unknown.
In this study we first assessed the expression of GFAP and DCX in RGCs in the telencephalon of adult turtles (*Chrysemys picta*) using immunohistochemistry. Surprisingly, GFAP and DCX were robustly co-expressed in the RGCs, suggesting their potential role in cell fate specification. Importantly, after telencephalic lesions, we found elevated expression of both GFAP and DCX, further suggesting their regulatory roles in differentiation. We extended the investigation to the developing mammalian brain and found that, at mouse embryonic day 13, RGCs also coexpress GFAP and DCX in the cortex, but this co-expression is lost by embryonic day 15.
DCX has traditionally been thought of as a marker of immature neurons, although recent work has demonstrated its expression in putative astrocytes during ischemic injury, which may harken back to their RGC ancestry and RGC responsiveness to injury signals. Although temporal and spatial co-expression of GFAP and DCX in RGCs had not been previously demonstrated, current work may help elucidate their molecular mechanisms in the developing cortex and subsequent implications for neural regeneration and repair.

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

Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 551.04/A76

Topic: A.10. Development and Evolution

Title: Identifying common genetic variants that influence Wnt signaling and proliferation in human neural progenitor cells

Authors: *J. M. WOLTER[1], B. LE[2], D. LIANG[2], M. J. LAFFERTY[2], K. COURTNEY[5], A. ELWELL[3], J. PIVEN[4], M. J. ZYLKA[1], J. L. STEIN[6];
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Abstract: An increase in the neural progenitor pool, present almost exclusively during fetal development, is a well-described mechanism that can lead to expansion of neocortical surface

area. Numerous autism-linked mutations affect genes involved in Wnt signaling, a pathway that regulates neural progenitor proliferation. In addition, common genetic variants near Wnt-pathway genes are associated with changes in cortical surface area in adults. Here, we test the hypothesis that common genetic variation modulates proliferation and Wnt signaling in human NPCs, and assess the degree of overlap with variants contributing to brain structures and autism risk. To achieve this, we utilize a library of 94 human neural progenitor cell lines derived from developing cortical tissue, which have previously undergone genome-wide genotyping, RNA-seq, and ATAC-seq. In these lines, we quantify sensitivity to three Wnt modulators (CT99021 - a highly selective GSK3B inhibitor, lithium chloride, valproic acid) at several concentrations using a Wnt sensitive transcriptional reporter (beta-catenin activated reporter). We also measure how these compounds effect proliferation rates using a DNA dye and EdU incorporation assay followed by flow cytometry. We observe dose dependent increases in Wnt signaling and proliferation in response to CT99021 and LiCl. In contrast, less than 5% of NPC lines responded to valproic acid using the reporter assay. VPA also decreased proliferation in all lines. We observe significant variation in inter-individual responsiveness to Wnt activation. Responsiveness also correlates to expression levels of key Wnt genes, including beta-catenin and Wnt ligands. While biological factors, such as gestational age and sex, do not detectably influence Wnt sensitivity, we do detect an effect of gestational age on proliferation. Ongoing experiments include, completing an association study for the remaining drugs and assays, identifying caQTLs that correlate with Wnt responsiveness, and assessing pleiotropy between variants that alter these cellular phenotypes, cortical surface area, and autism risk. Overall, this approach is designed to draw mechanistic connections from common genetic variants to molecular and cellular phenotypes to adult brain structure and disease relevant loci.

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Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 551.05/A77

Topic: A.10. Development and Evolution

Support: NIH NINDS R25NS095377

Title: Transcriptomic evidence that von Economo neurons are regionally specialized extratelencephalic-projecting excitatory neurons

Authors: ***J. A. MILLER**[1], R. D. HODGE[1], M. NOVOTNY[2], B. E. KALMBACH[1,4], J. T. TING[1,4], T. E. BAKKEN[1], B. D. AEVERMANN[2], E. R. BARKAN[1], M. L. BERKOWITZ-CERASANO[5], C. COBBS[6], F. DIEZ-FUERTES[2], S.-L. DING[1], J. MCCORRISON[2], N. J.

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Abstract: Von Economo neurons (VENs) are bipolar, spindle-shaped neurons restricted to layer 5 of human frontoinsula and anterior cingulate cortex that appear to be selectively vulnerable to neuropsychiatric and neurodegenerative diseases, although little is known about other VEN cellular phenotypes. Single nucleus RNA-sequencing of frontoinsula layer 5 identified a transcriptomically defined cell cluster that contained all VENs and fork cells, but also a subset of neurons with pyramidal morphologies. Cross-species alignment of this cell cluster with a well-annotated mouse classification shows strong homology to subcortically projecting extratelencephalic (ET) excitatory neurons. This cluster also shows strong homology to a putative ET cluster in human temporal cortex, but with a strikingly specific regional signature. Together these results predict VENs are a regionally distinctive type of ET neuron, and we additionally describe the first patch clamp recordings of VENs from neurosurgically resected tissue that show distinctive intrinsic membrane properties from neighboring pyramidal neurons.

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Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 551.06/A78

Topic: A.10. Development and Evolution

Support: NINDS
NIMH
CCXDP
HDF

Title: Identification of mouse and human Ppp1r1b/DARPP-32 striatal-specific enhancers

Authors: *M. D. CIRNARU[1], C. CORWIN[1], **J. CREUS-MUNCUNILL**[1], M. AUDRAIN[1], J. FULLARD[2], P. ROUSSOS[2], M. E. EHRLICH[1];
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Abstract: Background: DARPP-32 (dopamine and cyclic AMP-regulated phosphoprotein, 32 kDa), encoded by the PPP1R1B gene, is expressed in almost all medium spiny neurons (MSN), where it is a key modulator of neurotransmitter signal transduction, particularly dopamine. Enhancer sequences which contribute to cell-specific transcription specify cell identity and differentiation, may contribute to disease, e.g. Huntington's disease. We sought to identify Ppp1r1b MSN-specific cis-regulatory elements (CREs) in mouse and human. **Method:** We used transgenic deletion analysis to identify the Ppp1r1b mouse enhancer and ATAC-seq to identify the human enhancer (Fullard et al., 2018). The activity of the human enhancer was also validated via transgenesis in mouse. The activity of both was assayed in MSN-like neurons derived from mouse and human stem cells.**Results:** We identified mouse and human CREs which restrict transgene expression to MSNs in the forebrain. There was significant divergence between mouse and human enhancers in their location relative to the transcription starting site, expression in cerebellar Purkinje cells, a site of endogenous DARPP-32 expression, and in response to BDNF, a known inducer of DARPP-32 expression in mouse. **Conclusion:** This study highlights divergence of CREs between species, which could be disease-relevant. In addition, the enhancer sequences will provide useful tools for MSN specific gene delivery and for the study of MSN maturation.

Disclosures: M.D. Cirnaru: None. **C. Corwin:** None. **J. Creus-Muncunill:** None. **M. Audrain:** None. **J. Fullard:** None. **P. Roussos:** None. **M.E. Ehrlich:** None.

Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

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Topic: A.10. Development and Evolution

Support: NIH Grant R24NS092988
NIH Grant P51RR165
NSF Grant SBE-131719
NIMH Grant MH103517
JSPS Grant S2603

Title: Accelerated evolution of oligodendrocytes in human brain

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Abstract: Recent discussions of human brain evolution have largely focused on increased neuron numbers and changes in their connectivity and expression. However, it is increasingly appreciated that oligodendrocytes play important roles in cognitive function and disease. Whether both cell-types follow similar or distinctive evolutionary trajectories is not known. Here, we examined the transcriptomes of neurons and oligodendrocytes in the frontal cortex of humans, chimpanzees, and rhesus macaques. We identified human-specific trajectories of gene expression in neurons and oligodendrocytes and show that both cell-types exhibit human-specific upregulation. Moreover, oligodendrocytes have undergone accelerated gene expression evolution in the human lineage compared to neurons. In addition, oligodendrocytes human-specific signatures are enriched for variants associated with neuropsychiatric disorders. These results provide insight into the role of oligodendrocytes in human brain evolution and neuropsychiatric disorders.

Disclosures: S. Berto: None. **I. Mendizabal:** None. **N. Usui:** None. **K. Toriumi:** None. **P. Chatterjee:** None. **C. Douglas:** None. **C.A. Tamminga:** None. **T.M. Preuss:** None. **S. Yi:** None. **G. Konopka:** None.

Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

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Topic: A.10. Development and Evolution

Support: NSF REU# 1659604
UIW Undergraduate Research Award

Title: Characterization of a neoblast population in the regenerating model system, Lumbriculus variegatus

Authors: B. A. SALVADOR, *V. G. MARTINEZ ACOSTA;
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Abstract: Members of the annelid phyla demonstrate varying capabilities of regeneration however the processes are similar, including three phases: wound healing, blastema formation,

growth, and differentiation (epimorphosis). In Lumbriculus, it had been hypothesized that differentiation occurs via proliferation of a stem cell population termed ‘neoblasts’ (Dubois, 1956). Neoblasts are small populations of mesenchymal cells that are found in worms and are described as a cellular source of regeneration. Despite efforts taken to determine the molecular mechanisms that may be involved during regeneration in Lumbriculus, little work has been done to fully characterize stem cell populations which are involved in this process. Using worm fragments 24hr and 11d post-amputation, we describe a small population of cells that are labeled by 5-ethynyl-2’-deoxyuridine (Click-iT® EdU) and readily mobilize to the wound blastema. A sub-population of these EdU-positive cells are also labeled with a neoblast-specific marker (Ross et. al., 2015), 1D9-E11. Immunohistochemical analysis demonstrates 1D9 positive cells within regenerating blastema of anterior and posterior ends of a regenerating fragment. 1D9 cells are detected 24hr post-amputation and are increased in number at 1wk post-amputation. Increased localization of 1D9-cells is noted within anterior segments in comparison to posterior segments. Immunoblot analysis of protein epitopes labeled by 1D9 in Lumbriculus blastemal tissue detected 2 protein bands that measure 214 kDa and 137 kDa. Total worm lysates were then purified using an immunoaffinity column method with 1D9 antibody conjugated sephadex beads and then sent for mass spectrometry analysis using the MALDI-TOF method. This work will ultimately determine the protein identity of 1D9 immunoreactive protein epitopes involved in regeneration in Lumbriculus. We believe that the 1D9 labled proteins may be important contributors to stem cell differentiation and, as reported in other regenerative models, may be the cellular source of regeneration in Lumbriculid worms. Overall, understanding the mechanisms of regeneration utilized by Lumbriculus will further our understanding of these complex processes and the knowledge gained will expand the regeneration literature.

Disclosures: V.G. Martinez Acosta: None. **B.A. Salvador:** None.

Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

Location: Hall A

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Program #/Poster #: 551.09/A81

Topic: A.10. Development and Evolution

Support: LAVIS
PASPA
PAPIIT
DGAPA-beca CLV
CONACYT

Title: Conserved and divergent expression dynamics during early patterning of the telencephalon in mouse and in chick embryos

Authors: *V. Y. MULEY[1], C. J. LOPEZ-VICTORIO[1], J. T. AYALA-SUMUANO[1], A. GONZÁLEZ-GALLARDO[1], B. FARIAS-SERRATOS[1], L. GONZÁLEZ-SANTOS[1], G. WRAY[2], M. HERNÁNDEZ[3], A. VARELA-ECHAVARRÍA[1];
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Abstract: The telencephalon differs dramatically in the mammals and the reptiles, in various aspects, including the presence of a laminated cortex and a corpus callosum in the former and a dorsoventral ridge in the latter. The early embryonic vesicle that develops into telencephalon has similar morphology, but the pallium of these animals diverges morphologically in their adult form. The extent to which common and lineage-specific gene regulatory programs control the ontogenetic divergence of the pallium in these animal taxa is currently unknown. To address this issue, we studied the global gene expression dynamics in mouse and chick telencephalon at early patterning stages. Our findings indicate that early telencephalic patterning in mouse and chick is governed by less than 3,000 genes, with subtle differences in the regulation of common signaling and transcriptional regulatory networks. The differential expression of Gata6, Neurod2, Foxf2, Nr1h4, Elk3 transcription factors determines telencephalon development. Epigenetic factors such as Atrx, Cbx3, and Cbx5 seems to modulate global gene expression in species specific manner. Impaired telencephalon development is likely to results in autism spectrum disorders.

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Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

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Program #/Poster #: 551.10/A82

Topic: A.10. Development and Evolution

Support: P50 MH103222

Title: Widespread neuronal expression of class I major histocompatibility complex isotypes in the adult human brain

Authors: M. T. C. MOU[1], S. M. CLARK[2], M. L. LANE[1], ***L. H. TONELLI**[3];
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Abstract: Class I major histocompatibility complex (MHC-I) molecules have been implicated in developmental processes of the central nervous system (CNS), specifically in activity dependent

synapse elimination and refinement of neural circuitries. In the adult brain, they are believed to participate in neural plasticity in several regions including the hippocampus. However, the expression of these molecules in the adult human brain has been minimally studied. Here, high-sensitive radioactive in situ hybridization and RNAscope technology were used to examine MHC-I A, B & C transcripts and beta-2 microglobulin in neurons of several brain regions of the adult human brain and to compare their expression with that of the adult rat brain. Postmortem samples containing area 45 or 11 of the prefrontal cortex (PFC), dorsal thalamus (Thal), dorsal striatum and corpus callosum were obtained from the NIH NeuroBioBank's brain and tissue repository at the University of Maryland and from the Maryland Psychiatric Research Center. Strong MHC-I expression signals were identified in both gray and white matter of the PFC and dorsal striatum and in the corpus callosum, choroid plexus and ependymal cell layer of the subventricular zone. Low or no specific signals were identified in the Thal. Examination of MHC-I in the PFC showed stronger and wider expression in human compared to rat. Analysis of cellular expression revealed a widespread distribution in different types of cells in which perivascular cells were the most abundant types of cells expressing MHC-I isotypes. RNAscope analysis confirmed neuronal expression of beta-2 microglobulin in the PFC and dorsal striatum of the adult human brain. MHC-I expression was also localized to NG2 positive cells using RNAscope. These studies provide strong evidence of a widespread expression of MHC-I isotypes in neurons of the adult human PFC, as well as in cells of the brain vasculature. These results suggest a role for MHC-I molecules in neurons of the adult human brain beyond those shown during circuit formation and maturation. Moreover, expression in perivascular cells provides the neuroanatomical basis for direct interactions with CD8+ and natural killer T cells of the immune system in normal non-inflammatory conditions.

Disclosures: M.T.C. Mou: None. **S.M. Clark:** None. **M.L. Lane:** None. **L.H. Tonelli:** None.

Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

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Program #/Poster #: 551.11/A83

Topic: A.10. Development and Evolution

Support: Silvio O. Conte Center for Oxytocin and Social Cognition
The Leakey Foundation #38217
NIH RR¬00165

Title: Distribution of oxytocin and vasopressin v1a receptors in chimpanzees

Authors: *C. N. ROGERS[1,6,7], D. J. COPPETO[2,6,7], K. INOUE[3,8,6], J. K. RILLING[1,3,6,8,7], T. M. PREUSS[4,6,8,9,10], L. J. YOUNG[5,7,6,3,11];
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Abstract: Despite our close genetic relationship with chimpanzees, there are notable differences between chimpanzee and human social behavior. Oxytocin and vasopressin are two neuropeptides known to regulate social behavior across mammalian species. Moreover, the distribution of their receptors has been shown to contribute to species-specific social behavior in several taxa. Yet little is known about the neuroanatomy of these systems in primates, and virtually nothing in great apes. Here, we used receptor autoradiography with a competitive binding protocol to localize oxytocin and vasopressin v1a receptors in seven chimpanzee brains. Oxytocin receptors were found in the lateral septum, hypothalamus, corticomedial amygdala, nucleus basalis, and substantia nigra. Vasopressin v1a receptors were observed in the cortex, lateral septum, hypothalamus, entire amygdala, dentate gyrus, and substantia nigra. These findings suggest continuity with other primate species in several areas, including those important for social visual attention. They also suggest potential differences between humans and chimpanzees in neuropeptide receptor expression in the reward system as well as areas important for threat.

Disclosures: C.N. Rogers: None. **D.J. Coppeto:** None. **K. Inoue:** None. **J.K. Rilling:** None. **T.M. Preuss:** None. **L.J. Young:** None.

Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

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Program #/Poster #: 551.12/A84

Topic: A.10. Development and Evolution

Support: NSFC Grant 31872767
NSFC Grant 91732305

Title: Immediate early gene expression demonstrates ocular dominance columns in V1 of squirrel monkeys

Authors: *S. LI, S. YAO, Q. ZHOU, T. TAKAHATA;
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Abstract: The squirrel monkey is regarded as the only one anthropoid primate species which is lack of ocular dominance columns (ODCs). Although previous studies have demonstrated that strabismus can induce formation of ODCs in the striate cortex (V1) of squirrel monkeys, many

individuals of the squirrel monkey with normal vision are lack of ODCs, when they tested it by cytochrome oxidase (CO) histochemistry. On the other hand, all individuals of the squirrel monkey are shown to be capable of stereoscopic 3D vision. Hence, ODCs are considered as a byproduct of cortical development. Moreover, this paradigm has been generalized to all cortical columns of other species as well, urging researchers to discuss that cortical columns are functionally unimportant trait. However, the observation of lack of ODCs in normal squirrel monkeys may be due to technical limitation. Immediate-early genes (IEGs) are a group of genes whose expression level is up-regulated or down-regulated immediately after the onset or offset of neuronal activity, respectively, and the sensitivity of their expression change to neuronal activity is much greater than that of CO expression. Our Previous study has revealed that ODCs exist in V1 of owl monkeys by IEG expression patterns after monocular inactivation, whereas conventional CO method failed to reveal. Therefore, in this research two kinds of immediate-early genes, *ZIF268* and *c-FOS*, are used to show ODCs in squirrel monkeys. Five normally reared adult squirrel monkeys were monocularly inactivated by TTX injection or eye enucleation. As a result, ODC-like patches were seen in V1 of all cases by *ZIF268* and *c-FOS* expression pattern, although they were not as evident as that in other anthropoid primate species. Thus, it is not compelling that squirrel monkeys are lack of ODCs as previous studies have shown solely by CO staining method. This research reveals universal existence of ODCs across primate species and suggests researchers to reconsider about the functional importance of cortical columns in general.

Disclosures: S. Li: None. **S. Yao:** None. **Q. Zhou:** None. **T. Takahata:** None.

Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 551.13/A85

Topic: A.10. Development and Evolution

Title: Distribution of the calcium binding proteins calbindin-D28k, calretinin, and parvalbumin in the naked mole-rat brain

Authors: *R. J. EMBALABALA, J. L. CHEATWOOD, D. K. SARKO;
Anat., Southern Illinois Univ. Med. Sch., Carbondale, IL

Abstract: The naked mole-rat (*Heterocephalus glaber)* is a small, poikilothermic rodent endemic to hot, dry regions of east Africa, such as those found in Somalia, central Ethiopia and parts of northeastern Kenya. *H. glaber* are eusocial animals that tend to live in hypoxic, hypercapnic subterranean colonies which has ultimately led to anatomical and physiological adaptions specific to *H. glaber*. These adaptions include: longevity, resistance to cancer, and unique sensory specializations such as a significant representation in the somatosensory cortex

dedicated to tactile inputs from the incisors. Because of these specializations, the use of *H. glaber* as a research animal model is becoming increasingly more common, enhancing the need for a more comprehensive understanding of its brain architecture. In this study, three significant calcium binding proteins were selected and used to characterize major structures in the brain based on previous analyses of other rodent species. Cresyl Violet (Nissl) was used along with immunohistochemistry techniques for calbindin-D28k, calretinin, and parvalbumin. Characterization of the distribution of these calcium binding proteins are being used to construct portions of a chemoarchitectonic atlas to facilitate brain-related studies involving *H. glaber*. Typical immunoreactivity in major regions of the brain will be shown and discussed for each protein, with comparisons made to other rodent species.

Disclosures: R.J. Embalabala: None. **J.L. Cheatwood:** None. **D.K. Sarko:** None.

Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 551.14/A86

Topic: A.10. Development and Evolution

Title: Neuron-specific protein-coding genes are evolutionarily more conserved than genes specific to other brain cell types

Authors: *L. XU, S. DOS SANTOS, T. CAPRA, S. HERCULANO-HOUZEL;
Vanderbilt Univ., Nashville, TN

Abstract: There is high diversity in the morphologies and sizes of neurons across mammalian species and brain structures compared to other brain cell types such as glial cells. However, little is known about the potential genetic drivers of this diversity over evolutionary time scales. Could it be that protein-coding genes expressed in neurons are evolving more rapidly than the genes expressed by glial cells? To test this hypothesis, we quantified the evidence for natural selection on the sequence of ~2’000 brain cell type specific mouse genes, including genes specific to neurons, glial cells, glial subtypes, and endothelial cells. In particular, we computed the ratio of the rate of non-synonymous substitutions to the rate of synonymous substitutions (dN/dS) between mouse and 61 other species. If the diversityin neuronal sizes and morphologies is due to adaptive changes in protein-coding sequences, we would expect to see higher dN/dS scores for neuron-specific genes across a wide range of species in comparison with glial cell and endothelial cell-specific genes. Contrary to our expectation, neuron-specific genes are significantly more conserved than genes specific to endothelial cells, glial cells, and glial subtypes. We also found that neuron-specific genes are more conserved than glial cell-specific genes and endothelial cell-specific genes across a range of functional categories defined by Gene Ontology annotations. The abundance of microglia-specific immune system process related

genes, which have higher dN/dS scores, contributes to glial cell-specific genes' higher rate of evolution. Thus, other factors must explain why neuron-specific genes are more conserved while neurons are diverse in size and morphology, such as the important yet meticulous restoration of resting potential in neurons likely involving highly conserved genes, or the regulatory regions of neuron-specific genes being responsible for the diversity in neuronal morphology and size.

Disclosures: L. Xu: None. **S. Dos Santos:** None. **T. Capra:** None. **S. Herculano-Houzel:** None.

Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 551.15/B1

Topic: A.10. Development and Evolution

Title: Energy availability in the rat brain related to constrained capillary supply, not neuronal demand

Authors: *L. VENTURA-ANTUNES, M. DASGUPTA, L. WESOLOSKI, S. HERCULANO-HOUZEL;
Dept. of Psychology, Vanderbilt Univ., Nashville, TN

Abstract: What determines the metabolic rate of brain tissue: neuronal demand, blood availability, or both? To address this question, we use high-resolution confocal microscopy of sections through the entire rat brain to examine the relationship between local densities of neurons, of glial cells, and of capillary-associated cells (endothelial cells and pericytes) with measurements of the local rate of glucose use and blood flow in matching structures in the rat brain found in the literature. Previous results showed that local capillary density is linearly correlated with local rate of glucose utilization and blood flow across brain structures in the rat brain. However, those analyses did not examine whether glucose utilization and capillary density correlate with local density of neurons and glial cells, which would indicate demand-supply matching between the vascular bed and brain neurons. We find that local rates of glucose use and blood flow are linearly correlated with local densities of capillary-associated cells. Remarkably, local glucose utilization does not correlate with local density of neurons nor glial cells. Within an individual brain, neuronal density is highly variable across structures, whereas densities of glial cells and capillary-associated cells vary little across structures. As a consequence of the stable density of the capillary bed, the ratio of capillary-associated cells per neuron varies inversely across sites with the local density of neurons, such that neurons compete more intensely for a constant blood supply where there are more of them locally (i.e. where neuronal density is higher). We thus propose that it is not that larger neurons *require* more energy, but rather that they have more energy available to them because of decreased competition for limited blood

supply. Our results further suggest that the density of the capillary network is determined independently of neuronal activity, such that within the brain, neurons must adjust their metabolism according to the energy available. Consequently, the emergence of larger neurons, at lower neuronal densities, would result in fewer, larger neurons competing locally for energy, which might provide an evolutionary advantage to tissue function.

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Poster

551. Cellular and Molecular Mechanisms of Evolution and Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 551.16/B2

Topic: A.10. Development and Evolution

Title: Mosaic scaling of numbers of neurons in subcortical structures of bird and mammalian brains

Authors: *S. HERCULANO-HOUZEL;
Vanderbilt Univ., Nashville, TN

Abstract: Uncovering the mechanisms that led to the emergence of the large diversity of vertebrate brains requires examining brains of extant species for patterns that reveal the rules behind the origins of diversity. Comparative analyses of brain structure were for decades based on volumetric measurements. Analyses focusing on absolute structure size variation over several orders of magnitude emphasized similarities, and culminated with the influential concept of linked regularities in brain development and evolution. Later re-analyses of the same datasets, focusing instead on relative volumes, revealed that there are clade-specific variations in the relative size of certain structures, as if they had become uncoupled from others in those linked regularities, in what was termed mosaic evolution. Strikingly, the recent availability of data on the numbers of neurons that compose brain structures in a wealth of species has shown that the scaling of absolute or relative structure volume is a poor predictor of the scaling of numbers of neurons in the structure. So far, those data have focused on the cerebral cortex (pallium) and cerebellum, lumping together all other structures in the "rest of brain". Here I analyze the scaling of numbers of neurons in the subpallium, diencephalon, mesencephalon and hindbrain of 15 mammalian species (artiodactyls, marsupials and one afrotherian) and 24 bird species spanning a similar 100-fold range of numbers of neurons in the "rest of brain". Across mammals, the mesencephalon gains neurons more slowly than the hindbrain; the subpallium and diencephalon gain neurons slightly faster than the hindbrain; and in marsupials, but not in artiodactyls, the pallium has the fastest expanding population of neurons. This is strikingly different from birds: the bird mesencephalon gains neurons rapidly over the hindbrain, and the subpallium gains

neurons even more rapidly, faster even than the pallium. As a consequence, the subpallium of some parrots holds more neurons than even the elephant subpallium. This study reveals an unprecedented mosaicism of brain structure composition that is missed by volumetric analyses, and cautions strongly against evolutionary inferences made on the basis of brain structure volume across species.

Disclosures: S. Herculano-Houzel: None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.01/B3

Topic: B.02. Ligand-Gated Ion Channels

Support: Swedish Brain Foundation (Hjärnfonden) grant

Title: The evolution of the $GABA_A$ receptors in vertebrates

Authors: H. J. HAINES[1], D. LAGMAN[1,2], L.-G. LUNDIN[1], *D. LARHAMMAR[1];
[1]Unit of Pharmacology, Dept. of Neurosci., Uppsala Univ., Uppsala, Sweden; [2]Sars Intl. Ctr. for Marine Mol. Biol., Bergen, Norway

Abstract: GABA is the main inhibitory neurotransmitter in the vertebrate brain. It binds to two sites on the $GABA_A$ receptors, causing channel opening and influx of chloride ions, and thereby leads to hyperpolarization. Benzodiazepines, used to treat insomnia and anxiety among other conditions, bind at a different site and enhance the effect of GABA. The $GABA_A$ receptors are pentamers whose subunits belong to the superfamily of cysteine-loop ion channels along with the nicotinic acetylcholine, glycine and 5-HT_3 receptor subunits. We have analyzed the $GABA_A$ gene family in the jawed vertebrates by combining phylogenetic and sequence-based analyses with comparisons of chromosomal synteny. The results show that the vertebrate ancestor had 7 subunit genes: two α and one each of β, δ, γ, π and ρ. The two rounds of genome doubling (1R and 2R) in early vertebrate evolution, as well as a local duplication of ρ after 2R, resulted in 20 genes in the gnathostome ancestor. One of these, which we have named π_2, has not been previously reported. This gene was lost in the mammalian ancestor. The teleost fish genome doubling (3R) resulted in 29 subunit genes in the teleost ancestor. Three of these were lost in zebrafish, resulting in 26 subunit genes in this experimentally important species. The θ and the ε genes in placental mammals that have undergone rapid evolutionary change, were found to be orthologous to β_4 and γ_4 respectively. We therefore suggest that they are renamed accordingly. A number of chromosomal translocations were resolved in these analyses. We also identified extra exons that may introduce additional sites of phosphorylation, if incorporated into the subunit in the M3-M4 intracellular loop, and compared these across species. We also provide an analysis of

key residues in the ion channel pore as well as at the GABA and benzodiazepine binding sites. These analyses indicate the ion channel pore is highly conserved and that the benzodiazepine binding site was formed gradually by changes that began after the split of the β/δ/π/ρ ancestor from the α/γ ancestor and continued in the γ_2 gene until the split of lobe-finned and ray-finned fishes. These results will serve as a framework for understanding the functional specialization of the many $GABA_A$ subunits.

Disclosures: **H.J. Haines:** None. **D. Lagman:** None. **L. Lundin:** None. **D. Larhammar:** None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.02/B4

Topic: B.02. Ligand-Gated Ion Channels

Support: Austrian Science Fund Project P 26680-B24

Title: Distribution of $GABA_A$ receptor subunits in the monkey fore brain

Authors: ***G. SPERK**[1], E. KIRCHMAIR[1], I. KONDOVA[2];
[1]Dept. of Pharmacol., Med. Univ. Innsbruck, Innsbruck, Austria; [2]Div. of Pathology and Microbiology, Biomed. Primate Res. Ctr., Rijswijk, Netherlands

Abstract: $GABA_A$ receptors are composed of five subunits arranged around a central chloride channel. Their subunits originate from different genes or gene families. The majority of $GABA_A$ receptors in the brain consist of two α-, two β-subunits and one γ- or δ-subunit. This subunit constitution crucially determines the physiological and pharmacological properties of the $GABA_A$ receptors. Using immunhistochemistry we investigated the distribution of 10 $GABA_A$ receptor subunits (α1, α2, α3, α4, α5, β1, β2, β3, γ2 and δ) in the fore brain of three female Rhesus macaques. Within the cerebral cortex subunits α1, α5, β2, β3 and γ2 were abundant and distributed through all layers, whereas α2, α3 and β1 were more concentrated in the inner and outer layers of the cortex. The caudate/putamen was rich in α1, α2, α5, all three β subunits notably β2 and β3 and γ2 and δ. Subunits α3 and α5 were considerably more concentrated in the caudate than in the putamen. In contrast, subunits α3, α4, α5, β1, β2 (notably not β3), γ2 and δ were the most abundant ones in the globus pallidus. Subunits α1, α5, β1 and γ2 were the most abundant ones in the substantia nigra. In most thalamic nuclei α1, α2, β3 and γ2 were highly expressed. Within the amygdala, high concentrations of subunits α1, α2, α3, β1 and γ2 were found in the cortical nucleus, whereas in the lateral, basal and basolateral amygdala α1, α2, α5, β1, β2, β3 and δ, and in the central amygdala α1, α2, α3, and γ2 were most abundant. Interestingly, subunit α3-IR outlined intercalated nuclei of the amygdala. In the hippocampus, subunits α1, α2, α4, β2, β3, γ2 and δ were highly expressed in the molecular layer of the dentate

gyrus. Subunits α1, α2, α3, α5, β2, β3, γ2 were most abundant in sector CA1 and the subiculum. The distribution of $GABA_A$ receptor subunits in the monkey was similar as the one in the rat and mouse. Overall subunit α4 was only expressed at low concentrations. We did not detect subunit γ1 e.g. in the substantia nigra. We thank Karoline Fuchs and Werner Sieghart from the Medical University Vienna for supplying the antibodies.

Disclosures: G. Sperk: None. **E. Kirchmair:** None. **I. Kondova:** None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.03/B5

Topic: B.02. Ligand-Gated Ion Channels

Support: Special funds of Hasselt University
Interuniversity Attraction Pole, BELSPO

Title: Glycine alpha2-containing receptors in de the developing striatum of mice

Authors: *J.-M. RIGO[1], J. COMHAIR[1], J. DEVOGHT[1], S. N. SCHIFFMANN[2], G. MORELLI[1], R. J. HARVEY[3], D. GALL[2], B. BRÔNE[1];
[1]Hasselt Univ., Hasselt, Belgium; [2]Univ. libre De Bruxelles (ULB), Brussels, Belgium; [3]UCL Sch. of Pharm., London, United Kingdom

Abstract: In this research, we set out to find the presence of the glycine receptor in the early developing striatum and more specifically within the MSN population. We found that the glycine receptor alpha 2 ligand binding subunit (GlyRα2) is already present at E13.5. The GlyRα2 is also seen in neuronal precursors that are still proliferating. The number of postnatal MSNs is reduced in GlyRα2KO mice compared to wild-types, which could be potentially explained by altered mitotic profile at E13.5 and unsuccessful compensation at E16.5. The two important CCCs are also affected it the absence of embryonic glycinergic signalling. At E13.5, we can hypothesize that the chloride driving force is higher in the WT embryos, which could potentially explain, via calcium-related excitability, the increased activation of CREB. This is opposite at E16.5 where we found an increase in the inward chloride transporter NKCC1 that occurs concurrently with an increase in CREB activation in the GlyRα2KO LGE. Furthermore, relatively mild phenotypic changes were observed in the GlyRα2KO mice at early postnatal ages that could be of multifactorial nature.

Disclosures: J. Rigo: None. **J. Comhair:** None. **J. Devoght:** None. **S.N. Schiffmann:** None. **G. Morelli:** None. **R.J. Harvey:** None. **D. Gall:** None. **B. Brône:** None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.04/B6

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant GM118801

Title: Influence of the N265M mutation on intrinsic kinetics of α5β2γ2L GABAA receptors

Authors: *S. KLEIN, C. LOR, R. A. PEARCE;
Anesthesiol., Univ. of Wisconsin-Madison, Madison, WI

Abstract: Background: GABAA receptors containing α5 subunits (α5-GABAARs) are essential for etomidate-induced amnesia. This subunit partners with β2 or β3 subunits, and mice carrying mutations in these subunits have been used to study mechanisms of general anesthetic action. A mutation of the β-subunit, N265M, has been found to eliminate the effect of etomidate on the receptor. However, we (SFN abstracts 2019) and others have found that even under drug-free conditions these mutant mice exhibit impaired memory. Therefore, we sought to characterize changes in intrinsic receptor properties caused by the β2(N265M) mutation. Additionally, we sought to confirm that the β2N265M mutation does confer insensitivity to etomidate.
Methods: HEK293 cells were transfected with cDNA encoding α5β2γ2L (WT) or α5β2(N265M)γ2L (MUT) at a ratio of 1α:1β:3γ with eGFP co-transfected to identify cells with successful transfection. A brief pulse of GABA (10 mM, 10 ms) was applied to outside-out patches via a multibarrel pipette mounted on a piezoelectric stage. Several responses (5-10) were averaged for analysis. Activation and deactivation were characterized by 10-90% rise time and fits to a biexponential decay function.
Results: MUT receptors deactivated more rapidly than WT, with a weighted time constant (tau-wt) of 60 ± 7.0 ms (MUT, mean ± SE) vs. 107 ± 9.6 ms (WT; p=0.002). This difference reflected an increase in the relative fraction of the fast component of biexponential decay (WT 0.60 ± 0.02 vs. MUT 0.68 ± 0.02; p=0.025) as well as the time constants (WT 41 ± 3.4 vs MUT 22 ± 2.1 tau-fast; p=0.0007, WT 211 ± 22 vs MUT 137 ± 14 tau-slow; p=0.02). In addition, the rise time was faster in the WT (1.20 ± 0.13 ms) than the MUT receptor (1.6 ± 0.7 ms; p=0.019). As expected, etomidate (1 uM) slowed deactivation of WT (tau-wt ETOM/CTRL = 267.8 ± 14.1%; p=0.000021) but not MUT receptors (111.9 ± 13.5%, p=0.4684).
Conclusion: Our findings show that the N265M mutation in the β2 subunit substantially affects the kinetics of the GABAA receptor by increasing the rate at which the receptor deactivates and decreasing the rate of activation. These alterations in intrinsic kinetics may be sufficient to significantly impair memory in mutant mice (SFN abstracts 2019) even in drug-free conditions.

Disclosures: **S. Klein:** None. **C. Lor:** None. **R.A. Pearce:** None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.05/B7

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant EY015573
NIH Grant EY029869
Plum Foundation

Title: Feedback signaling from horizontal cells to cone photoreceptors in mammalian retina mediated by GABA-induced pH changes

Authors: ***S. A. BARNES**[1,2], J. C. R. GROVE[3], A. A. HIRANO[2], N. C. BRECHA[2]; [1]Doheny Eye Inst., Los Angeles, CA; [2]UCLA, Los Angeles, CA; [3]Univ. of California, San Francisco, San Francisco, CA

Abstract: Hybrid actions of GABA pit a classical neurotransmitter system together with proteins that change the alkaline milieu within the photoreceptor synaptic cleft to mediate horizontal cell feedback signaling to photoreceptors. This mechanism is responsible for enhancing key features of temporal and spatial contrast adaption (e.g., synaptic gain control and receptive field antagonism). It has been shown that mammalian horizontal cells respond via rho-subunit containing GABA receptors to their own persistent GABA release, and that the results of this autaptic action affect cone Ca channel gating through changes in pH as a result of the high bicarbonate permeability of the GABA receptor anion channels. The magnitude of bicarbonate efflux is dictated by the driving force on this anion, which has an equilibrium potential near -15 mV. The rate of efflux changes rapidly in response to horizontal cell membrane potential, with depolarization causing reduced efflux, which increases acidity, and hyperpolarization causing greater bicarbonate efflux, which increases cleft alkalinity. In addition, steady-state activation of these GABA receptors can contribute to depolarization of horizontal cells, which increases cleft acidity via sodium/hydrogen exchanger proton extrusion, an action resulting in cone Ca channel inhibition via surface charge effects. But this inhibition is effectively counteracted during broad field illumination when horizontal cells are sufficiently hyperpolarized, which increases bicarbonate efflux that alkalinizes the cleft and disinhibits cone Ca channels. **System Modulation:** The hybrid actions of GABA operate in parallel to effect voltage-dependent pH changes, a novel mechanism for regulating presynaptic output. In addition, the GABA-pH hybrid system is modified by the adaptation signal, dopamine. Whereas under fully dark-adapted light levels, application of the GABA agonist muscimol disinhibits calcium channel activation in cones, when the slices are incubated in dopamine (5 µM), the polarity of this response is

reversed. Several likely sites of action may account for the dopamine-induced sign change: D1 receptor and D2 receptor activation modulates calcium channels, glutamate receptors, and GABA receptors, as well as other membrane proteins. This means that signaling from horizontal cells to photoreceptors is dependent on modifiable parameters that regulate feedback properties, enabling the system to be adjusted for different states of light adaptation.

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Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.06/B8

Topic: B.02. Ligand-Gated Ion Channels

Support: MRC programme grant MR/K005537/1

Title: Regulation of tonic and phasic inhibition by phosphorylation of α5-$GABA_A$ Receptors

Authors: *C. KIVISILD, D. P. BRIGHT, T. G. SMART;
Neuroscience, Physiol. & Pharmacol., Univ. Col. London, London, United Kingdom

Abstract: In the adult brain, the main role for γ-aminobutyric acid receptors ($GABA_ARs$) is to control neural excitability via a combination of transient phasic and persistent tonic inhibition. Phasic inhibition is mediated by receptors located at inhibitory synapses, while extrasynaptic receptors give rise to tonic inhibition. These two forms of inhibition are known to have distinct functional characteristics that differentially impact upon their control of neuronal excitation. Receptors containing the α5 subunit (α5-$GABA_ARs$) exhibit properties that associate with both forms of inhibition and due to their predominant location in the hippocampus, these receptors are thought to play a significant role in learning and memory. Several selective negative and positive allosteric modulators (NAM/PAMs) of α5-$GABA_ARs$ have been proposed as therapeutic targets for cognitive dysfunction associated with disorders such as Down syndrome, Alzheimer's disease, schizophrenia and autistic spectrum disorder. However, it is unclear how phasic and tonic inhibition, mediated by α5-$GABA_ARs$ in the hippocampus are proportionately regulated. Using whole-cell patch clamp recording and structured illumination microscopy (SIM) in cultured hippocampal neurons, we show that phosphorylation of the α5 subunits can alter the cell surface location of these receptors and thus regulate distinct forms of GABA-mediated inhibition. We propose that the underlying molecular mechanism behind these changes is altered binding between phosphorylated α5-$GABA_ARs$ and inhibitory synapse scaffold proteins. Although there are several drugs that target α5-$GABA_ARs$, a greater understanding of the molecular mechanisms by which neurons control the accumulation of $GABA_ARs$ at synaptic or

extrasynaptic sites and thus regulate phasic and tonic inhibition respectively, is needed in order to elucidate the role of α5-$GABA_A$Rs in cognition.

Disclosures: C. Kivisild: None. **D.P. Bright:** None. **T.G. Smart:** None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.07/B9

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH grant NS102131 (KWG)
NIH grant DA041454 (KWG)

Title: Targeting extrasynaptic gammaaminobutyric acid receptors to prevent and reverse opioid antinociceptive tolerance in mice

Authors: K. GENARO, R. F. YOSHIMURA, D. HOGENKAMP, T. B. C. JOHNSTONE, *K. W. GEE;
Pharmacol., Univ. of California Irvine, Irvine, CA

Abstract: Tolerance to the analgesic effect is the main side effect of chronic administration of opioids. Several drugs have been studied to try to find agents to prevent the development of this phenomenon. Research on a relatively new class of agents known as neurosteroids has revealed novel modulatory sites and mechanisms of action that are providing insights into the pathophysiology of pain. In the present study we aimed to evaluate the effect of different compounds targeting α4β3δ $GABA_A$ receptors on morphine-induced tolerance to its analgesic effect. Groups of male mice were randomly assigned to groups that received daily morphine (10 mg/kg, subcutaneously) in combination with enaminone 2-261 (10 mg/kg, intraperitoneally) or 2-261 vehicle twice daily. 2-261 is a non-steroidal positive allosteric modulator of extrasynaptic receptors with similar efficacy as the prototypical neurosteroids allopregnanolone and ganaxolone. Nociception was measured using the warm water tail immersion test and the tail flick latency was recorded. Treatments and evaluations continued (15 days) until tolerance developed to the analgesic effect of morphine. The second aim of this study was to investigate the acute effect of compounds that modulate α4β3δ $GABA_A$ receptors on morphine antinociceptive tolerance including 2-261 (3 mg/kg), ganaxolone (10 mg/kg), etifoxine (50 mg/kg; modulates $GABA_A$ receptors via stimulation of neurosteroid production) and 2-301 (20 mg/kg), a compound that has negligible efficacy at α4β3δ $GABA_A$ receptors relative to 2-261. Our findings indicated that full tolerance was achieved following 9 days of morphine administration, while 2-261 pre-treatment (chronic) was able to prevent tolerance. Moreover, acute administration of 2-261 on day 9 reversed the morphine-induced tolerance. Similarly,

etifoxine reversed morphine tolerance on a different time course compared to 2-261; ganaxolone attenuated the analgesic tolerance to morphine but did not restore full analgesia; and 2-301 treatment did not significantly affect morphine-induced tolerance. Our findings suggest that α4β3δ $GABA_A$ receptors may be a promising pharmacological target to prevent or reverse morphine-induced tolerance to its analgesic effect.

Disclosures: K. Genaro: None. **R.F. Yoshimura:** None. **D. Hogenkamp:** None. **T.B.C. Johnstone:** None. **K.W. Gee:** None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.08/B10

Topic: B.02. Ligand-Gated Ion Channels

Title: MicroRNA regulation of inhibitory synaptic plasticity

Authors: *D. RAJGOR[1], A. M. PURKEY[1], T. M. WELLE[1], J. D. GARCIA[2], M. DELL'ACQUA[1], K. R. SMITH[1];
[1]Pharmacol., Univ. of Colorado, Denver, Aurora, CO; [2]Pharmacol., Univ. of Colorado, Anchutz, Aurora, CO

Abstract: The molecular mechanisms underlying the long-term post-synaptic plasticity of inhibitory synapses is poorly characterized. Recruitment and clustering of $GABA_AR$s at the inhibitory post-synaptic domain is a major mechanism which rapidly increases inhibition in the brain during inhibitory Long-Term Potentiation (iLTP). However, it is unclear how $GABA_AR$s are maintained at the surface in a manner which sustains iLTP. We show protein synthesis via miRNA regulation is important for maintaining persistent iLTP. We identify novel roles for miRNAs in silencing *GABRA1* and *GABRG2*, which encode for the important synaptic $GABA_AR$ sub-units $GABA_AR\alpha1$ and $GABA_AR\gamma2$ respectively. During chemical-iLTP, miRNA down-regulation promotes increased translation and maintenance of surface $GABA_AR\alpha1$ and $GABA_AR\gamma2$. This pathway is essential for chemical-iLTP and can be blocked by miRNA overexpression which impairs inhibitory neurotransmission. Finally, we show *de novo* synthesis of $GABA_AR\alpha1$ occurs exclusively in dendrites during chemical-iLTP, which supports plasticity-induced local translation of $GABA_AR$s.

Disclosures: D. Rajgor: None. **A.M. Purkey:** None. **T.M. Welle:** None. **J.D. Garcia:** None. **M. Dell'Acqua:** None. **K.R. Smith:** None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.09/B11

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant EY022730

Title: GABAergic interneurons in mice excite neonatal hippocampus but inhibit isocortex

Authors: Y. MURATA[1], ***M. T. COLONNESE**[2];
[1]Pharmacol. and Physiol., George Washington Univ., Washington, DC; [2]Pharmacol. and Physiol., The George Washington Univ. Sch. of Med., Washington, DC

Abstract: Low expression of the neuronal K-Cl co-transporter KCC2 during development renders $GABA_A$ receptors depolarizing and sometimes excitatory in excised tissue preparations. Recent studies in mice suggest that GABA and GABAergic interneurons are inhibitory in isocortex and hippocampus *in vivo* during the first postnatal week. However, the role of local interneurons in regulating excitability of cortical circuits *in vivo* has not been directly examined. Here we investigated the role of GABAergic neurons in early cortical and hippocampal network activity using chemogenetics and *in vivo* electrophysiology. Chemogenetic receptors (KORD for suppression of activity and hM3Dq for its enhancement), were expressed in GABAergic neurons by locally injecting Cre-dependent AAVs into the visual cortex or hippocampus of GAD2-Cre mice on postnatal day (P) 0-1. This approach allowed us to bi-directionally manipulate activity of GABAergic neurons in un-anesthetized mice as early as P3, while simultaneously monitoring LFP and neuronal firing using multi-electrode recordings. In the hippocampus, suppressing GABAergic neuron activity on P3 *decreased* multi-unit firing rates in the pyramidal cell layer of CA1 by ~50% and reduced the amplitude of early sharp waves. Enhancing GABAergic neuron activity *increased* firing rates by ~150% with no effect on sharp wave amplitude. On P7, this 'excitatory' effect of GABAergic neurons was no longer observed: suppression of GABAergic neurons increased firing rates in the pyramidal cell layer ~200%, while increasing GABAergic activity reduced firing by ~75%. By contrast, in the visual cortex, suppressing GABAergic neuron activity on P3 increased cortical multi-unit firing rates by ~300% without substantially altering the frequency of spontaneous spindle-burst oscillations. Enhancing GABAergic neuron firing decreased network firing by ~60%. This inhibitory effect of interneurons was also present at P7. An excitatory effect of hippocampal interneurons was observed in CA1 only when viral expression was restricted to hippocampus. Widespread expression within cortex in addition to hippocampus resulted in and 'inhibitory' interneuron action at P3, suggesting that reduced activity in cortex, which provides the major input to neonatal hippocampus, can swamp local excitation by interneurons in CA1 on P3. Our results reveal regionally diverse roles for

GABAergic interneurons in modulating excitability in cortical structures during development. They further suggest that regardless of their inhibitory or excitatory effect, interneurons are not critical for the normal patterning of spontaneous activity during circuit formation.

Disclosures: Y. Murata: None. **M.T. Colonnese:** None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.10/B12

Topic: B.02. Ligand-Gated Ion Channels

Support: CIHR Foundation Grant FDN-154312
University of Toronto Scholarship - Dr. Kirk Weber Research Award in Anaesthesia

Title: Anesthetic drug activation of $GABA_A$ receptors in astrocytes drives a persistent increase in extrasynaptic $GABA_A$ receptor function in neurons

Authors: *A. PINGUELO[1], K. KANESHWARAN[1], G. LEI[1], D.-S. WANG[1], B. A. ORSER[1,2,3];
[1]Physiol., [2]Anesthesia, Univ. of Toronto, Toronto, ON, Canada; [3]Anesthesia, Sunnybrook Hlth. Sci. Ctr., Toronto, ON, Canada

Abstract: We have previously shown that a brief exposure to commonly used general anesthetic drugs triggers a sustained increase in cell-surface expression of extrasynaptic $GABA_A$ receptors ($GABA_ARs$) in hippocampal neurons. The resulting increase in inhibition causes subtle, yet sustained postanesthetic cognitive deficits. Interestingly, astrocytes are necessary to trigger this overexpression of $GABA_ARs$; however, the mechanisms underlying this cross-talk with neurons are unknown. In addition, the proinflammatory cytokine IL-1β also increases cell-surface expression of extrasynaptic $GABA_ARs$ via a p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway. Further, anchoring of extrasynaptic $GABA_ARs$ to the cell membrane is regulated by the phosphorylation of radixin. As astrocytes express anesthetic-sensitive $GABA_ARs$, we hypothesize that anesthetic drugs activate $GABA_ARs$ in astrocytes and stimulate the release of IL-1β, which acts via a p38 MAPK- and radixin-dependent signaling pathway to increase cell-surface expression of extrasynaptic $GABA_ARs$ in neurons. Cultured hippocampal neurons and cortical astrocytes were prepared from fetal mice. Whole-cell voltage clamp recording was used to measure tonic inhibitory current mediated by extrasynaptic $GABA_ARs$ in neurons. Astrocyte cultures were treated with the anesthetic etomidate (1 μM) +/- the $GABA_AR$ antagonist bicuculline (20 μM) for 1 h, then washed. Two hours later, the astrocyte-conditioned media was applied to the neurons and 24 h later, tonic current was recorded in neurons. In further

experiments, conditioned media from etomidate-treated astrocytes was applied to neurons +/- an IL-1 receptor antagonist (IL-1ra, 100 ng/ml) or an inhibitor of p38 MAPK (SB203,580, 20 μM). Also, mice were injected with etomidate (8 mg/kg, i.p.) or vehicle then IL-1β, p38 MAPK, and radixin levels in the hippocampus were studied 24 h later through Western blot. The results showed that bicuculline prevented the etomidate-induced increase in tonic current in neurons (n=10-12). Furthermore, IL-1ra and SB203,580 also prevented this effect of etomidate (n=9-13). Etomidate increased the levels of IL-1β, phosphorylated p38 MAPK, and phosphorylated radixin (n=3-4). Thus, anesthetic activation of $GABA_A$Rs in astrocytes triggers a sustained increase in extrasynaptic $GABA_A$R function in hippocampal neurons via a pathway of IL-1β, p38 MAPK and radixin. Our results identify a novel cross-talk mechanism between astrocytic $GABA_A$Rs and neuronal $GABA_A$Rs that might be targeted to mitigate postanesthetic cognitive deficits.

Disclosures: **A. Pinguelo:** None. **K. Kaneshwaran:** None. **G. Lei:** None. **D. Wang:** None. **B.A. Orser:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Orser is an inventor named on a Canadian patent (2,852,978), a US patent (9,517,265) and a pending US patent (62/268,137)..

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.11/B13

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH grant MH097446
DOD grant AR140209
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NIH grant NS081735
NIH grant NS080064
NIH grant NS087662

Title: Mis-trafficking of $GABA_A$ receptor subunits in mouse models of autism spectrum disorder

Authors: C. CHOI, J. L. SMALLEY, Q. REN, S. J. MOSS, ***P. A. DAVIES**;
Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: Tonic and phasic inhibition arise from activation of extrasynaptic and synaptic $GABA_A$Rs respectively. Extrasynaptic and synaptic $GABA_A$Rs are comprised of different subunit combinations which instills unique biophysical and pharmacological properties upon the receptors. While tonic inhibition controls overall excitation of the neurons, phasic inhibition is important for information processing. Because of their distinct functions, tonic and phasic

inhibition requires precise trafficking of $GABA_A$Rs to their discrete locations. The trafficking of α4-containing extrasynaptic $GABA_A$Rs in healthy and pathological states remains unknown. We have examined the Fragile X model, *Fmr1 KO,* and the autistic model, β3 S408/9A, and found that compared to wild-type (WT) mice, *Fmr1 KO* and β3 S408/9A mice had a deficit in tonic current while phasic inhibition has increased amplitude and decay time. We hypothesized that in ASD α4-containing $GABA_A$Rs can be mis-trafficked from the extrasynaptic space to synaptic regions *Methods*. We used whole-cell patch-clamp to measure phasic and tonic currents from dentate gyrus granule cells (DGGCs) in hippocampal slices from male WT, Fmr1 *KO*, and β3 S408/9A mice. We also isolated native α4 and α1 subunit-containing $GABA_A$Rs from the cortex and hippocampus of *Fmr1 KO,* β3 S408/9A and WT mice and analyzed their subunit composition, and the associated proteins these $GABA_A$Rs are associated with using liquid chromatography coupled with mass spectroscopy (LC-MS/MS). *Results.* Using the α4βγ2 specific benzodiazepine Ro15-4513, phasic currents from Fmr1 KO mice were modulated whereas those from WT remained unaltered. Additionally, we observed an increase in α4 subunit immunoreactivity at gephyrin positive structures in hippocampal slices from brains of *Fmr1 KO* mice. Results from the LC-MS/MS studies demonstrate that in WT mice α1 and α4 $GABA_A$Rs are mutually exclusive, however they form mixed receptors in *Fmr1 KO* mice causing an association of the α4 subunit with synaptic proteins. *Conclusion.* Pathological mis-trafficking of α4 subunits to GABAergic synapses depletes extrasynaptic GABAARs to reduce tonic inhibition, alters phasic inhibition, causing an increase in neuronal activity. Aberrant trafficked GABAARs are a potential novel therapeutic target that could reverse excessive circuit excitation by reversing tonic inhibition deficits.

Disclosures: C. Choi: None. **J.L. Smalley:** None. **Q. Ren:** None. **S.J. Moss:** F. Consulting Fees (e.g., advisory boards); SAGE Therapeutics, AstraZeneca. **P.A. Davies:** None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.12/B14

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH Grant MH111461
NIH Grant AA026753

Title: δ-subunit containing $GABA_A$ IPSCs are driven by both synaptic and diffusional GABA in mouse dentate granule neurons

Authors: *M.-Y. SUN[1], L. ZIOLKOWSKI[1], A. BENZ[1], S. MENNERICK[1,2];
[1]Psychiatry, [2]Taylor Family Inst. for Innovative Psychiatric Res., Washington Univ. in St. Louis, St. Louis, MO

Abstract: $GABA_A$ receptors are the major inhibitory neurotransmitter receptors in the central nervous system. Two distinct $GABA_AR$ classes are those containing a δ subunit (δ receptors) and those with a γ2 subunit. The decay time constants from δ IPSCs are slower than those from γ2 IPSCs, but the reasons are unclear. Slower δ IPSCs could represent transmitter diffusion, rebinding, or slow deactivation kinetics of channels. We used gene editing to confer picrotoxin resistance on the δ subunit in mice, and pharmacologically isolated δ receptors in dentate granule cells to explore IPSCs. We also used rapid application of GABA onto nucleated patches from dentate granule cells to explore deactivation kinetics. To differentiate the effects of diffusion vs local/synaptic GABA on δ IPSCs, we applied 5% dextran to reduce GABA diffusion, thereby enhancing local synaptic [GABA] and slowing/reducing access to extrasynaptic receptors. Dextran accelerated the decay and increased the peak amplitude of evoked δ IPSCs, suggesting that the peak amplitude is driven by non-saturating synaptic GABA, while the decay may normally be driven by some GABA escape to distal extrasynaptic δ receptors. Dextran also increased the peak amplitude of evoked γ2 IPSCs but did not alter γ2 IPSC decay, suggesting peak amplitude of evoked γ2 IPSCs is also driven by unsaturating synaptic GABA, with little or no GABA diffusional effects on the decay. Dextran had no effect on spontaneous γ2 or δ IPSC decay or peak amplitude, suggesting that GABA actions during spontaneous IPSCs (sIPSCs) are local for both receptor types, although frequency of δ sIPSCs is low, suggesting that many synapses may not contain appreciable δ. The slower decay of δ sIPSCs compared with γ2 sIPSCs might result from slower deactivation of δ receptors. To examine this, we used rapid iontophoretic application of varied [GABA] onto nucleated patches. PTX-isolated δ currents activated by either iontophoresis or by theta-tube application exhibited a deactivation rate equivalent to that of sIPSCs, consistent with the idea that deactivation and local GABA actions drive sIPSCs. Overall, our results indicate that δ IPSCs are driven by both synaptic and diffusional GABA, and are only slightly more sensitive to altered GABA diffusion than γ2 IPSCs. Our results are consistent with a relationship between δ and γ2 $GABA_A$ receptors akin to that of NMDA and AMPA receptors at glutamate synapses.

Disclosures: **M. Sun:** None. **L. Ziolkowski:** None. **A. Benz:** None. **S. Mennerick:** None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.13/B15

Topic: B.02. Ligand-Gated Ion Channels

Support: MH111461
AA026753

Title: Neurosteroids, $GABA_A$ receptors, and neuronal synchrony

Authors: *X. LU[1], P. LAMBERT[1], A. BENZ[1], C. F. ZORUMSKI[1], J. H. STEINBACH[2], S. J. MENNERICK[1];
[1]Psychiatry, [2]Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Electrical oscillations reflecting the synchronized activity of large numbers of neurons play key roles in learning, memory, and cognition. Abnormal synchrony underlies seizures. In rodent hippocampal slices, electrical oscillations are chemically induced by activating kainate receptors or muscarinic acetylcholine receptors. Nevertheless, the oscillations are eliminated by the application of $GABA_A$ receptor antagonists, indicating an essential role of inhibitory neurotransmission in neuronal synchrony. The role of subsets of $GABA_A$ receptors in generating neuronal synchrony in hippocampus represents an attractive object for study, given the role of oscillations in normal and abnormal brain function. We introduced a mutation in the mouse $GABA_A$ receptor γ2 subunit gene that slightly accelerates IPSC decays. The γ2 mutation in fact entirely prevented oscillations induced by kainate (200 nM) and blocked by picrotoxin/gabazine in WT CA3 region of slices. To test whether the deficit directly results from faster IPSCs, we prolonged IPSCs pharmacologically with allopregnanolone (3α5αP, 100 nM). As expected, 3α5αP increased the power of oscillations in WT tissue. By contrast, 3α5αP did not restore kainate induced oscillations in γ2 mutant hippocampus. We conclude that yet-to-be defined developmental changes may contribute to the deficits in synchrony observed in γ2 mutant animals. Overall, our results likely have relevance the impact of inhibition in abnormalities of brain function, including epilepsy.

Disclosures: X. Lu: None. **P. Lambert:** None. **A. Benz:** None. **C.F. Zorumski:** None. **J.H. Steinbach:** None. **S.J. Mennerick:** None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.14/B16

Topic: B.02. Ligand-Gated Ion Channels

Support: MH111461
AA026753
GM007200

Title: Subtle changes to IPSC kinetics have profound implications on larger scale brain activity

Authors: *P. M. LAMBERT, M. KEISER, M.-Y. SUN, L. ZIOLKOWSKI, H. SHU, A. BENZ, S. MENNERICK;
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Abstract: We have generated a mouse line carrying a point mutation (T6'Y) in the γ2 subunit of $GABA_A$ receptors (γ2*) to precisely alter synaptic inhibition. The presence of the γ2* subunit renders the receptor resistant to the nonselective antagonist picrotoxin allowing for the confirmation of the presence of the mutant receptors in a recording. We observe that the γ2* mutation speeds up the decay kinetics of $GABA_A$ responses in N2A cells as well as the decay kinetics of dentate granule cell and CA1 pyramidal cell IPSCs in γ2* homozygote mice. While the effects of γ2* seem limited to receptor deactivation kinetics on the cellular level, we find large changes in the EEG of γ2* mice. When compared to wild-type littermates, γ2* homozygotes exhibit a significant increase in total spectral power, slowing of the theta rhythm, and suppression of gamma power during active exploration. Additionally, γ2* mice show a lack of normal theta-gamma phase amplitude coupling, indicating that these mice have significant deficits in producing coordinated neural activity. Finally, γ2* mice exhibit severe deficits in prepulse-inhibition of the startle response. Taken together, these results show that even slight perturbations of synaptic inhibition can have a significant impact on larger scale brain activity.

Disclosures: P.M. Lambert: None. **M. Keiser:** None. **M. Sun:** None. **L. Ziolkowski:** None. **H. Shu:** None. **A. Benz:** None. **S. Mennerick:** None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.15/B17

Topic: B.04. Ion Channels

Support: NIH/NINDS Intramural Research Program

Title: A novel GABAA receptor auxiliary subunit controlling benzodiazepine anxiolysis and hypnosis

Authors: *W. HAN[1], J. LI[1], K. PELKEY[2], S. PANDEY[1], X. CHEN[3], Y.-X. WANG[4], K. WU[1], T. LI[1], D. CASTELLANO[1], C. LIU[5], R. PETRALIA[4], J. LYNCH[3], C. MCBAIN[2], W. LU[1]; [1]NIH/NINDS, North Bethesda, MD; [2]NIH/NICHD, North Bethesda, MD; [3]Queensland Brain Inst., The Univ. of Queensland, Brisbane, Australia; [4]Advanced Imaging Core, NIH/NIDCD, North Bethesda, MD; [5]Transgenetic Core Facility, NIH/NHLBI, North Bethesda, MD

Abstract: In the mammalian central nervous system $GABA_A$ receptors ($GABA_A$Rs) mediate the majority of fast inhibitory transmission and serve as major targets for the treatment of a number of neurological and psychiatric disorders, including epilepsy, anxiety and sleep disorders. In addition, impaired GABAergic transmission has been implicated in the pathogenesis of many neurological/psychiatric illnesses and modulating inhibitory tone through the benzodiazepine-binding site of $GABA_A$Rs is an effective therapeutic strategy for several mood disorders. Thus, it

is important to understand the molecular mechanisms underlying the regulation of $GABA_AR$ trafficking, function and pharmacology in the brain. We have characterized a $GABA_AR$ associated protein and examined its regulation of $GABA_AR$ synaptic abundance, channel kinetic properties, and pharmacology. Functional investigations in gene knockout mice, including synaptic physiology and behavioral analysis, indicate the importance of this molecule in controlling inhibitory transmission and benzodiazepine-induced sleep.

Disclosures: **W. Han:** None. **J. Li:** None. **K. Pelkey:** None. **S. Pandey:** None. **X. Chen:** None. **Y. Wang:** None. **K. Wu:** None. **T. Li:** None. **D. Castellano:** None. **C. Liu:** None. **R. Petralia:** None. **J. Lynch:** None. **C. McBain:** None. **W. Lu:** None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.16/B18

Topic: B.02. Ligand-Gated Ion Channels

Support: NIH/NINDS 1K08NS091248
NIH/NINDS 5R01NS40109-14

Title: Mannitol decreases neocortical epileptiform activity during early brain development via co-transport of chloride and water

Authors: E. DUQUETTE[1], N. RAHMATI[1], K. DUQUETTE[1], K. J. STALEY[1], ***J. GLYKYS**[2]; [1]Massachusetts Gen. Hosp., Boston, MA; [2]Univ. of Iowa. Carver Col. of Med., Iowa City, IA

Abstract: Seizures and brain injury result in water and Cl^- accumulation in neurons. Neocortical neuronal membranes have a low water permeability as they lack aquaporins necessary to move free water. Instead, neurons use cotransport of ions including Cl^- to move water. Thus, increasing the extracellular osmolarity during seizures should result in an outward movement of water and salt, reducing $[Cl^-]_i$ and improving $GABA_A$ receptor-mediated inhibition. We tested the effects of hyperosmotic therapy with a clinically relevant dose of mannitol (20 mM) on epileptiform activity, spontaneous multiunit activity (sIPSCs), $[Cl^-]_i$, and neuronal volume in layer IV/V of the developing neocortex of C57BL/6 and Clomeleon mice. Using electrophysiological techniques and multiphoton imaging in acute brain slices (post-natal day 7-12) and organotypic neocortical slice cultures, we observed that mannitol: 1) decreased epileptiform activity, 2) decreased neuronal volume and $[Cl^-]_i$ through CCCs, 3) decreased spontaneous multi-unit activity frequency but not amplitude, and 4) restored the anticonvulsant efficacy of the $GABA_A$ receptor modulator diazepam. We conclude that an increase in extracellular osmolarity by mannitol mediates the efflux of $[Cl^-]_i$ and water through CCCs, which results in a decrease in epileptiform activity and enhances benzodiazepine actions in the developing neocortex in vitro.

Novel treatments aimed to decrease neuronal volume may concomitantly decrease $[Cl^-]_i$ and improve seizure control.

Disclosures: J. Glykys: None. **E. Duquette:** None. **N. Rahmati:** None. **K. Duquette:** None. **K.J. Staley:** None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.17/B19

Topic: B.10. Epilepsy

Support: Natural Science Foundation of China 31771188 and 31471027

Title: Potassium chloride cotransporter-2 is an important facilitator for epileptogenesis

Authors: *Y. WANG;
State Key Lab. of Med. Neurobio. and MOE Frontiers Ctr. for Brain Sci., Fudan Univ., Shanghai, China

Abstract: $GABA_A$ receptor-mediated inhibition depends on the maintenance of low level intracellular $[Cl^-]$ concentration, which in adult depends on neuron specific K^+-Cl^- cotransporter-2 (KCC2). Previous studies have shown that KCC2 was downregulated in both epileptic patients and various epileptic animal models. However, the temporal relationship between KCC2 downregulation and epileptogenesis is still unclear. In this study, we explored the relationship and the influence of KCC2 downregulation on epileptogenesis. Both pilocarpine and cyclothezide induced *in vivo* and *in vitro* epilepsy models were used in this study. Patch clamp electrophysiology, western blotting and immunohistochemistry were used to detect the structure and functional change of hippocampal neurons during epileptogenesis. Our results showed that significant downregulation of plasma membrane KCC2 was directly associated with severe (Racine Score III and above) behavioral seizures *in vivo*, and interestingly, occurred before the epileptiform bursting activities. Suppression of membrane KCC2 expression by $shRNA_{KCC2}$ both *in vitro* and *in vivo*, induced spontaneous epileptiform bursting activities and seizure behavior. Furthermore, either overexpression of KCC2 using KCC2 plasmid or blockade of KCC2 down regulation with Frusemide, a KCC2 inhibitor, effectively enhanced the resistance to convulsant stimulation induced epileptiform activities. In addition, blockade of KCC2 down regulation both in acute and silent period prevented the occurrence of chronic seizure. In conclusion, our findings demonstrated that altered expression of KCC2 is not the consequence, but likely is the contributing factor for both induction and progression of chronic seizure.

Disclosures: Y. Wang: None.

Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.18/B20

Topic: B.02. Ligand-Gated Ion Channels

Support: DFG SPP 1665 Grant (HO 2156/3–1/2, KI 1816/1–1/2, KI 1638/3–1/2, HU 800/8-1/2)
DFG CRC/TR 166 Grant (B3)
BMBF Grant (01GQ0923)
IZKF Jena Grant (K.K., K.H.)

Title: Hippocampal network dynamics in the conditional absence of NKCC1

Authors: *K. KIRMSE[1], J. GRAF[1], C. ZHANG[1], T. HERRMANN[2], T. FLOSSMANN[1], V. RAHMATI[3], O. W. WITTE[1], S. J. KIEBEL[3], C. A. HÜBNER[2], K. HOLTHOFF[1];
[1]Hans-Berger Dept. of Neurol., [2]Inst. of Human Genet., Jena Univ. Hosp., Jena, Germany; [3]Dept. of Psychology, Technische Univ. Dresden, Dresden, Germany

Abstract: NKCC1 is the primary transporter mediating chloride uptake in immature principal neurons, but its role for network dynamics in the developing brain remains controversial. To address this question, we generated mice lacking NKCC1 in the vast majority of forebrain glutamatergic cells. Using a combination of electrophysiological and optical approaches *in vitro* and *in vivo*, we demonstrate that NKCC1-dependent GABAergic depolarization promotes spontaneous network activity during early postnatal development in a model-, event type- and region-specific manner. Unexpectedly, long-term effects of a chronic absence of NKCC1 on synaptic development, network dynamics and behavioral performance are subtle or absent. Our data provide evidence for a neural network function of NKCC1 in the immature hippocampus *in vivo* and, at the same time, challenge the idea that NKCC1 expression by cortical principal neurons is indispensable for major aspects of hippocampal development.

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Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.19/B21

Topic: B.02. Ligand-Gated Ion Channels

Title: Role of psychosine in cognitive deficits in the Krabbe brain (KD)

Authors: *R. REBIAI[1], M. MARSHALL[1], M. PERGANDE[2], D. NGUYEN[1], S. COLOGNA[2], M. I. GIVOGRI[1], E. R. BONGARZONE[1];
[1]Anat. and Cell Biol., [2]Dept. of Chem., Univ. of Illinois At Chicago (UIC), Chicago, IL

Abstract: The abnormal assembly and loss of synaptic components cause synapses to fail maintaining cell-to-cell communication. This synaptic failure usually leads to synaptic death, largely irreversible, which is the basic contributor to cognitive impairment in neurological diseases. In Krabbe disease (KD), a lysosomal deficiency of galactosylceramidase that causes toxic accumulation of psychosine in membranes, severe cognitive impairment is observed. However, it is unknown whether synaptic dysfunction contributes to cognitive problems in KD. We hypothesize that the gradual accumulation of psychosine in the membrane of Krabbe synapses disrupts lipid rafts, altering the assembly of synaptic components and signaling, and lead to synaptic failure and cognitive decline. Using Golgi Cox staining, we found a significant decrease in the number of dendritic spines in cortical neurons of sick twitcher mice, the natural mouse model for KD. Electron microscopy data confirmed ultrastructural alterations in KD synapses, with reduced contact area and lower number of synaptic vesicles, in parallel to increased levels of psychosine in the pre and post-synaptic membrane. Western blotting also showed altered levels and subcellular localization of the synaptic scaffolding protein, PSD-95, suggesting abnormal assembly of synaptic components. These results provide direct evidence that synapses are structurally disrupted in KD, which may contribute to the severe cognitive impairment observed in Krabbe patients. Ongoing studies are evaluating how psychosine accumulation may involve local changes in the stability and fluidity of synaptic membranes, altering lipid raft synaptic function and promoting some of the ultrastructural changes observed in our experiments.

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Poster

552. GABA and Glycine: Receptors, Inhibition, and Neuronal Excitability

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 552.20/B22

Topic: B.02. Ligand-Gated Ion Channels

Support: Wellcome Trust 101696/Z/13/Z
National Institute for Health Research
BMA Foundation for Medical Research (Vera Down Award 2017)
National Organisation for Rare Disorders (16006)

Title: Human glycine receptor autoantibodies disrupt inhibitory neurotransmission

Authors: *S. J. CRISP[1,2], C. L. DIXON[2], L. JACOBSON[3], E. CHABROL[2], A. VINCENT[3], D. M. KULLMANN[2];
[1]Univ. of Cambridge, Cambridge, United Kingdom; [2]Dept. of Clin. and Exptl. Epilepsy, Inst. of Neurol., London, United Kingdom; [3]Nuffield Dept. of Clin. Neurosciences, Univ. of Oxford, Oxford, United Kingdom

Abstract: Chloride-permeable glycine receptors have an important role in fast inhibitory neurotransmission in the spinal cord and brainstem. Human autoantibodies to glycine receptors are found in a substantial proportion of patients with progressive encephalomyelitis with rigidity and myoclonus (PERM), and in other variants of stiff person syndrome (SPS). The symptoms of PERM/SPS could be explained by a failure of inhibitory neurotransmission, and at least some patients respond to immunotherapies. However, it remains unknown whether and how glycinergic neurotransmission is impacted by autoantibody binding. We purified immunoglobulin G (IgG) antibodies from four PERM/SPS patients with glycine receptor autoantibodies and four control subjects. We incubated cultured rat spinal motoneurons in each IgG sample, then recorded 'miniature' synaptic currents by whole cell patch clamp to assess the consequences of autoantibody binding on glycinergic neurotransmission. Glycinergic synaptic currents were almost completely abolished following incubation in all four patient IgGs (100.0% after 16 h incubation ($p = 0.003$)). Human autoantibodies targeting other CNS neurotransmitter receptors, such as NMDA receptors, only affect whole cell currents after several hours' incubation and this effect depends on divalency of the antibodies suggesting that a predominant pathogenic mechanism is antibody-mediated crosslinking and internalisation of receptors. In contrast, we observed substantial reductions in glycinergic currents within 15 minutes of exposure to patient IgGs ($75.3 \pm 14.1\%$ ($p = 0.021$)). When monovalent Fab fragments were generated from patient IgG samples, these also profoundly reduced glycinergic currents in three out of four cases. We conclude that human glycine receptor autoantibodies disrupt glycinergic neurotransmission, demonstrating a pathogenic role for these autoantibodies in PERM/SPS.

Furthermore our results suggest that the pathogenic mechanisms include direct antagonistic actions on glycine receptors, which has important implications for therapeutic strategies.

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Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 553.01/B23

Topic: B.07. Synaptic Plasticity

Support: NSF Research Training Grant 1547394

Title: A computational model of two-photon calcium imaging with GCaMP6 in dendrites and spines

Authors: *B. B. SCHNEIDERS[1], M. ADOFF[2], A. ABOUZEID[1], D. A. DOMBECK[2], W. L. KATH[1];
[1]Engin. Sci. and Applied Mathematics, [2]Neurobio., Northwestern Univ., Evanston, IL

Abstract: Recent *in vitro* uncaging experiments (Sheffield 2017) in CA1 pyramidal neurons investigated the spatiotemporal patterns of calcium influx, measured with GCaMP6f, resulting from different stimulation patterns of multiple dendritic spines. Spines were stimulated over 10-20 micron stretches, first individually, typically resulting in no detectable calcium transients, and then near-simultaneously until a local, branch-isolated calcium transient was generated. Depending on the laser power this often occurred with stimulation of 3-8 spines. We developed a morphologically detailed computational model of GCaMP6f fluorescence, calibrated to these *in vitro* experiments. The model features a reconstructed CA1 morphology with morphologically realistic dendritic spines, calcium influx from voltage-gated calcium channels (R-type, T-type and L-type), calcium buffering, calcium-induced calcium release, AMPA and NMDA receptors, and calcium transmembrane pumps.
We verify that the model reproduces a number of results from these uncaging experiments. In particular, dendritic and spine compartments exhibit appropriate changes in indicator fluorescence in response to simulated synaptic stimulation. A unitary event, with a depolarization of 20-25 mV in the spinehead and 10-15 mV in the local dendrite, evokes a fluorescence change that is sub-visible ($dF/F < 10\%$), as observed in the experiments. We also reproduce fluorescence changes between 40-600% in dendrite and spine for multiple and nearly coincident spine stimulations, with a larger fluorescence increase in the spinehead than dendrite for coincident synaptic input.
With the model calibrated to *in vitro* conditions, we are now employing it to understand *in vivo*

observations, mechanisms underlying the generation of local dendritic calcium transients (~5-15 microns in length), for example. Thus far it seems clear that clustered and coactive inputs are a requirement to generate such calcium transients. With sufficient clustered and co-activated synaptic input, the local dendritic calcium transients appear to result from the generation of a local regenerative nonlinear event. The model also allows us to explore what factors lead to the observation of a transient in a single spine. When we implement smaller spinehead geometries (as reported in Harris 1989), early indications are that we can generate observable transients from single spine stimulations. This takes into account that smaller spines are found to have less PSD area, and therefore fewer NMDA channels.

Disclosures: B.B. Schneiders: None. **M. Adoff:** None. **A. Abouzeid:** None. **D.A. Dombeck:** None. **W.L. Kath:** None.

Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 553.02/B24

Topic: B.07. Synaptic Plasticity

Support: AFOSR MURI FA9550-18-1-0051
NIH Grant T32EB009380
San Diego Fellowship

Title: Geometric effects on the electrochemical activity in dendritic spines

Authors: *M. BELL, P. RANGAMANI;
Univ. of California San Diego, La Jolla, CA

Abstract: Dendritic spines are centers of synaptic communication and are hotspots of electrical and chemical activity in neurons. These spines are known to have characteristic shapes that are related to their function and indicative of aging, diseases, and learning. However, this shape-function relationship is not well understood. In particular, how the shape of the dendritic spine affects the propagation of electrical activity in response to activation of glutamatergic receptors has not been well studied. This electrical activity and depolarization of the membrane causes calcium influx that triggers downstream signaling cascades that lead to long term potential and depression, and synaptic weight changes. Here we propose a spatial continuum model of calcium influx dependent on membrane voltage based on explicit ion concentration and ion influx including sodium, potassium, chloride, and calcium ion channels and AMPAR. We predict that i) the size and shape of the spine head can modify the propagation of membrane voltage, ii) internal organelles can modulate the membrane voltage through the creation of nanodomains,

and iii) the spine apparatus can potentially play a role in electrical communication through its own membrane potential changes.

Disclosures: **M. Bell:** None. **P. Rangamani:** None.

Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 553.03/B25

Topic: B.07. Synaptic Plasticity

Support: Canadian Institutes of Health Research
Canada Research Chair Program

Title: Optogenetic induction of long term potentiation at somatostatin interneuron excitatory synapses causes metaplasticity in pyramidal cell afferent pathways in hippocampus

Authors: *A. ASGARIHAFSHEJANI, I. LAPLANTE, J.-C. LACAILLE;
Univ. De Montreal, Montreal, QC, Canada

Abstract: Somatostatin-expressing cells in CA1 hippocampus (SOM-INs) are dendrite-projecting inhibitory interneurons. SOM-INs, particularly O-LM cells, differentially regulate afferents onto pyramidal cells: via distal dendritic inhibition, they downregulate activity and long-term potentiation (LTP) in the temporo-ammonic pathway (TA); via proximal dendritic disinhibition, they upregulate activity and LTP in the CA3-CA1 Schaffer collateral pathway (SC). The main excitatory inputs onto SOM-INs are from pyramidal cells and these synapses show mGluR1a-mediated LTP. This plasticity at SOM-IN input synapses results in metaplasticity in the CA1 pyramidal cell network and contributes to spatial and contextual memory consolidation. Here we aimed to establish conditions to induce synaptic plasticity in SOM-INs by optogenetics in slices and determine if optogenetically induced SOM-IN plasticity differentially affects metaplasticity in pyramidal cell SC and TA pathways. For optogenetic activation of pyramidal cell excitatory inputs to SOM-INs, we injected AAV-CaMK2a-ChR2 (E123T/T159C)-mCherry in CA1 of SOM-Cre-eYFP mice. Whole-cell recordings showed that single optogenetic stimulation locally in oriens-alveus (Polygon 400; 5mW, 470nm) elicited EPSPs ($EPSP_{opto}$) in SOM-INs in slices. Optogenetic theta burst stimulation (TBS_{opto}) produced LTP of $EPSP_{opto}$. LTP was absent with low frequency TBS_{opto} or in untetanized cells. LTP of $EPSP_{opto}$ was mediated by mGluR1a (blocked by LY367385) and mTORC1 (absent in conditional SOM;$Rptor^{-/-}$ mice). Optogenetically-induced LTP is thus analogous to electrically-evoked LTP in SOM-INs. In addition, TBS_{opto} produced LTP of electrically-evoked EPSPs ($EPSP_{elect}$) via mGluR1a and mTORC1. Furthermore, TBS_{opto} using whole field fiber illumination (300 µm diameter; Thorlabs) elicited similar LTP of $EPSP_{opto}$. Next we tested if

whole field TBS_{opto}, that produce mGluR1a- and mTORC1-mediated LTP at SOM-IN synapses, would result in a differential regulation of SC- and TA-LTP using field potential recordings in slices. 25 min after TBS_{opto}, LTP of fEPSPs induced by weak theta burst electrical stimulation was enhanced in the SC and depressed in the TA pathway. Thus, optogenetic stimulation induces mGluR1a- and mTORC1-mediated LTP at CA1 pyramidal cell excitatory synapses onto SOM-INs and is sufficient to result in differential metaplasticity in SC and TA pathways onto CA1 pyramidal cells. The optogenetic protocol for induction of LTP in SOM-INs provides a tool to determine in vivo the role of SOM-IN synaptic plasticity in hippocampal-dependent learning and memory.

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Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 553.04/B26

Topic: B.07. Synaptic Plasticity

Title: A biochemical mechanism for time-encoding memory formation within individual synapses of Purkinje cells

Authors: *A. MANDWAL, J. ORLANDI, C. SIMON, J. DAVIDSEN;
Univ. of Calgary, Calgary, AB, Canada

Abstract: Within the classical eye-blink conditioning, Purkinje cells (PCs) in the Cerebellum suppress their tonic firing rates for a well defined time period in response to a conditioned stimulus after training. Recent experiments have shown that metabotropic glutamate-based receptor type 7 (mGluR7), which resides on the PC synapses, is responsible for the initiation of the suppression of firing rate, suggesting an intrinsic mechanism within the PC for the temporal learning. These receptors activate G-protein coupled Inward Rectifier Potassium (GIRK) ion channels at the PC's synapses which causes the pause in the tonic firing rate of the cell. However, the mechanism by which the PC encodes the time-memory signature is not fully understood. We propose a biomolecular model which explains how the cell learns, stores and alters any specific time-duration memory at synapes depending upon training conditions. According to the proposed mechanism, the learning process involves trafficking of mGluR7 receptors to the PC's synapses. mGluR7 receptor opens the GIRK ion channel, while Protein Kinase A and Protein Phosphatase 1 closes the GIRK ion channel via a G-protein with the help of RGS8 proteins. The pause duration is encoded within effective rate constants of their biochemical interactions. In addition, all these proteins form together a protein complex consisting of one GIRK ion channel. We propose that such protein complex can bind more receptors which results in slower GIRK gating dynamics. As there are several such protein

complexes present at the synapse, their collective dynamics allow the PC to produce any pause duration just by changing the total amount of receptors at the synapse. While the learning process involves placing of receptors at synapses, their removal causes memory loss. To validate the mechanism, we implement a mathematical model focussing on biomolecule interactions governing GIRK ion channels gating dynamics and combined it with a realistic biophysical model of the PC. With this, we are able to reproduce the ensemble of pause durations, consistent with experimental results. This implies that individual PC's synapses can also store more complex memories such as time-duration memory within itself than simply synaptic strengths.

Disclosures: **A. Mandwal:** None. **J. Orlandi:** None. **C. Simon:** None. **J. Davidsen:** None.

Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 553.05/B27

Topic: B.07. Synaptic Plasticity

Support: ZonMw – The Netherlands Organisation for Health Research and Development, grant nr. 733050106, dementia research and innovation programme 'Memorabel'

Title: Variance analysis on synaptic currents predicts the source of plasticity at hippocampal synapses

Authors: *A. N. VAN HUIJSTEE[1,2], C. A. P. SILVA[2], C. LOHMANN[2], H. W. KESSELS[1,2]; [1]Swammerdam Inst. for Life Sci., Univ. of Amsterdam, Amsterdam, Netherlands; [2]Netherlands Inst. for Neurosci., Amsterdam, Netherlands

Abstract: Experiences can remodel neural circuitries by strengthening some synapses and weakening others. The strength of synaptic transmission onto a neuron largely depends on three parameters: the number of functional release sites (N), the presynaptic probability of vesicle release (P_r), and the quantal size (Q), defined as the amplitude of the postsynaptic response to the release of a single vesicle of neurotransmitter. Current electrophysiological techniques cannot directly assess which of these parameters is altered when a change in synaptic strength is observed. Instead, statistical tools based on the quantal model of synaptic transmission can be used to acquire information about which of the three parameters is the source of plasticity by analyzing the variance in the amplitude of stimulus-evoked excitatory postsynaptic currents (EPSCs) before and after a synaptic modulation using binomial statistics. We show that the Variance-to-Mean Ratio (VMR) is determined by P_r and Q, but is independent of N. Combining this tool with the conventional quantal measure of $1/CV^2$ (CV = coefficient of variation), which is not dependent on Q but instead on P_r and N, allows for a simple and reliable prediction of the mechanisms underlying synaptic plasticity. We used this variance analysis to assess the subunit-

specific distribution of AMPA- and NMDA-receptors at synapses. Our analysis suggests that while AMPA-receptors are evenly distributed across synapses, GluN2A- and GluN2B-containing NMDA-receptors appear to be largely segregated from each other at different synapses.

Disclosures: A.N. Van Huijstee: None. **C.A.P. Silva:** None. **C. Lohmann:** None. **H.W. Kessels:** None.

Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 553.06/B28

Topic: B.07. Synaptic Plasticity

Title: Identification of a novel calcineurin a phosphorylation site as marker of neuronal activity through phosphoproteome analysis

Authors: *K. PEREZ DE ARCE[1], L. LI[1], R. ASHMAD[2], A. CAMPBELL[1], A. GOSHAL[1], M. E. FITZPATRICK[1], M. NAGIEC[1], J. MADISON[1], K. DUONG[1], R. HOFFING[1], M. WEIWER[1], F. F. WAGNER[1], M. J. SUCZ[2], J. SHAW[3], A. J. KOLESKE[3], S. A. CARR[2], E. M. SCOLNICK[1], Y.-L. ZHANG[1], J. R. COTTRELL[1];
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Abstract: The highly polygenic nature of psychiatric diseases is one of the major challenges in the study of the mechanisms underlying the etiology of these disorders. To address this challenge we took advantage of unbiased proteomic and phosphoproteomic analysis to uncover the specific biochemical signaling pathways of synaptic plasticity controlled by disease-associated genetic perturbations. We identify novel readouts for synaptic plasticity signaling using chemical LTP in neuronal cultures: 9370 proteins and 13904 phosphosites with statistically significant phopshorylation changes at >60 sites. Interestingly, calcineurin A subunit alpha isoform (CNAα), one of the first phosphatases activated by calcium influx downstream NMDAR, showed over 5-fold increase at 5min post-chemical LTP in the phosphorylation of a novel serine residue associated for first time to synaptic plasticity. Crystal structure analysis and biochemical studies indicated that phosphorylation of this site enhance CNAα activity. We generated phosphospecific antibodies to CNAα and verified increased CNAα phosphorylation at the serine site in vitro and in hippocampal slices. Moreover, using high-content imaging we observed this phosphorylation event increased under multiple stimuli inducing network activity but was blocked by network activity inhibition with TTX suggesting a key role as neuronal activity marker. In addition, mapping of the signaling pathways resulting in this phosphorylation were performed using a library of siRNA in combination with in vivo disease-relevant perturbations. Our findings point to a novel role of calcineurin phosphorylation in synaptic function and

highlight the power of unbiased phosphoproteomics for defining the signaling pathways of synaptic plasticity

Disclosures: **K. Perez De Arce:** None. **L. Li:** None. **R. Ashmad:** None. **A. Campbell:** None. **A. Goshal:** None. **M.E. Fitzpatrick:** None. **M. Nagiec:** None. **J. Madison:** None. **K. Duong:** None. **R. Hoffing:** None. **M. Weiwer:** None. **F.F. Wagner:** None. **M.J. Sucz:** None. **J. Shaw:** None. **A.J. Koleske:** None. **S.A. Carr:** None. **E.M. Scolnick:** None. **Y. Zhang:** None. **J.R. Cottrell:** None.

Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 553.07/B29

Topic: B.07. Synaptic Plasticity

Support: German-Israeli-Foundation; GIF G-1317-418.13/2015

Title: Tumor necrosis factor modulates hippocampal synaptic plasticity through intracellular calcium stores

Authors: *D. KLEIDONAS[1,2,3], M. LENZ[1], N. MAGGIO[4,5,6,7], A. VLACHOS[1,8];
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Abstract: The role of the pro-inflammatory cytokine tumor necrosis factor (TNF) in synaptic plasticity has been extensively studied. Nevertheless, it remains unclear how TNF asserts its effects on neural plasticity. Although TNF mediated effects on glial cells are well-described, the neuronal targets through which TNF modulates the ability of neurons to express plasticity remain unknown. Here, we used organotypic entorhino-hippocampal tissue cultures to test for TNF-induced modulation of Schaffer-collateral CA1 synapses. Using extracellular recordings, whole-cell patch-clamp recordings and immunostainings we show that TNF modulates neural circuits in a dose-dependent manner: high concentrations of TNF impair synaptic plasticity, whereas low concentrations of TNF improve the ability of neurons to express plasticity. These metaplastic effects of TNF are accompanied by changes in the actin-associated protein synaptopodin which has been firmly linked to the expression of associative and homeostatic plasticity. In line with

these findings, 24 h TNF-treatment (6nM) causes changes in synaptopodin expression. These results further elucidate the role of TNF in modulating synaptic plasticity, here by acting through synaptopodin-associated intracellular calcium stores.

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Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 553.08/B30

Topic: B.07. Synaptic Plasticity

Support: NIH Grant R01 NS044916
NIH Grant F31 NS100300

Title: The role of AnkyrinR in perineuronal nets in parvalbumin-positive inhibitory interneurons

Authors: *S. R. HA[1], J. OSES-PRIETO[2], A. L. BURLINGAME[2], M. N. RASBAND[1]; [1]Dept. of Neurosci., Baylor Col. of Med., Houston, TX; [2]Dept. of Pharmaceut. Chem., Univ. of California, San Francisco, CA

Abstract: The ankyrin family of proteins, AnkR, AnkB and AnkG, corresponding to the genes *ANK1-3*, respectively, are critical for membrane domain organization and protein stabilization in many cell types throughout the body. In the nervous system, AnkG and AnkB are known to function as important domain organizers; however, AnkR's role in the nervous system is poorly understood. Intriguingly, several large independent epigenome-wide association studies (EWAS) identified differentially methylated regions of the *ANK1* gene, in which hypermethylation was correlated with onset and neuropathology of Alzheimer's disease. Moreover, AnkR has been linked to de novo mutations in schizophrenia. Our expression analyses show AnkR is highly expressed in the somatodendritic domain of a subset of neurons, including forebrain parvalbumin-positive (Pv^+) interneurons with 94 ± 1.2% and 93 ± 0.9% of Pv^+ cells expressing AnkR in the cortex and hippocampus, respectively. Interestingly, AnkR's spatial expression overlaps with that of perineuronal nets (PNNs), preferentially surrounding Pv^+ cells. Moreover, AnkR increases expression levels during postnatal development, following a similar temporal expression pattern as PNNs. To elucidate the role of AnkR in these cells, we used the Cre/Lox system to create AnkR conditional knockout mice (AnkR cKOs). AnkR floxed animals were crossed with Nestin-Cre and Dlx5/6-Cre to investigate the role of AnkR in the nervous system as a whole and specifically in forebrain GABAergic neurons, respectively. To identify the molecular mechanisms underlying these changes, we performed mass spectrometry screens and biochemical analysis yielding AnkR's interactors, including PNN proteins brevican, versican, and tenascin-R. Furthermore, our data show AnkR has multiple spectrin binding partners in the

brain, including beta-I spectrin that is also highly expressed in the somatodendritic domain of Pv^+ cells. Both *in vitro* and *in vivo* immunoprecipitation protein interaction assays show AnkR interacts with Neuropilin-1, PlexinA1, and PlexinA4. These proteins function as signal transduction receptors for Semaphorin3A previously shown to be enriched in PNNs. Taken together, these data suggest AnkR is important for tethering somatodendritic molecules, including membrane proteins interacting with PNNs, to the spectrin cytoskeleton in specific neuronal membrane domains. Future work will focus on increasing our understanding AnkR's role in PNN function, which may enable further characterization of the molecular mechanisms underlying altered cortical excitability observed in neurodegenerative and neurodevelopmental disorders.

Disclosures: S.R. Ha: None. **J. Oses-Prieto:** None. **A.L. Burlingame:** None. **M.N. Rasband:** None.

Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 553.09/B31

Topic: B.07. Synaptic Plasticity

Support: CIHR Project Grant (PI)

Title: Characterization of perineuronal nets in human entorhinal cortex, hippocampus and ventromedial prefrontal cortex

Authors: *C. BELLIVEAU[1,2], A. TANTI[1], A. MCFARQUHAR[2], F. DENUX[1], M. DAVOLI[1], N. MECHAWAR[1,2];
[1]Douglas Hosp. Res. Ctr., Montreal, QC, Canada; [2]McGill Univ., Montreal, QC, Canada

Abstract: Background: Childhood and adolescence are marked by profound changes in functional cortical connectivity and a period of heightened plasticity. One of the major mechanisms involved in shutting down these critical windows of plasticity is the development of perineuronal nets (PNNs), a lattice-like condensed extracellular matrix structure that forms around various types of neurons in the brain, most notably parvalbumin-positive (PV) inhibitory interneurons and pyramidal cells. By acting as a mechanical and chemorepellent barrier around neurons, PNNs restrict axonal and dendritic growth and limit the mobility of neurotransmitter receptors playing an important role in modulating functional neural networks. Our work aims to further characterize the cellular and molecular features of PNNs in the post-mortem human brain. **Methods**: Blocks of frozen post-mortem human entorhinal cortex (EC), hippocampal and ventromedial prefrontal cortex (vmPFC) samples (Douglas-Bell Canada Brain Bank) were dissected, shortly fixed in formalin, cut on a cryostat and free-floating sections were processed

for immunohistochemistry (PV and NeuN). PNNs were visualized using biotin-conjugated Wisteria Floribunda Lectin followed by immunofluorescent detection using fluorophore-conjugated streptavidin. Whole slide images were analyzed using QuPath and ImageJ. **Results**: We show that we can reliably label PNNs in combination with neuronal markers using immunofluorescence in human postmortem samples, warranting that we can apply this procedure to further characterize cellular and molecular features of PNN formation during normal and pathological development. Our preliminary observations show that PNNs display region-specific quantitative and qualitative features in the different subfields of the hippocampus, the EC and the vmPFC. **Conclusions**: Our exploratory results suggest that PNNs display region-specific features that are likely to be associated with differences in information processing. Further understanding the cellular and molecular properties of these structures in different regions of the human brain will allow better appreciation of the nature of the PNN changes that have been associated with various CNS disorders.

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Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 553.10/B32

Topic: B.07. Synaptic Plasticity

Support: NEI R01 EY028212

Title: Subanaesthetic ketamine reactivates adult visual cortical plasticity to restore vision from amblyopia

Authors: *S. F. GRIECO[1], Q. QIAO[1], X. ZHENG[1], T. HOLMES[1], S. P. GANDHI[2], X. XU[3]; [1]UCI, Irvine, CA; [2]Neurobio. and Behavior, Univ. of California Irvine Dept. of Neurobio. and Behavior, Irvine, CA; [3]Anat. and Neurobio., Univ. California, Irvine, Irvine, CA

Abstract: A low dose of ketamine can elicit rapid and long-lasting antidepressant effects in patients for up to 2 weeks, well beyond ketamine's chemical half-life time of ~2 hours. This suggests that ketamine modulates adult brain plasticity. Here we show that subanaesthetic ketamine reactivates visual cortical plasticity. We subjected mice (P90-P120) to monocular deprivation (MD) for four days, which is known not to induce ocular dominance plasticity. Robust ocular dominance plasticity is induced after MD and ketamine treatment (administered at the start of 4-day MD). We further tested if ketamine can restore visual perception from critical-period amblyopia, using the visual water task. This shows a restoration of acuity with ketamine. We identify that in vivo single-dose ketamine treatment results in sustained down-regulation of

neuregulin-1 (*nrg1*) expression in parvalbumin-expressing (PV) inhibitory interneurons in mouse primary visual cortex (V1), at 24, 48 and 72 hours post treatment. Translating ribosome affinity purification was employed to measure cell-specific mRNAs under different conditions. In contrast, there is no significant change of NRG1 expression in excitatory neurons while there is sustained enhancement of pCREB activity in excitatory neurons following ketamine treatment. To test if subanaesthetic ketamine increases cortical excitability by attenuating inhibitory inputs onto pyramidal neurons (disinhibition), we performed whole-cell recording of electrically-evoked inhibitory postsynaptic currents (IPSCs) in pyramidal neurons in V1 cortical layer 2/3. Single-dose ketamine treatment evokes sustained reduction in synaptic inhibition to excitatory neurons up to a week. To test if PV neurons are the initial circuit locus for ketamine's action, we mapped excitatory inputs (EPSCs) to PV inhibitory neurons in L2/3 of the visual cortex using laser scanning photostimulation (LSPS). Correlating with cortical disinhibition, single-dose ketamine treatment evokes sustained reduction in excitatory inputs to PV neurons. PV-specific ErbB4 ablation abolishes ketamine-induced plasticity. Reciprocally, exogenous NRG1 rapidly restores excitatory inputs onto PV neurons in ketamine-treated cortex to enhance cortical inhibition. Thus, ketamine effects on cortical plasticity are mediated by sustained cortical disinhibition via downregulation of neuregulin-1 (NRG1) signaling in parvalbumin-expressing (PV) inhibitory interneurons. Our findings reveal molecular, cellular and circuit mechanisms of ketamine-mediated induction of cortical plasticity to promote functional recovery from amblyopia.

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Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 553.11/B33

Topic: B.07. Synaptic Plasticity

Support: MINECO-FEDER (BFU2014-56164-P)
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Fundación Tatiana Perez de Guzmán el Bueno
UCLM Reseach Programme

Title: Role of GirK channels in long-term potentiation of synaptic inhibition in an *in vivo* mouse model of early amyloid-β pathology

Authors: *J. NAVARRO-LOPEZ[1], I. SÁNCHEZ-RODRÍGUEZ[2], A. GRUART[3], J. DELGADO-GARCIA[4], L. JIMENEZ-DIAZ[5];
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Abstract: Imbalances of excitatory/inhibitory synaptic transmission occur early in the pathogenesis of Alzheimer's disease (AD), leading to hippocampal hyperexcitability and causing synaptic, network, and cognitive dysfunctions. G-protein-gated potassium (GirK) channels play a key role in the control of neuronal excitability, contributing to inhibitory signaling. Here, we evaluate the relationship between GirK channel activity and inhibitory hippocampal functionality in vivo. In a non-transgenic mouse model of AD, field postsynaptic potentials (fPSPs) from the CA3-CA1 synapse in the dorsal hippocampus were recorded in freely moving mice. Intracerebroventricular (ICV) injections of amyloid-β (Aβ) or GirK channel modulators impaired ionotropic ($GABA_A$-mediated fPSPs) and metabotropic (GirK-mediated fPSPs) inhibitory signaling and disrupted the potentiation of synaptic inhibition. However, the activation of GirK channels prevented Aβ-induced changes in $GABA_A$ components. Our data shows, for the first time, the presence of long-term potentiation (LTP) for both the $GABA_A$ and GirK-mediated inhibitory postsynaptic responses in vivo. In addition, our results support the importance of an accurate level of GirK-dependent signaling for dorsal hippocampal performance in early amyloid pathology models by controlling the excess of excitation that disrupts synaptic plasticity processes.

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Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

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Program #/Poster #: 553.12/B34

Topic: B.07. Synaptic Plasticity

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National Medical Research Council Collaborative Research Grant NMRC-OFIRG-0037-2017
National University of Singapore Strategic and Aspiration Research Funds, and Ministry of Education Academic Research Fund Tier 3 Grant MOE2017- T3-1-002

Title: Inhibition of G9a/GLP complex rescues synaptic plasticity deficits in the hippocampal area CA1 in APP/PS1 mouse model of Alzheimer's disease

Authors: *K. PANG[1,2], J. LEE[1,2], S. SAJIKUMAR[1,2];
[1]Dept. of Physiol., Natl. Univ. of Singapore, Singapore, Singapore; [2]Neurobiology/Aging Programme, Life Sci. Institute, Ctr. for Life Sci., Singapore, Singapore

Abstract: Memory impairments are characteristic symptoms of Alzheimer's disease (AD), a progressive neurodegenerative disorder. Synaptic dysfunction has been widely considered to contribute to the cognitive deficits, especially in the early stages, in AD. Characterizing such synaptic impairments and the underlying molecular mechanisms could aid in the development of therapeutic interventions. Using *in vitro* field electrophysiological recordings, we examined long-term potentiation (LTP) and synaptic tagging and capture (STC), the cellular correlates of long-term memory and associative memory, in three- to five-months-old male APP/PS1 mice, a mouse model of AD. In particular, we investigated the role of G9a/GLP complex, a histone methyltransferase implicated in learning and memory, in regulating the expression of synaptic plasticity-related proteins in AD conditions. Our data suggest that short-term pharmacological inhibition of the G9a/GLP complex ameliorated LTP and STC impairments in CA3-CA1 synapses in acute hippocampal slices of APP/PS1 mice. This rescue of synaptic plasticity was dependent on *de novo* protein synthesis. In addition, biochemical analysis results shed light on some of the molecular mechanisms that mediated this restoration of synaptic plasticity by G9a/GLP blockade. All electrophysiology experiments were conducted in at least seven hippocampal slices from at least five animals per series. And data were subjected to statistical tests including Wilcoxon signed-rank test, Mann-Whitney U-test and ANOVA as appropriate. Our study not only suggests that G9a/GLP could be a potential therapeutic target for early stage AD-related dementia, but it also delineates the role of G9a/GLP complex in mediating transcription and translation in synaptic plasticity.

Disclosures: K. Pang: None. **J. Lee:** None. **S. Sajikumar:** None.

Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

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Program #/Poster #: 553.13/B35

Topic: B.07. Synaptic Plasticity

Support: NIAAA R01-AA026186-01

Title: Extended amygdala circuits in alcohol use disorder

Authors: *N. D. WINTERS, S. PATEL;
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Abstract: Alcohol use disorder (AUD) is characterized by compulsive alcohol consumption and a shift from use to dependence. Negative affective states during withdrawal, such as anxiety, are major drivers of relapse and are intractable to current therapies for these conditions. Given a prevalence of approximately 30% of the US population and the lack of effective therapies for AUD, these challenges warrant investigation into novel treatment mechanisms for AUD. Chronic alcohol consumption and withdrawal have been shown to alter synaptic function in the central amygdala (CeA), a heterogeneous brain structure critical in the regulation of fear and anxiety. The CeA has been consistently demonstrated to be a critical locus in the generation of alcohol dependence and anxiety disorders, however, the cell type- and circuit-specific mechanisms mediating these effects have not been determined. Preliminary data from our lab demonstrate that in an animal model of AUD, chronic alcohol self-administration and withdrawal in mice results in an enhancement of spontaneous glutamatergic drive selectively onto somatostatin-expressing neurons in the CeA, an effect that persists 2 weeks into abstinence. Future studies will employ optogenetic projection-targeting strategies aimed at systematically interrogating excitatory inputs to the CeA in order to identify the source input for this enhanced glutamate release, as well as retrograde-tracing techniques to probe the effects of chronic alcohol on distinct CeA efferent projections. Additionally, the efficacies of many inputs onto CeA neurons are regulated by endocannabinoids (eCBs), bioactive signaling lipids that are released by neurons as retrograde messengers that act to reduce presynaptic neurotransmitter release probability. The eCB system has been consistently implicated in the regulation of stress and anxiety-like states, and pharmacological augmentation of eCB signaling *in vivo* has been demonstrated to be anxiolytic in animal models of AUD. The proposed studies are aimed at identifying the cell type- and circuit-specific mechanisms by which chronic alcohol consumption and protracted withdrawal result in maladaptive synaptic remodeling within the CeA to produce heightened states of anxiety, and the role of eCBs in modulating these effects. Collectively, these studies will provide novel insight into the neurobiological mechanisms underlying negative affect generation associated with AUD, as well as explore the therapeutic potential of developing eCB-based therapies for treating this disorder.

Disclosures: **N.D. Winters:** None. **S. Patel:** None.

Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

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Topic: B.07. Synaptic Plasticity

Support: Craig H. Neilsen Foundation SCIRTS Pilot Research Grant #476951 (Gonzalez-Rothi)
NIH F31 HL145831-01 (PI: Sunshine)

Title: Phrenic evoked response is enhanced after daily acute intermittent hypoxia in rats

Authors: *R. RODRIGUES PERIM, M. D. SUNSHINE, A. HOLLAND, J. SANTIAGO, G. S. MITCHELL, E. GONZALEZ-ROTHI;
Physical Therapy, Univ. of Florida, Gainesville, FL

Abstract: Plasticity is a hallmark of the respiratory system controlling breathing. A long-lasting increase in phrenic nerve activity is observed following acute intermittent hypoxia (AIH), known as phrenic long-term facilitation (pLTF). AIH induces cell signaling cascades within phrenic motor neurons, activating serotonin type 2 receptors and initiating new synthesis of BDNF protein. However, there is no direct evidence that pLTF arises via increased strength of monosynaptic inputs to phrenic motor neurons. Thus, we tested the hypothesis that AIH enhances short-latency evoked phrenic responses elicited by ventrolateral funiculus (VLF) stimulation. Respiratory cycle-triggered VLF stimulation was performed while recording phrenic nerve activity in anesthetized, paralyzed, mechanically ventilated rats, with the stimulating electrode placed 2mm below the C2 dorsal root entry zone. During baseline conditions and 60 min post-AIH, 10 bipolar pulses (1ms) of progressively increasing intensity (100 to 700μA) were applied during either the inspiratory or post-inspiratory phase of successive breaths defined by a threshold of 50% of peak activity. Although robust pLTF (~60% above baseline) was observed after AIH (3 x 5 min, PaO_2: 35-55 mmHg), there was no significant change in amplitude of evoked phrenic responses during inspiration or post-inspiration, contrary to our hypothesis. In an additional set of rats, which were treated with two weeks of daily AIH preconditioning, both baseline phrenic nerve activity and the amplitude of evoked phrenic responses were increased (during both inspiratory and post-inspiratory phase), suggesting longer duration treatment may be required to enhance synaptic strength. Further studies are needed to understand the impact of AIH and daily AIH preconditioning on synaptic inputs to phrenic motor neurons.

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Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

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Program #/Poster #: 553.15/B37

Topic: B.07. Synaptic Plasticity

Title: Molecular mechanism of non associative learning in earthworms

Authors: *Y. KITAMURA, D. SOUDA, H. FUJITA;
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Abstract: Molecular mechanism of non-associative learning in the earthworm *Eisenia fetida* is investigated. Electrophysiological recording from the ventral nerve cord of the earthworm revealed that repeated tactile stimulus to the body wall gradually decreases number of action potential. We previously reported that habituation by repeated tactile stimulus to the body wall in the earthworm is induced assumedly due to via nitric oxide (NO)-cGMP signaling, because relatively high concentration of NO or cGMP accelerated decrease of number of action potentials by single tactile stimulus. In this study, for clarifying molecular mechanism and recovery process of habituation in the earthworm, we investigated effect of 5-HT receptor antagonists and cyclic nucleotide analogues on establishment of habituation. From these results, it is revealed that 5-HT receptor antagonist delayed establishment of habituation, and only cGMP but not cAMP induced habituation. After establishment of habituation, action potential generation by tactile stimulus fully recovered after 120 min. In summary, non-associative learning such as habituation in the earthworm is short term memory and is due to via 5-HT-NO-cGMP signaling.

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Poster

553. Synaptic Plasticity: Other Mechanisms

Location: Hall A

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Program #/Poster #: 553.16/B38

Topic: B.07. Synaptic Plasticity

Support: BECA CONCYTEC 2015/UK Embassy and FONDECYT

Title: Automated quantitative assessment and classification of neuromuscular junctions

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Abstract: The neuromuscular junction (NMJ) is a peripheral synapse between the axon terminal of a lower motor neuron and a muscle fibre. In motor neuron diseases (MNDs), NMJ denervation may be concomitant with either muscle wasting, motor neuron death or both, but the underlying mechanisms leading this process are largely unknown. Studies on NMJ pathology and the morphological changes driving denervation have not been carried out across all MND mouse models. Moreover, mouse NMJ denervation is most often assessed visually. The high inter-rater variability makes such an assessment difficult to reproduce and limits further analyses on association with NMJ morphological characteristics. To overcome these limitations, in this study, morphological characteristics among which volume, surface, shape factor, length and diameter, compactness and fragmentation of pre- and post-synaptic NMJ components, were

automatically extracted and used as input of a support vector machine (SVM) learning algorithm trained in a 10-fold cross-validation setting for classification purposes. Here, we used hindlimb lumbrical muscles of Charcot-Marie-Tooth disease (CMT) type 2D ('Gars') (1-month old males) and amyotrophic lateral sclerosis (ALS, SOD1-*G93A*) (1- and 3-month old males) mouse models to follow the morphological changes of the pre- and post-synaptic NMJ components. For both mouse models, more than 5000 NMJs were manually studied and automatically characterised. Both volume and surface of CMT2D-NMJ pre- and post-synaptic components were smaller than wild-type littermates, whereas in SOD1-*G93A* the size of motor endplate remained similar at 1- and 3-months old. However, the presynaptic volume of SOD1-*G93A* was significantly smaller at 3-months old. 'Coverage', defined as the percentage of motor endplate with overlapping pre-synaptic volume staining, is reduced in both CMT2D and SOD1-*G93A* at 3 months, but not at 1 month. NMJs of SOD1-*G93A* at 1-month of age were visually classified as fully innervated in 98.6% of the cases vs 99.6% in wild-type littermates; at 3-months, only 49.8% of NMJs remained fully innervated vs 94.3% in wild-type littermates. Quantitative measurements were compared to existing licensed software output for validation of the analysis. Taken together, we confirmed the validity of our method for automated characterisation of NMJ morphology in two MND mouse models. Volume, coverage and surface appeared to be highly relevant for the distinction between disease states of NMJs and were successfully used for the automated classification of the different subtypes with an accuracy of 95%. Future work will further investigate the patterns of these pathological changes.

Disclosures: A. Mejia maza: None. **C. Sudre:** None. **J.N. Sleigh:** None. **E.M. Fisher:** None.

Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 554.01/B39

Topic: B.08. Intrinsic Membrane Properties

Support: NIH Grant DC004274
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Title: Resurgent sodium and high threshold potassium currents underlie the maturation of a zebra finch vocal motor nucleus

Authors: *B. ZEMEL[1], A. A. DAGOSTIN[2], P. V. LOVELL[3], S. R. FRIEDRICH[4], C. V. MELLO[3], H. P. VON GERSDORFF[5];
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Abstract: Zebra Finches develop learned vocalizations that are refined from unstructured notes known as subsong, to increasingly structured songs that become stable and reproducible in a process known as crystallization. The songbird brain possesses interconnected nuclei utilized for acquisition and production of learned song. Nucleus RA integrates and relays signals from the HVC and the lateral magnocellular nucleus of the nidopallium (LMAN) via its descending projections out of the telencephalon onto motor neurons innervating the finch's vocal organ, the syrinx. Its function is analogous to laryngeal motor cortex neurons that project to brainstem nucleus ambiguus in human speech circuitry, components of which are absent in non-vocal learners. RA neurons develop temporally precise, high-frequency action potential (AP) firing during the song learning period that define the acoustic structure of song syllables. The molecular determinants underlying this development are unknown. We studied developmental changes within RA of the voltage-gated sodium channel beta 4 subunit, Navβ4, and the voltage gated potassium channel alpha subunit, Kv3.1. Navβ4 acts as a fast open channel blocker that reduces the ability of Nav channels to accumulate in the inactivated state and produces resurgent currents (I_{NaR}). Kv3 subunits provide the repolarizing force needed to initiate Nav channel recovery from inactivation before the next AP. Both Navβ4 and Kv3.1 are implicated in high frequency AP firing in other systems, thus we hypothesized they might be critical for maintaining high frequency and reliable firing in RA neurons. *In situ* hybridizations at various ages during the critical period for song learning revealed expression of Navβ4 and Kv3.1 mRNA in RA, but not in the surrounding arcopallium of adult male finches or in the RA of non-vocal 20 day old juveniles. Whole-cell voltage clamp recordings in slices showed an increase in I_{NaR}, decrease in AP half-width, and increase in AP number during a current stimulus in projection neurons within RA during development. Intracellular administration of a peptide containing the Navβ4 C-terminal blocking sequence was sufficient to make juvenile RA neurons appear developmentally mature by increasing both I_{NaR} and AP firing frequency. Injection and subtraction of *in silico* I_{NaR} via dynamic clamp was sufficient to decrease and increase AP interspike intervals in juvenile and adult neurons respectively. Together, these findings reveal the developmental regulation of novel molecular determinants of neuronal excitability in a zebra finch song nucleus that plays critical roles in the production and acquisition of learned vocalizations.

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Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 554.02/B40

Topic: B.08. Intrinsic Membrane Properties

Title: Similarities in response non-linearities in macaque lateral prefrontal cortex visual neurons during *in vivo* and *in vitro* experiments. Implications for normalization models

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Abstract: Visual neurons in many brain areas show non-linear response profiles as a function of the stimulus shown inside their receptive fields. These can be fit with different non-linear functions to obtain the tuning curve of the neuron for a particular feature. One example is the contrast response function, e.g., increases in the contrast of a stimulus inside a neuron's receptive field produce changes in its response profile that can be fitted by a sigmoid function. Such properties have been attributed to lateral inhibition and normalization within a network of interconnected neurons. Here we test the hypothesis that non-linearities in response functions of single neurons during *in vivo* recordings can be at least in part attributed to their intrinsic (not network dependent) response properties. To address this issue, we first obtained response functions from single neuron recordings in the lateral prefrontal cortex (LPFC areas 8A/9/46) of two macaques to gratings of varying contrast inside their receptive fields. We then conducted patch clamp *in vitro* recordings in slices extracted from the same LPFC area of 4 macaques using square current pulses of varying intensities that attempted to simulate increases in input strength when increasing contrast. In both datasets we convert spikes trains to firing rates over 250ms of stimulus presentation (*in vivo*) or pulse duration (*in vitro*) and fit the data with a sigmoid and a linear function. From 27 *in vivo* neurons, 52% were best fitted by the sigmoid and 48% were best fitted by a line. From 31 *in vitro* neurons 45% were best fitted by the sigmoid and 55% by a line. The proportions of neurons fitted with either function was not significantly different between areas ($p>0.1$, Chi-Square test) suggesting that non-linearities in the responses of visual neurons can be explained to a large degree by intrinsic cell properties.

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Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 554.03/B41

Topic: B.08. Intrinsic Membrane Properties

Support: P50AA010761

Title: Intermittent access to alcohol enhances the intrinsic excitability of lateral orbitofrontal cortex neurons

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Abstract: In humans, chronic consumption of alcohol is often associated with dysfunction of frontal cortical areas including the orbitofrontal cortex (OFC). Recent findings from this laboratory have demonstrated that mice exposed to repeated cycles of chronic intermittent ethanol (CIE) vapor also show deficits in OFC-mediated behaviors. This was accompanied by an increase in the intrinsic excitability of lateral OFC (lOFC) neurons, reduced sensitivity to ethanol inhibition of firing and altered spontaneous synaptic transmission. In the current study, a two-bottle choice intermittent alcohol access (IAA) paradigm was used to examine whether voluntary ethanol consumption would also alter the intrinsic excitability of lOFC neurons in C57BL/6J male mice. Mice were given 24 hr access to alcohol (20% v/v) every other day for 1-day, 1-week, 4-week or 7-week. Water was provided each day and the location of the alcohol bottle was alternated each session. Mice were sacrificed 24 hr following the final day of the drinking paradigm and brain slices containing the lOFC were prepared for whole-cell patch-clamp electrophysiology recording. While no difference in spike number was noted between controls and 1-day IAA mice; mice that received 1-week, 4-week and 7-week IAA showed a significant increase in current-evoked action potential (AP) spiking as compared to their water-drinking counterparts. In particular, neurons from the 4-week IAA group showed a near doubling in APs as compared to their water-drinking counterparts. We then tested whether IAA would also alter the inhibition of firing during bath application of ethanol. Ethanol (11, 33 and 66 mM) produced a significant reduction in AP spiking in 1-day, 1-week, 4-week and 7-week water-drinking groups in a concentration-dependent manner. Similarly, significant decreases in spike firing by acute ethanol were observed in 1-day, 1-week and 7-week IAA drinkers. However, there was a total loss of ethanol inhibition in lOFC neurons from the 4-week IAA mice. Unlike CIE-induced increases in sEPSCs and sIPSCs, no change in amplitude and frequency of sEPSCs and sIPSCs in IAA animals. Overall, these results suggest that similar to that reported in mice following

chronic ethanol vapor exposure, voluntary ethanol consumption leads to enhanced intrinsic excitability of lOFC neurons and blunted responsiveness to acute ethanol. These alterations may contribute to the impairment of OFC-dependent behaviors often observed in alcohol-dependent individuals. Supported by P50AA10761.

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Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

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Topic: B.08. Intrinsic Membrane Properties

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Title: Impact of a novel slow afterhyperpolarization (sAHP) on spike encoding by serotonergic (5-HT) dorsal raphe (DR) neurons

Authors: M. ISHIBASHI[1], E. A. BERRY[2], N. E. MOLINA[2], T. SATO[2], A. FUKUDA[1], *C. S. LEONARD[2];
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Abstract: Serotonergic dorsal raphe neurons regulate numerous functions including behavioral state, reward and mood and are themselves regulated by orexin peptide inputs. Indeed, orexin receptor signaling at these neurons rescues cataplexy in the sleep disorder narcolepsy. We recently reported that in addition to activating a depolarizing cation current, orexin-A strongly enhances the post-spike afterhyperpolarization in 5-HT DR neurons. This orexin-enhanced AHP (oeAHP) requires Ca^{2+} influx and has two distinct components: a shorter one (tau ~ 0.5s), mediated by enhanced SK channel activation; and a longer one (tau ~ 5s), that is apamin-insensitive (ai-oeAHP). The ai-oeAHP is a novel sAHP since it not blocked by internal cesium but is blocked by flufenamic acid or NMDG substituted for Na^+ in the ACSF and is accompanied by a reduced membrane noise and conductance suggesting it results from transient Ca^{2+}-mediated inhibition of the depolarizing orexin cation current. Here we have utilized current clamp and dynamic clamp recordings in mouse brain slices to investigate the role of the ai-oeAHP in regulating 5-HT DR neuron firing. Apamin increased excitability of 5-HT DR neurons but orexin-A still reduced steady-state repetitive firing without reducing initial firing indicating the ai-oeAHP enhances spike-frequency adaptation. Since membrane conductance is decreased

during the ai-oeAHP, we postulated that synaptic responsiveness might be preserved during the ai-oeAHP, rather than shunted as expected from the classical sAHP. To test this, we delivered either a virtual ai-oeAHP or virtual classical sAHP conductance by dynamic clamp and compared their effects on responsiveness to a virtual EPSP burst. Preliminary findings indicate that both virtual sAHPs slowed firing produced by either a constant driving current or virtual noisy orexin current, but that spike induction by the virtual EPSP burst was better preserved during the ai-oeAHP. This supports the idea that in addition to the high-pass filtering of inputs conferred by the oeAHP, the novel mechanism underlying the ai-oeAHP functions to preserve spike encoding of transient synaptic signals. Thus, the loss of orexin in narcolepsy would be expected to degrade this function and interfere with the ability of 5-HT neurons to adequately encoding synaptic signals which thereby may contribute to the expression of cataplexy.

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Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

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Topic: B.08. Intrinsic Membrane Properties

Support: NIH Grant R01 DA041808

Title: Pathophysiological concentrations of acetic acid from ethanol metabolism increases excitability of medium spiny neurons in the nucleus accumbens shell

Authors: *A. D. CHAPP[1], P. G. MERMELSTEIN[2], M. THOMAS[3];
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Abstract: Ethanol metabolism leads to increased concentrations of acetic acid in both the peripheral system and brain. In brain, peak acetic acid concentrations can reach 2-5 mM and remain elevated for several hours following metabolism and clearance of a modest dose of ethanol ingestion. Given the biological activity of acetic acid *in vivo* and *in vitro*, and the limited degree to which it has been explored in alcohol research, we investigated whether acetic acid is capable of altering neuronal function. As the nucleus accumbens is a key node in the mammalian reward circuit that contributes to the rewarding aspects of alcohol use, we focused our study on medium spiny neurons (MSN) of the nucleus accumbens shell (NAcSh). We performed a time-course (pre acetic acid, 1 min post acetic acid and 3 min post acetic acid), of whole-cell miniature excitatory postsynaptic current (mEPSC) recordings of MSNs within the NAcSh in the presence and absence of acetic acid. Bath application of a pathophysiological acetic acid

concentration (4 mM) significantly ($p < 0.05$) increased mEPSC frequency (Hz) in a time-dependent manner (3.6 ± 0.95, 5.3 ± 1.3 and 6.1 ± 1.1 respectively, n=4). Time-course control displayed no significant ($p = 0.91$) alterations in mEPSC frequency (2.4 ± 0.7, 2.7 ± 0.6 and 2.6 ± 0.6, n=3). mEPSC amplitudes (pA) were unaltered in acetic acid treated cells (15.2 ± 1.6, 15.9 ± 2.5 and 15.6 ± 2.2 respectively) or time-course control cells (15.2 ± 1.5, 14.8 ± 1.5 and 14.3 ± 1.3). In current-clamp, we performed a current injection response curve with both time-course (pre, 5 min and 10 min) and dose response of acetic acid (0, 2 and 4 mM). Acetic acid (2 and 4 mM) produced a left shift in the stimulus response curve compared to pre-acetic acid application ($p < 0.05$). Likewise, acetic acid (4 mM) significantly ($p = 0.002$) increased E_{max} firing frequency compared to pre-acetic acid (19.69 ± 3.24 Hz vs 14.69 ± 3.32 Hz, n=4). Time course control displayed no significant changes ($p = 0.84$) in E_{max} (15.00 ± 0.51 Hz vs 14.69 ± 1.07 Hz, n=4) or stimulus response curve. These data suggest that the generation of acetic acid through ethanol metabolism is capable of increasing glutamatergic activity and excitability in MSNs of the NAcSh. Future studies will be needed to determine the extent to which this modulation may contribute to the rewarding effects of alcohol consumption.

Disclosures: A.D. Chapp: None. **P.G. Mermelstein:** None. **M. Thomas:** None.

Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

Location: Hall A

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Topic: B.08. Intrinsic Membrane Properties

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Title: Oxytocin modulates the electrical properties of liver-projecting DMV neurons

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Abstract: The dorsal motor of vagus nucleus (DMV) is the main parasympathetic output of central nervous system to the periphery, including to gastrointestinal tract, such as liver, with the involvement of the paraventricular nucleus oh hypothalamus (PVN) in this neuronal circuit, through a PVN-DMV-liver communication, to control hepatic glucose production (HGP). Previous studies from our laboratory have shown that after i.c.v injection of insulin, Wistar rats presents a decrease on HGP, an effect not observed in an animal model of sympatho-vagal

imbalance, the spontaneously hypertensive rats (SHR). However, when SHR are subjected to aerobic exercise training on treadmill for 4 weeks, the response was similar to Wistar rats. Based on literature that there is an oxytocin (OT) secretion, coming from PVN to DMV and that physical exercise may improves this signaling, herein we analyzed the OT effects on liver-projecting DMV neurons electrical properties from Wistar (W), SHR (SHRs) and trained SHR (SHRt) using the whole-cell patch-clamp technique.
We observed that: a) OT produced a depolarization of the resting membrane potential in W (-59,4 ± 0,748 mV vs -56,2 ± 1,209 mV, n = 10, p < 0,05) and SHRt (-61,33 ± 1,283 mV vs -59,61 ± 1,453 mV, n = 18, p < 0,05), reflecting increases in the firing frequency of these cells (W = 1,86 ± 0857Hz vs 3.044 ± 0,97Hz, n = 10, p < 0,001, and SHRt = 3.924 ± 0.67Hz vs 4.762 ± 0.645Hz, n = 18, p < 0,01). However, these changes were not observed in SHRs (Vm = -59.0 ± 1.267mV vs -57.75 ± 1.175 mV, n = 12, p = 0,1007; Frequency= 2.856 ± 0.638 Hz vs 4.144 ± 0,607Hz, n = 12, p = 0,159); b) no changes were found in excitability and in the input resistance in all groups analyzed.
These findings contribute for a better understanding of how an imbalance of sympathetic and parasympathetic nervous system could affect the central nervous system control of hepatic glucose production.

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Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

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Topic: B.08. Intrinsic Membrane Properties

Support: BBSRC Grant BB/N019512/1

Title: Spontaneous spike homeostasis as a protective mechanism against reactive oxygen species (ROS) saturation

Authors: *C. CHINTALURI, T. VOGELS;
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Abstract: The spontaneous firing rate of neurons varies according to cell-type, but it's also affected by nutrient levels, fatigue, and circadian phase. Spontaneous firing often persists in the absence (and even deprivation) of synaptic input. This seems perplexing, especially given that action potentials are metabolically expensive, and the majority of neuronal energy resources are allocated to maintain sodium (Na) and potassium (K) gradients. In line with recent results on the involvement of mitochondrial respiration in homeostatic firing-rate regulation, we propose a

model that links the metabolic creation of reactive oxygen species (ROS) with the regulation of spontaneous firing rates, so to serve as a protective mechanism against ROS saturation.
The majority of cellular ROS --- which is toxic to many cellular processes --- is generated in the mitochondria under two well-established conditions. Firstly, in situations nearing ATP-depletion, the high mitochondrial respiration rates necessary to replenish ATP levels also generate excessive ROS. Neurons are especially vulnerable to this "exhaustive-ROS" saturation under conditions that also lead to excitotoxicity. Secondly, in situations of low ATP demand, ATP production is stalled and electrons taxiing in the transport chain jump the production line to combine with intracellular oxygen to produce ROS. We postulate that quiescent neurons in the absence of sensory inputs are ATP saturated and thus vulnerable to this second type of "energetic-ROS" saturation. Using a conductance-based neuron model that includes mitochondrial ATP production and ROS generation we can explore the interaction of well-established ROS-driven changes in voltage-gated Na, K and Ca channels and ATP-sensitive K channels. In our model, cellular processes act to minimize ROS either through ROS-mediated ion-channel changes that lead to ATP-consuming spikes which relieve the cell of energetic-ROS, or by making spikes less frequent that allow replenishment from ATP depletion during exhaustive-ROS. We thus propose a direct and self-regulating negative feedback mechanism between spontaneous neuronal firing and ROS concentration.

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Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

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Topic: B.08. Intrinsic Membrane Properties

Support: NCCIH Intramural Research Program

Title: Electrophysiological properties of genetically distinct nociceptive neurons in the central amygdala

Authors: *A. ADKE[1], A. KHAN[1], H. H. AHN[1], Y. K. SUGIMURA[2], T. WILSON[1], Y. CARRASQUILLO[1];
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Abstract: Despite the high incidence of chronic pain, therapeutic options are limited and much of the underlying neurobiology is unknown. Recently, the central nucleus of the amygdala (CeA) emerged as a critical center for pain processing, receiving direct nociceptive input from the parabrachial nucleus (PBN). Research in our lab found that distinct GABAergic CeA cell types

contribute differently to pain-related behaviors in mice. For example, during pain states, cells expressing Protein Kinase C delta (CeA-PKCδ) display increased excitability and promote hypersensitivity while somatostatin-expressing (CeA-Som) neurons suppress excitability and promote hyposensitivity. The cellular mechanisms driving this dual and opposing modulation of pain-related behaviors remain unknown. To begin to address this, we aim to determine whether intrinsic membrane properties of and PB inputs to CeA neurons are cell-type-specific. Using optogenetically-assisted circuit mapping of PBN-CeA circuits, we found that both CeA-PKCδ and CeA-Som cells receive PBN inputs and respond to PB terminal stimulation with similar magnitude. Interestingly, experiments using whole-cell patch-clamp recordings in acute slices demonstrated that CeA-PKCδ cells, which are more excitable in pain states, are less excitable than CeA-Som neurons at baseline. In contrast, CeA-Som cells are more excitable in baseline states but show decreases in excitability following nerve injury. Further analyses of firing properties and action potential waveforms demonstrated that in pain states, CeA-PKCδ cells have increased input resistances, decreased latencies to fire, and longer action potential durations. These results are consistent with decreased transient A-type potassium currents (I_A) following nerve injury. Ongoing experiments aim to establish a causal relationship between nerve injury, changed I_A current density, and behavioral hypersensitivity. Altogether, our results characterize firing properties of genetically distinct cells and suggest that pain-related hyperexcitability in CeA-PKCδ cells is due, at least in part, to alterations at the intrinsic level, thus identifying a potential source of pain plasticity and therapeutic target.

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Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

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Topic: B.08. Intrinsic Membrane Properties

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Title: Microglia-triggered plasticity of intrinsic excitability modulates psychomotor behaviors in acute cerebellar inflammation

Authors: *G. OHTSUKI[1], M. YAMAMOTO[2], M. KIM[1], H. IMAI[3], Y. ITAKURA[4];
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Abstract: Cerebellar dysfunction is involved in various psychiatric disorders, including autism-spectrum and depressive disorders. However, the physiological aspect is less-advanced. We have previously reported the induction of intrinsic plasticity of the cerebellar Purkinje cells and its associated plasticity of the dendrite excitability (Belmeguenai et al. 2010, J. Neurosci.; Ohtsuki et al., 2012, Neuron; Ohtsuki and Hansel, 2018, iScience). Here, we comprehensively investigated the immune-triggered hyperexcitability in the cerebellum. Activated microglia via exposure to bacterial endotoxin lipopolysaccharide or heat-killed Gram-negative bacteria induced a potentiation of the intrinsic excitability in Purkinje neurons, which was suppressed by microglia-activity inhibitor and microglia-depletion. An inflammatory cytokine, tumor necrosis factor-<alpha> (TNF-<alpha>) released from microglia via toll-like receptor 4 triggered this plasticity. While our two-photon FRET ATP-imaging showed an increase in ATP concentration following endotoxin exposure, both TNF-<alpha> and ATP secretion facilitated synaptic transmission. Region-specific inflammation in the cerebellum in vivo showed depression- and autistic-like behaviors. Such behavioral modulation was reverted by both TNF-<alpha>-inhibition and microglia-depletion. Resting-state functional MRI revealed overconnectivity between the inflamed cerebellum and prefrontal neocortical regions. Thus, immune activity in the cerebellum induces neuronal hyperexcitability and disruption of psychomotor behaviors in animals (Yamamoto et al., Cell Reports, 2019).

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Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

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Topic: B.08. Intrinsic Membrane Properties

Support: NIH Grant NS62771

Title: Cholinergic modulation of intrinsic plasticity in layer 2/3 pyramidal neurons of the mouse barrel cortex

Authors: D. F. GILL, ***C. HANSEL**;
Neurobio., Univ. of Chicago, Chicago, IL

Abstract: Long-term potentiation of synaptic inputs is widely considered the cellular mechanism underlying learning and memory. However, the degree to which EPSPs generated in the distal dendrite control spike output depends on intrinsic excitability that regulates EPSP propagation toward the soma (Larkum et al., *J. Physiol.* 533, 2001). Here, we sought to examine the mechanisms by which cortical pyramidal neurons can modify their excitability to enhance spike output. Using whole-cell patch-clamp recordings from layer II/III pyramidal neurons in slices prepared from the mouse (P28-40) primary somatosensory cortex (S1), we studied mechanisms underlying plasticity of membrane excitability ('intrinsic plasticity', IP). Measuring spiking responses (spike count) elicited by depolarizing current injection in wild-type (WT) mice, we could induce an average change in excitability of 148 ± 13% compared to baseline spiking (n=14). After this finding, we hypothesized this change was due to internalization of SK2 channels. SK2 channels are small-conductance, calcium-gated potassium channels, which serve to hyperpolarize the cell in response to burst activity. When the somatic protocol was tested in SK2-KO mice, we could no longer elicit changes in excitability (105 ± 8% in comparison to baseline, n=8) suggesting IP occlusion. We went on to test for the involvement of protein kinases in this SK2-dependent excitability regulation. Using an adapted synaptic protocol, we attempted to induce IP in a mouse with a mutant CaMKII which is permanently inhibited, the CaMKII 305D line (Elgersma et al., *Neuron* 36, 2002). However, changes in IP were CaMKII independent with a 165 ± 27% and 148 ± 21% change in excitability for WT and CaMKII 305D neurons, respectively (n=7 and 13). We then tested if SK2 channels were internalized (PKA-dependent) using the PKA inhibitor H89, and we could not induce IP under these conditions (82 ± 9%, n=6). Lastly, we sought to understand the role and convergence of muscarinic signaling on IP. To test this, we bath applied oxotremorine-m (oxo-m, muscarinic agonist) alone and during the somatic depolarization protocol. Oxo-m was able to increase excitability 147 ± 14% and showed enhancement to 212 ± 20% when paired with somatic stimulation (n=7 and 8). When oxo-m was applied to SK2-KO neurons, it no longer had an effect on the excitability of the cell (105 ± 9%; n=5). These findings demonstrate that cholinergic signaling enhances spike output in layer II/III pyramidal neurons, which may promote the integration of these neurons into cortical memory engrams (see Titley et al., *Neuron* 95, 2017).

Disclosures: **C. Hansel:** None. **D.F. Gill:** None.

Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 554.11/B49

Topic: B.08. Intrinsic Membrane Properties

Support: NIH Grant R01AG047296
Louisiana Board of Regents RCS (LEQSF(2016-19)-RD-A-24)

COBRE on Aging and Regenerative Medicine (5P20GM103629)
The Oliver Fund Scholars Award of Tulane University

Title: Increased excitability and decreased inhibition in layer 5 primary somatosensory cortex pyramidal neurons of aged mice

Authors: *I. R. POPESCU[1], K. Q. LE[2], A. E. LELAND[2], R. MOSTANY[3];
[1]Pharmacol., [2]Tulane Brain Inst., [3]Pharmacol. and Tulane Brain Inst., Tulane Univ., New Orleans, LA

Abstract: Increased excitability and decreased inhibition in the principal cortical neurons are hypothesized to contribute to expanded receptive fields and increased seizure susceptibility in aged humans and rodents. Here we asked whether age-related changes in excitability and inhibition are evident in layer 5 (L5) pyramidal neurons. Our strategy built on the differential expression of synaptic and intrinsic properties in pyramidal neuron subtypes, and age comparisons were made accordingly. We recorded intrinsic active properties enabling pyramidal type classification, and spontaneous IPSCs, in primary somatosensory cortex neurons, in acute mouse brain slices. L5 pyramidal neurons can be classified by co-varying active properties. “Adapting” neurons display larger adaptation of action potential (AP) frequency, larger slow afterhyperpolarization (sAHP), smaller sag and slower APs than “non-adapting” neurons. Cluster analysis of two active properties unaffected by age, AP duration and sAHP, yielded two neuron groups. Active properties and IPSC frequency co-varied in these groups in agreement with previous reports. Aged adapting neurons (18-29 months) had a more negative AP threshold, and strong trends towards decreased rheobase and adaptation compared with young adapting neurons (2-6 months). Non-adapting neurons displayed an age-dependent increase in sag, a decrease in rheobase and adaptation, and a decrease in IPSC frequency. Both neuron types exhibited age-dependent increases in AP frequency, but at different current step amplitudes. We conclude that aging causes an increase in excitability and a decrease in synaptic inhibition in L5 primary somatosensory cortex pyramidal neurons. However, changes were specific to adapting and non-adapting neuronal subtypes.

Disclosures: I.R. Popescu: None. **K.Q. Le:** None. **A.E. Leland:** None. **R. Mostany:** None.

Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 554.12/B50

Topic: B.08. Intrinsic Membrane Properties

Support: National Natural Science Foundation of China Projects 31630029
National Natural Science Foundation of China Projects 31661143037

National Natural Science Foundation of China Projects 11622542
National Natural Science Foundation of China Projects 31430038

Title: Non-thermal modulation of neuronal signaling by electromagnetic mid-infrared stimulation

Authors: *X. LIU[1], Y. XIAO[1], C. CHANG[2], B. SONG[3], Y. SHU[1];
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Abstract: Selective manipulation of activities in certain brain regions through neuromodulation approaches is a highly effective strategy to regulate brain functions and treat brain disorders. Most of these approaches exert their effects mainly though electrical stimulation of the neural tissue. Optogenetic stimulation is now a potential neuromodulation method, but the expression of exogenous genes hampers its use in human subjects. Here we show that mid-infrared stimulation (MIRS) with a specific wavelength provides non-thermal and reversibly regulatory effects on neuronal properties. To exclude the thermal effect of MIRS, we measured the temperature increase surrounding the tip of MIRS fiber and performed whole-cell recording from mouse (aged P14 to P25) neocortical pyramidal cells outside the region with temperature increase. We found that MIRS reversibly inhibits neuronal spiking responses to weak current injections but enhances those to strong current injections, indicating a gain modulation. Moreover, MIRS shapes the AP waveform by dramatically shortening its voltage integral by ~26% (from 131.7 ± 9.4 to 97.8 ± 5.7 mV·ms, $t_8 = 22.9$, $P = 0.1 \times 10^{-7}$, paired Student's *t*-test). MIRS also reduces the input resistance (from 194 ± 17 to 169 ± 14 MΩ, $t_8 = -6.91$, $P = 0.1 \times 10^{-3}$, paired Student's *t*-test) and the membrane time constant (from 38.5 ± 1.5 to 34.9 ± 0.9 ms, $t_8 = 2.78$, $P = 0.024$, paired Student's *t*-test). We then performed dynamic clamp experiments and found that a similar decrease in the input resistance (though adding leak conductance) only impedes spiking activities but has no effect on AP waveform. In dual soma-axon recording experiments, MIRS substantially accelerates AP conduction velocity along the axon by ~15% (from 0.24 ± 0.02 to 0.27 ± 0.02 m/s, $t_5 = -8.85$, $P = 0.3 \times 10^{-3}$, paired Student's *t*-test). Considering the crucial roles of voltage-gated sodium channels and potassium channels in AP generation and conduction, we examined whether MIRS exerts its effects via the regulation of activities of these channels. Consistent with AP waveform changes, MIRS selectively augments potassium currents (from 555 ± 54 to 651 ± 69 pA, $t_6 = -4.71$, $P = 0.003$, paired Student's *t*-test) and accelerates the gating kinetics. Together, our results indicate that MIRS represents a novel neuromodulation approach that can effectively regulate neuronal spiking activities, AP waveform and conduction velocity. Because there is no need to express exogenous genes, MIRS could be a potential optical neuromodulation method for clinical use.

Disclosures: **X. Liu:** None. **Y. Xiao:** None. **C. Chang:** None. **B. Song:** None. **Y. Shu:** None.

Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 554.13/B51

Topic: B.08. Intrinsic Membrane Properties

Title: A biophysical mechanism for epigenetic inheritance of enhanced complex learning capabilities

Authors: *S. ZIDAN, E. BARKAI;
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Abstract: Training rats in a difficult olfactory discrimination (OD) task initiates a period of accelerated learning of other odors, manifested as a dramatic increase in the rats' capacity to acquire memories for new odors once they have learned the first discrimination task, implying that rule learning has taken place. Here we show that the acquired superb learning capability is transferred to descendants epigenetically.
We found that exposure of parents to OD task affects learning abilities of their offspring; Regardless which parent went through the training, or whether they have interacted with the offspring or not, trained rats' offspring (males and females) learned the same OD task significantly faster compared to pseudo-trained' offspring even when training odors differed from those used to train the FO generation. Such enhanced learning capabilities extended well beyond the OD task: descendants of OD trained parents, showed a remarkably enhanced learning capabilities in Morris water maze (MWM) as well. Showing a general enhancement in learning capabilities.
At the cellular level, intracellular recordings with sharp electrodes show that the biophysical properties of CA1 pyramidal neurons of trained rats' descendants differ significantly from neurons taken from control rats' descendant's, their intrinsic excitability is higher and they are capable of generating repetitive spike firing at a higher frequency than neurons taken from controls, such enhanced excitability is mediated by reduction in the post-burst AHP, presumably generated by the slow calcium-dependent potassium current (sI_{AHP}). Our previous studies show that these are the exact changes that are induced in the brains of rats after they acquire the rule, all experiments were performed blindly and replicated.
Together, the observed changes, which occur simultaneously at the behavioral and single cell levels, suggest that acquired enhanced learning capabilities of complex tasks may be transferred to the next generation(s) via an epigenetic mechanism. Trained rats' descendants are superb learners, since they are born with neurons that are intrinsically more excitable than neurons from control rats. This change occurs in their ancestors brains only after the rule learning and is transferred to them at birth, so they need less training to acquire new rules.

Disclosures: **S. Zidan:** None. **E. barkai:** None.

Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 554.14/B52

Topic: B.08. Intrinsic Membrane Properties

Support: Icelandic Research Fund 152715-053
Icelandic Research Fund 163068-051

Title: Mitf links neuronal activity and intrinsic plasticity in olfactory bulb projection neurons

Authors: ***P. H. PETERSEN**, D. ATACHO, H. REYNISSON, T. EYSTEINSSON, E. STEINGRÍMSSON;
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Abstract: The Microphthalmia associated transcription factor (MITF) is a basic helix-loop-helix-leucine zipper transcription factor essential for the development of melanocytes and mast cells. *Mitf* is also expressed in the glutamatergic projection neurons of the mouse olfactory bulb. Using the $Mitf^{mi\text{-}vga9}$ mouse model, we have determined that lack of Mitf leads to an increase in the ability of the $Mitf^{mi\text{-}vga9}$ mouse to distinguish between odors, while its capacity to detect odor is similar to the wild type mice. However, the ability of the mutant mice to adapt to odors over a period of hours is changed. We have identified tentative target genes of MITF in the projection neurons of the OB, including the potassium channels subunit Kcnd3, which is important for type A potassium current. *Mitf* has been shown in melanocytes to be regulated by glutamate signaling. As the nervous system is shaped and regulated by glutamate signaling, we determined whether MITF takes part in activity-induced responses at the transcriptional level. Expression of both Mitf and Kcnd3 is activity-dependent and expression of Kcnd3 is Mitf dependent. MITF binds to a strong enhancer of the Kcnd3 gene, suggesting that MITF regulates Kcnd3 expression directly. A decrease in Type A- potassium current in $Mitf^{mi\text{-}vga9}$ mouse M/T neurons is also observed, and a concomitant increase in neuronal activity of the M/T neurons of the $Mitf^{mi\text{-}vga9}$ mouse. Function of other putative target genes of MITF in OB projection neurons, suggest a general role of MITF as a negative regulator of neuronal activity. We propose a model, where MITF regulates intrinsic plasticity in the olfactory bulb projection neurons. The role of MITF in neuronal homeostasis following activity suggests that MITF plays a major role in long-term selective olfactory habituation and homestatic plasticity.

Disclosures: **P.H. Petersen:** None. **D. Atacho:** None. **H. Reynisson:** None. **T. Eysteinsson:** None. **E. Steingrímsson:** None.

Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 554.15/B53

Topic: B.08. Intrinsic Membrane Properties

Support: NIH/NINDS

Title: Hyperexcitability of pyramidal neurons caused by BRAFV600E is partially rescued by dominant negative REST

Authors: *G. AKGÜL, J. DUNNACK, J. J. LOTURCO;
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Abstract: BRAF V600E mutation is the cause of up to 70 % of low grade neuroepithelial tumor cases. Intractable focal epilepsy is comorbid with 25-80 % of these cases. The mechanisms of epileptogenesis in low grade brain tumors is poorly understood. However, BRAF V600E mutation harboring mouse brain tumor tissue has been recently reported to exhibit differential expression profile of REST (RE1-silencing transcription factor) mRNA. Therefore, we investigated the hyperexcitability of BRAF V600E expressing neurons and the role of REST as a mediator. By using *in utero* electroporation, we introduced BRAF V600E mutation to radial glia cells in mouse embryos at E13-15, to generate a mouse model for BRAF V600E carrying low grade brain tumors. We delivered the recombinant DNA in a *piggybac* vector along with *piggybac* transposase expressing vector to ensure stable expression of BRAF V600E in mouse brain. To study the role of REST in neuronal hyperexcitability, we delivered dominant negative REST (dnREST) alone (as control) or with BRAF V600E (to test REST rescue of hyperexcitability). We probed brain sections of mice transfected with BRAF V600E and dnREST with a GFP antibody to confirm dnREST expression due to low expression of YFP. Confocal images showed that dnREST expressing neurons exist in cortex. Interestingly, focal cortical dyplasia (FCD) is also apparent in those brains. Whole cell electrophysiology recordings from neurons expressing BRAF V600E alone (V600E), BRAF V600E and dnREST (V600E+dnREST), dnREST alone and nonfluorescent neighbors in acute brain slices of mice at P17-24 showed that the frequency of action potentials fired from V600E and V600E+dnREST are the same with each other and significantly different from AP frequency of dnREST expressing or nonfluorescent neighbor neurons, over the period of the incremental increase in injected current [-80 - +300 pA]. V600E or V600E+dnREST expressing neurons had also high SAG ratio at hyperpolarizing current injections (calculated at -40 pA step) (V600E: 27.4 ± 13.3 %; V600E+dnREST: 20.3 ± 11.6 %) compared to dnREST (5.8 ± 5.8 %) or nonfluorescent neurons (5.5 ± 2.8 %). However, the waveform of the first action potential fired from the neurons displayed significant differences that could be implicated hyperexcitability, across groups. For

example, action potential threshold was significantly higher in V600E+dnREST (-47.6 ± 1.3 mV) compared to V600E (-42.6 ± 3.2 mV; p=0.004). These results show that, V600E expressing neurons go through multiple changes that make them hyperexcitable and REST is involved in some of the molecular mechanisms in this process.

Disclosures: G. Akgül: None. **J. Dunnack:** None. **J.J. LoTurco:** None.

Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 554.16/B54

Topic: B.08. Intrinsic Membrane Properties

Support: JST ERATO (JPMJER1801)
JSPS Grants-in-Aid for Scientific Research (18H05525)
the Human Frontier Science Program (RGP0019/2016)

Title: Fibronectin is heterogeneously expressed in the mouse subiculim

Authors: *T. KASHIMA, A. NOGUCHI, Y. IKEGAYA, N. MATSUMOTO;
The Univ. of Tokyo, Tokyo, Japan

Abstract: The subiculum is anatomically and physiologically heterogeneous at the single neuron level. Recent studies have investigated the diversity of the dorsal subiculum in terms of gene and mRNA expression. However, few studies have investigated the heterogeneity of the entire subiculum. To reveal the heterogeneity of the whole subiculum, we examined fibronectin protein because its mRNA (FN1 mRNA) is known to be expressed in the subiculum. We horizontally sectioned the mouse brains, performed immunohistochemistry against fibronectin and NeuN, and characterized the expression pattern of fibronectin protein in the entire subiculum along three axes (i.e., the dorsoventral, proximodistal, and superficial-deep axes). We first found that FN1 mRNA is translated into protein inside cells although fibronectin is generally distributed in extracellular regions. Based on the immunofluorescence pattern of NeuN-positive cells, we defined the pyramidal cell layer of the subiculum and transformed the pyramidal field into a virtual rectangle. Unexpectedly, we found that the fibronectin protein was widely distributed in the pyramidal cell layer of the dorsal subiculum, whereas in the ventral subicular pyramidal field, fibronectin was concentrated around more superficial and distal corner. To exclude the possibility that this heterogeneous expression pattern of fibronectin was totally dependent on the plane of sectioning, we performed the same immunohistochemistry with coronally sectioned slices. In coronal sections, we found almost the same expression pattern of fibronectin as shown in the horizontal sections. Moreover, we investigated the functional relevance of fibronectin-positive cells in the subiculum. A previous study reported that vesicular glutamate transporter 2

(VGluT2) functions as a specific marker protein for bursting neurons in the subiculum (Wozny *et al*., 2018). Thus, we immunostained VGluT2 as well as fibronectin and consequently found that the expression of fibronectin and VGluT2 did not overlap. These results suggest that fibronectin-positive excitatory neurons exist more locally in the ventral subiculum than in the dorsal subiculum and might exhibit a regular-spiking firing pattern. Therefore, fibronectin may be useful as a marker protein for investigating the heterogeneity of principal cells in the entire subiculum.

Disclosures: **T. Kashima:** None. **A. Noguchi:** None. **Y. Ikegaya:** None. **N. Matsumoto:** None.

Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 554.17/B55

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Which cellular mechanism yields compatibility between brain states, synaptic plasticity and neuromodulation?

Authors: *K. COUTISSE, G. DRION;
Electrical Engin. and Computer Sci., Univ. of Liege, Liege, Belgium

Abstract: Learning and memory are attributed to the ability of neurons to modify their connections with other cells based on experience, a property called *synaptic plasticity*. On the other hand, brain information processing is shaped by fluctuations in neuronal rhythms at the cellular and population levels, each defining distinctive *brain states*. Switches between these brain states, driven by *neuromodulation*, can be fast and localized, such as those observed in Parkinson disease patients stopping, almost instantaneously, tremor symptoms when deep-brain stimulation is turned on. Switches can also be global and long lasting, such as those observed during the wake-sleep transition. The coexistence of these two mechanisms raises challenging questions: how can switches in brain states remain reliable despite constant rewiring of neuron connectivity and how is synaptic plasticity affected by switches in brain states?
Here, we highlight the role of *slow regenerativity*, a cellular dynamical property, in the generation of brain state switches that are robust to cellular heterogeneity, independent from network connectivity, and thus compatible with synaptic plasticity. This key mechanism is accessible by all neurons that embed *slowly activating voltage-gated calcium channels or slowly inactivating potassium channels* in their membrane. Yet, in computational neuron models, this channel dynamics is often considered as an instantaneous event and it is absent from all available hybrid models.
To demonstrate this point, we compare the robustness of 6 published thalamic neuron conductance-based models at the cellular, circuit and population levels [Destexhe, 1996;

Destexhe, 1998; Drion, 2018; Huguenard and McCormick, 1992; Rush and Rinzel, 1994; Wang, 1994]. We show that the robustness of rhythms at the population level correlates with the presence of slow regenerativity at the cellular level. We extend our results to 3 subthalamic nuclei neuron (STN) conductance-based models [Terman et al, 2002; Kubota et al, 2011; Santaniello et al, 2007]. It confirms that this key dynamical property is also required to reproduce switches in STN neuron activity robust to variability. Our work highlights that slow regenerativity is independent on the type of neurons, the intrinsic frequency of the firing pattern and valid for global and lasting brain state switches as well as local and fast. Second, we show that this mechanism can be embedded in simple hybrid neuron models without increasing the model complexity. These results open the possibility to study the interactions between switches in network rhythmic activity and synaptic plasticity in large neuronal populations.

Disclosures: **K. Coutisse:** None. **G. Drion:** None.

Poster

554. Neuronal Firing Properties: Modulation, Development, and Pathologies II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 554.18/B56

Topic: B.06. Synaptic Transmission

Title: Differential effect of oxytocin on cell types in medial prefrontal cortex: A comparison between single and pair fear-exposed adolescent rats

Authors: *J. TAESUB;
Dankook Univ., Young-in si, Korea, Republic of

Abstract: The prosocial hormone oxytocin activates the medial prefrontal cortex (mPFC) and fear-related behaviors during pair exposure are under tight control of the mPFC, but the underlying cellular mechanism of oxytocin action for mPFC in pair-exposed condition is poorly understood. To determine this issue, we performed a slice current-clamp patch recording in single- and pair-exposed electric shocked rats. Here we distinguished two types of cells, pyramidal neurons and interneurons, in mPFC with their morphologic and electrophysiologic characteristics. There were not significant differences of resting membrane potential alteration in both cell types between single and pair rats. We found that the treatment of oxytocin in interneurons induced the increase of neuronal spikes in single rats compared with pair rats, whereas the oxytocin exposure in pyramidal neurons decreased the spikes in both single and pair rats, suggesting that the activity of mPFC in single rats is reduced by oxytocin compared to that in the pair rats. These results reveal oxytocin-mediated interneuronal activity reduction in mPFC of pair-exposed shocked rats represents a reinforcement of mPFC activity and induces a reduction of fear-related behavior compared with single-exposed shocked rats. (supported by NRF-2016R1D1A1B03934263 and NRF-2019R1A2C1002963).

Disclosures: J. Taesub: None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.01/B57

Topic: B.10. Epilepsy

Support: Camden Health Initiative
Cooper Medical School of Rowan University
Thomas Jefferson University Medical School

Title: Further characterization of a genetic mouse model of adult-onset epilepsy

Authors: *T. N. FERRARO[1], A. I. BATTERMAN[1], I. SALEM[2], E. MOGILYANSKY[2], R. DACI[1], L. K. YOUNG[1], D. R. MILLER[3], F. PARDO-MANUEL DE VILLENA[3], R. J. BUONO[1], L. D. SIRACUSA[4,2];
[1]Biomed. Sci., Cooper Med. Sch. of Rowan Univ., Camden, NJ; [2]Microbiology and Immunol., Thomas Jefferson Univ., Philadelphia, PA; [3]Genet., Univ. of North Carolina, Chapel Hill, NC; [4]Hackensack Meridian Sch. of Med. at Seton Hall Univ., Nutley, NJ

Abstract: Epilepsy is a common neurological disease with the highest incidence occurring in the youngest and oldest segments of the population. Genetic mouse models have led to important clues regarding the etiology of epilepsy; however, the phenotypes of known mouse mutants that exhibit spontaneous, recurring seizures emerge early in life, generally by one month of age. Prior work at Thomas Jefferson University established a colony of inbred mice that exhibited recurring generalized tonic-clonic seizures beginning between 6-18 months of age. The index case was a male mouse that was the offspring from a cohort of the Collaborative Cross strain CC039/Unc. The pedigree has been expanded to 5 generations with the epilepsy phenotype segregating according to an apparent autosomal dominant or semi-dominant mode of transmission. Males from the founder family develop epilepsy significantly earlier than females, and seizure episodes become more frequent with advancing age. Whole-genome analysis of single nucleotide polymorphisms was performed in epilepsy (N = 6) and non-epilepsy (N = 5) mice from the founder family. Several chromosomal deletions were identified; however, none segregated with the epilepsy phenotype. An F1 generation (N = 99) was created by mating CC039 epilepsy mice with DBA/2J (D2) mice. Currently, F1 mice range in age from 70-140 weeks with only approximately 10% of the population exhibiting epilepsy, i.e. spontaneous seizures. This result suggests incomplete penetrance of the mutation on the D2 genetic background. An N2 backcross generation (N = 115) was created by mating F1 epilepsy mice with D2 mice. As observed in the F1 generation, about 10% of the N2 population over 1 year of age have demonstrated spontaneous seizures to date. Production and phenotyping of F1 and N2 mice remains ongoing.

Complete genetic dissection of this novel mouse model may lead to important insight into the mechanisms of adult-onset epilepsy in humans.

Disclosures: **T.N. Ferraro:** None. **A.I. Batterman:** None. **I. Salem:** None. **E. Mogilyansky:** None. **R. Daci:** None. **L.K. Young:** None. **D.R. Miller:** None. **F. Pardo-Manuel de Villena:** None. **R.J. Buono:** None. **L.D. Siracusa:** None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.02/B58

Topic: B.10. Epilepsy

Support: Alberta Children's Hospital Research Institute
Alberta Children's Hospital Foundation

Title: Targeted deletion of mitochondrial cyclophilin D mediates neuroprotection in epileptic brain

Authors: *B. R. VILLA[1], C. N. GAVRILOVICI[2], G. TESKEY[1], J. M. RHO[3];
[1]Cell Biol. & Anat., [2]Paediatrics, Univ. of Calgary, Calgary, AB, Canada; [3]Alberta Children's Hospital, Univ. of Calgary, Calgary, AB, Canada

Abstract: Epilepsy is a chronic neurological disease affecting over 50 million people worldwide. It is characterized by spontaneous recurrent seizures (SRS) arising from hyperexcitable and hypersynchronous brain activity. Seizure activity leads to debilitating co-morbid problems (e.g. cognitive impairments) that ultimately impair quality of life. Current therapies fail to control seizures in one-third of people with epilepsy. There is a strong need to develop new treatments that block seizures and the progression of the disease, thus preventing deleterious consequences. Mitochondria are critically important for cell energy homeostasis and survival. Recently, it has been shown that a mitochondrial protein known as cyclophilin D (CypD) - which regulates the mitochondrial permeability transition pore (mPTP) - a determinant of cell death - when inhibited, significantly reduces seizures in a mouse model of human epilepsy. Despite this intriguing observation, it is unclear how CypD regulates seizure activity.
We used immunohistochemistry and confocal microscopy techniques to show that hippocampal parvalbumin (PV)-positive GABAergic interneurons, which are fast-spiking and thus very energy-consuming, express high levels of mitochondrial CypD in a clinically relevant model of developmental epilepsy (*Kcna1*-null mouse). We proposed that this elevated expression increases the sensitivity of these interneurons to mPT and subsequent cell loss. As PV-positive interneurons project onto hundreds to thousands pyramidal cells, any decrease in interneuron firing may contribute to seizure generation.

We found that most neurons with high immunoreactivity to CypD in the dorsal CA1 hippocampal area of wild-type mice express parvalbumin. *Kcna1*-null mice showed significant PV-positive cell loss, which was prevented by specific deletion of CypD in those mice. In addition, targeted deletion of CypD in wild-type mice is itself neuroprotective by increasing the survival of PV-positive cells. Furthermore, we observed that GAD67 interneurons in wild-type, *Kcna1*-null, CypD-deficient *Kcna1*-null, and CypD-deficient wild-type mice are unchanged, indicating that the vast majority of interneurons survive in epileptic *Kcna1*-null mice, but that only a subpopulation of (most likely PV) interneurons are reduced in CA1 hippocampus. Further studies will detail the role of CypD in GABAergic interneurons and in modulation of the hippocampal inhibitory network. Collectively, our results will provide further evidence for a direct link between metabolism and seizures genesis, and will establish CypD as a promising therapeutic target for medically intractable epilepsy.

Disclosures: B.R. Villa: None. **C.N. Gavrilovici:** None. **G. Teskey:** None. **J.M. Rho:** 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.; non-paid consultant for Cypralis Ltd.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.03/B59

Topic: B.10. Epilepsy

Support: NIH Grant R01 NS094461
NIH Grant T32 HL007446

Title: Leveraging intrinsic ion channel plasticity in the hippocampus to dampen seizure susceptibility

Authors: *C. M. CARVER, M. S. SHAPIRO;
Univ. of Texas Hlth. San Antonio, San Antonio, TX

Abstract: M-type (KCNQ2/3) K+ channels have important roles in neuronal regulation of resting potential, spike-frequency adaptation, and hyper-excitatory states. We have previously shown M channel transcription to be upregulated in sympathetic ganglia and in hippocampus after a seizure. In a model of hyperactivity that does not provoke epileptogenesis, we monitored activity-dependent KCNQ2 transcription in the hippocampus. We used transgenic mice with a KCNQ2-EGFP reporter to detect region-specific mRNA expression maps, in which transcription of KCNQ2 mRNA occurs concomitantly with EGFP protein expression. Mice were challenged with pilocarpine (230 mg/kg) or pentylenetetrazole (60 mg/kg) and brain tissue was examined 48

hours later. We observed significant increases in KCNQ2 transcription in CA1 and CA3 pyramidal neurons 48 hours after hyperexcitability, which dissipated after 7 days, but no significant change was observed in the dentate gyrus (DG) due to moderate hyperexcitability. In response to status epilepticus (300 mg/kg pilocarpine), DG granule cells exhibited robust upregulation of KCNQ2, whereas CA1 and CA3 expression was reduced. *In situ* hybridization paralleled fluorescent experiments investigating KCNQ2, however KCNQ3 was not upregulated in hippocampus.
Using brain-slice electrophysiology, CA1 pyramidal neurons demonstrated increased M-current amplitudes after hyperexcitability; there were no significant changes in DG granule cell M-current amplitudes between control and pilocarpine challenged mice. In current-clamp recordings of action potential firing properties, DG granule cells demonstrated hyperexcitability, along with cFos activity, despite no significant change to M-current. We examined *in vivo* seizure susceptibility 48 hour after an initial hyperexcitability challenge, at which time heightened KCNQ2 transcription and protein expression was observed. After a secondary challenge with pentylenetetrazole, mice were highly susceptible to tonic-clonic seizures and death, whereas mice given the M-channel opener retigabine were protected from seizures. This study demonstrates that independent of the mechanism of hyperexcitability, activity-dependent excitation promotes KCNQ2 upregulation in the hippocampus in a cell-type specific manner, and may serve as a compensatory mechanism after a hyperexcitable event. The transient upregulation we describe may serve as a protective mechanism against the deleterious cascade of hyperexcitability, which could be potentially leveraged in anticonvulsant enhancement of KCNQ2 channels as therapeutic target for preventing onset of seizures.

Disclosures: C.M. Carver: None. **M.S. Shapiro:** None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.04/B60

Topic: B.10. Epilepsy

Support: NIH Grant F31NS105161
Bertarelli Fellowship
NIH Grant K24NS088568
NIH Grant R01NS062092

Title: Prediction of seizures by active probing neurostimulation

Authors: *C. KREMPP[1], S. EBRAHIM[2], E. ROGGE[2], B. F. COUGHLIN[3], A. AZMI[2], N. F. FUMEAUX[2], A. KADAMBI[2], M. F. MORAES[4], S. S. CASH[5];
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Abstract: Objective: Seizure prediction by analyzing continuous EEG has been a long-term therapeutic goal for closed loop seizure preemption. Yet, current approaches remain suboptimal. An alternative approach is to examine responses to active perturbation of the system instead of spontaneous activity. In this work, we explored both spontaneous data over long time periods and the use of single pulse electrical stimulation (SPES) to actively probe the ictogenic neural circuitry and examined neural responses between and before seizures with an eye toward seizure forecasting. **Methods:** Young male SD rats (2-3 mo, n = 18) were implanted with surface electrodes, EMG pads and intrahippocampal depth electrodes bilaterally. Unilateral intrahippocampal injections of kainic acid were administered to induce chronic epilepsy, while video and EEG recordings were recorded continuously for 3 months. Multichannel EEG data was analyzed by computing standardized features in time and frequency domains for 5-second windows, and seizure segments were also manually labelled by an expert. In two animals, SPES was delivered at 0.5 mA every three to five seconds for active probing. We developed pooled and individualized predictors using multiple methods applied to passive and active data, including support vector machines (SVM). **Results:** SVM analysis of the spontaneous data without stimulation yielded an AUROC of 0.70 on our pooled dataset of 1012 rodent seizures across 16 animals. From the active data, we identified multiple features across time and frequency domains, including evoked HFOs that significantly change in preictal periods. In the two subjects with active probing via SPES, we trained individualized SVM classifiers that perform at AUROCs of 0.94 and 0.98.
Conclusions: We predicted seizures in a rodent epilepsy models with a high degree of sensitivity and specificity, with a significant improvement in AUROC relative to the state of the art. These results offer new insights into the mechanisms underlying seizure initiation, and may help improve diagnostic and therapeutic approaches for patients suffering from focal epilepsy.

Disclosures: C. Krempp: None. **S. Ebrahim:** None. **E. Rogge:** None. **B.F. Coughlin:** None. **A. Azmi:** None. **N.F. Fumeaux:** None. **A. Kadambi:** None. **M.F. Moraes:** None. **S.S. Cash:** None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.05/B61

Topic: B.10. Epilepsy

Support: CIHR Grant
Toronto General and Western Hospital Foundation

Savoy Foundation

Title: The effect of inflammation on behavioral outcome and seizure susceptibility after experimental traumatic brain injury

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Abstract: Objective and Rationale: Traumatic brain injury (TBI) can lead to cognitive impairment, motor abnormalities and post-traumatic epilepsy, which can significantly impact quality of life. The inflammatory response mounted after TBI has both beneficial and detrimental consequences. A direct comparison between pro- and anti-inflammatory strategies after TBI has not been performed. Our goal was to investigate the effect of post-TBI inflammation on behavioral outcome and seizure susceptibility. We hypothesized increased inflammation would lead to more severe behavioral deficits and increased seizure susceptibility, while decreased inflammation would lead to milder behavioral deficits and lower seizure susceptibility.
Methods: Experiments were performed in four groups of young adult male Sprague-Dawley rats: Group 1) sham injury; Group 2) severe TBI via fluid percussion injury; Group 3) TBI plus minocycline (45 mg/kg ip twice on day of injury and daily thereafter for 18 days); Group 4) TBI plus lipopolysaccharide (LPS; 100 ug/kg ip immediately pre-injury) (n=7-18 rats/group). A battery of behavioral tests consisting of a composite neuroscore, rotarod, novel object recognition (NOR), and Barnes maze was performed at various time points within one month post-TBI. Rats were later implanted with intracranial recording electrodes, and approximately nine months post-injury a subset of rats from each group were injected with a single dose of 30 mg/kg pentylenetetrazol (PTZ) to determine seizure susceptibility.
Results: Similar levels of neuromotor deficits were seen in all TBI groups early after injury as compared to sham controls. Barnes maze testing showed the TBI+mino group had better spatial memory than the TBI and TBI+LPS groups ($p<0.05$). No difference between groups was found in NOR testing. The TBI+mino group had shorter seizure duration in response to PTZ compared to the TBI group, comparable to the sham group. The TBI+LPS group had longer seizure duration than all other groups. However, the sham and TBI+mino groups had a higher number of interictal spikes after PTZ than the TBI and TBI+LPS groups.
Conclusions: These results suggest certain TBI-related dysfunctions, such as spatial memory disturbance and increased seizure susceptibility, can be ameliorated by decreasing inflammation in the acute post-injury period. Heightened levels of post-TBI inflammation did not appear to affect many behavioral outcomes, but did further increase susceptibility to PTZ-induced seizures. Further work is needed to understand the complex effects of pro- and anti-inflammatory therapies on post-TBI behaviors in order to develop potential therapeutic strategies.

Disclosures: **Y. Lin:** None. **C. Wu:** None. **J. Liu:** None. **A.Y. Reid:** None.

Poster

555. Animal Models of Epilepsy II

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.06/B62

Topic: B.10. Epilepsy

Support: CONACyT 243247 to JRE
CONACyT 243333 to CC
VIEP-BUAP to Cuerpo Académico en Neuroendocrinología BUAP-CA-288

Title: Effects of the testicular androgens in absence seizures in the myelin mutant taiep male rat

Authors: *C. CORTES, E. GRADOS, J. R. EGUIBAR;
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Abstract: Absence seizure is a type of generalized type of epilepsy and it is most frequent during childhood. Importantly, the major proportion of children with this type of epilepsy develop the absence crisis during childhood and most of them change after puberty. The availability of animal models in which it is possible to do a long-term electroencephalography (EEG) recordings are limited, the two available absence seizure rat models are Genetic Absence Epilepsy Rat from Strasbourg (GAERS) and Wistar Albino Glaxo rats from Rijswijk (WAG/Rij). The *taiep* rat is as myelin mutant rat with a recessive trait inheritance. *Taiep* is an acronym of tremor, ataxia, immobility episodes, epilepsy and paralysis. Recently, we characterized this abnormal waves as an absence seizure that affects differentially male and female rats, being the male more susceptible with respect to female *taiep* rats. Thus, the aim of this study was to analyze the susceptibility to have in adulthood absence seizures with different hormonal conditions male *taiep* rats. Adult sham-operated rats and adult orchiectomized males (n=8 per group) were used. Stereotaxic surgery was performed to implant a bipolar of electrode in the CA1 region of the hippocampus, and also stainless-steel electrodes in the frontal and occipital cortex and in the muscles of the neck and ocular orbit in order to analyze absence seizures. A 24-hour video-EEG recording was used to analyze the absence seizures every 2-hour bias. Our results show that adult orchiectomy increased significantly the frequency of absence seizures, being the MESOR value 187.875 ± 69.974 with respect to just 86.142 ± 30.422 (*t student,* T=0.052, $p<0.02$) in the control group. There was also a significant increase in the mean duration of the absence seizures in adult orchiectomized males with the highest peak in duration of orchiectomized rats at 11:00 of 2.3175 ± 01.2271 S.E.M (*t student, T*=-15.095, $p<0.001$) and a MESOR of 2.08 ± 0.029 sec ($F(2104) = 85.94$, $p<0.001$). Meanwhile, MESOR value of seizures for control male rats was of 1.77 ± 0.027 sec (t student, $F(2104) = 85.94$, $p<0.001$). This is the first demonstration absence seizures depend on testicular androgens and with different effects

depending on time of castration and then in the modulation of thalamo-cortical circuit that support that absence seizures increased in non-androgen condition.

Disclosures: C. Cortes: None. **E. Grados:** None. **J.R. Eguibar:** None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.07/B63

Topic: B.10. Epilepsy

Title: Electrophysiological characterization of CA1 neurons in a mouse model of Dravet syndrome

Authors: *M. MARTINA[1], S. SCHOCK[2], D. DYMENT[2];
[1]Human Hlth. Therapeut. Res. Ctr., Natl. Res. Council of Canada, Ottawa, ON, Canada;
[2]Children's Hosp. of Eastern Ontario Res. Inst., Ottawa, ON, Canada

Abstract: Dravet Syndrome (DS) is the archetypal Early-onset Infantile Epileptic Encephalopathy (EIEE) which affects 1-2 per 10,000 individuals and are heterogeneous both in their underlying genetic etiologies and clinical presentation. DS often manifests in the first year, with characteristic clinical and EEG findings. The seizures are typically refractory to anti-epileptic medications and, possibly, as a result of this, are associated with mild to profound cognitive and developmental deficits. It is estimated that 85% of individuals with a clinical diagnosis of DS have a mutation in the voltage gated sodium channel ($Na_v1.1$) encoding gene SCN1A. SCN1A mutations are thought to operate through different mechanisms with both altered function of the channel and complete loss-of-function mutations observed. To gain insight into these mechanisms, a mouse model of DS based on a Canadian patient was created (Care4Rare Consortium) in collaboration with The Centre for Phenogenomics (TCP) in Toronto, Canada. The mouse was generated by microinjection of Cas9 RNA guided nuclease (Cas9-RGN) and guide RNAs (gRNAs) that specify the target site into the zygotes. The patient specific mutation (p.H939R) mice were bred on a C57BL/6N background. We have characterized the mouse seizures and overall behavior. We found that heterozygous mice carrying the Nav1.1 substitution displayed seizures. To study the neuronal network makeup causing seizures in these mice and to gain insight on the possible effects of any future therapeutic intervention, we have studied the electrophysiological properties of pyramidal neurons and interneurons of the CA1 region of the mouse hippocampus and compared them with wild type (WT), using whole cell patch clamp recording in brain slices. We found that pyramidal neurons and interneurons in DS had a significantly more depolarized resting membrane potential compared to WT. In addition, DS interneurons showed a reduced firing frequency compared to WT. These features could be

responsible for the hyper-excitability of the CA1 circuit under certain conditions, such as temperature, which can trigger seizures.

Disclosures: **M. Martina:** None. **S. Schock:** None. **D. Dyment:** None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.08/B64

Topic: B.10. Epilepsy

Support: RO1 NS 040337
RO1 NS 044370

Title: Severe, refractory status epilepticus following cortical injury

Authors: *T. SINGH, S. JOSHI, J. WILLIAMSON, J. KAPUR;
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Abstract: Status epilepticus (SE) is a common complication of cortical injury. However, there are no animal models. Therefore, our goal was to develop a model of SE resulting from neocortical injury. Cobalt was implanted (2.1 mg) in the supplementary motor cortex and 18h later homocysteine (845 mg/kg i.p.) was administered. Seizures were evaluated using video, and EEG recorded from bilateral frontal and parietal electrodes. Focal seizures commenced 13.5 ± 1.5 min following homocysteine administration which manifested as focal dystonia with clonus. During these seizures, frontal onset rhythmic spike wave discharges were observed. The focal seizures then evolved into generalized continuous convulsive activity. Continuous behavioral seizures lasted 1-2 h and consisted of generalized tonic stiffening, bilateral limb clonus, and generalized tonic clonic activity. There were generalized rhythmic spike wave discharges, generalized polyspikes discharges, and generalized high frequency (β and γ) low amplitude activity during this phase. After prolonged seizures, animals became still with intermittent bilateral myoclonic seizures or jerks. EEG at this time evolved to seizures interspersed with generalized period discharges on a suppressed background. This evolved to burst suppression and then to profound and persistent suppression. Following SE animal were stuporous, comatose and then died. Seizures were refractory to diazepam (10, and 30 mg/kg i.p.) administered 10 min after onset of continuous seizures. Blood brain barrier was disrupted as evident from Evan's blue staining and presence of albumin in the ipsilateral and frontal part of the brain. We have developed an animal model of severe, refractory SE which began in the frontal cortex. SE ended in coma, burst suppression and death. We will study mechanism underlying this form of SE.

Disclosures: **T. Singh:** None. **S. Joshi:** None. **J. Williamson:** None. **J. Kapur:** None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.09/B65

Topic: B.10. Epilepsy

Title: Seizure susceptibility in a PCDH19 epilepsy mouse model

Authors: *N. SABETFAKHRI[1], A. D. GUEMEZ-GAMBOA[2];
[1]Physiol., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [2]Physiol., Nortwestern Univ., Chicago, IL

Abstract: PCDH19-related epilepsy is an early-onset epileptic encephalopathy characterized by short and repeated seizure clusters. Patients present with predominantly focal seizures, which are often followed by developmental decline and intellectual disability. PCDH19-related epilepsy is caused by heterozygous loss-of-function mutations in the X-linked gene, *Protocadherin 19* (*PCDH19*). Pathogenic *PCDH19* variants are inherited in an atypical X-linked dominant pattern in which heterozygous females present with seizures, while hemizygous carrier males are asymptomatic. It is hypothesized that this unusual pattern of inheritance results from cellular interference, a mechanism in which the co-existence of neurons expressing wild-type or mutant *PCDH19* disrupts cell-cell interactions. Recent cases of affected males with somatic mosaicism for *PCDH19* mutations provide further support for cellular interference as the disease mechanism. To investigate seizure susceptibility in a PCDH19 epilepsy mouse model, we induced generalized and focal seizures in female *PCDH19* heterozygous and knock-out mice, male *PCDH19* hemizygous mice, and their wild-type littermates. All genotypes showed comparable levels of seizure susceptibility to induced generalized seizures. However, female *PCDH19* heterozygous and knock-out mice showed significantly increased susceptibility to induced focal seizures. Interestingly, they displayed comparable levels of increased seizure susceptibility and severity. These results suggest that a pathogenic mechanism in addition to cellular interference may contribute to the PCDH19 seizure phenotype.

Disclosures: N. Sabetfakhri: None. **A.D. Guemez-Gamboa:** None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.10/B66

Topic: B.10. Epilepsy

Support: AOD18013-001-00000

Title: Endogenous activation of cannabinoid receptor type 1 (CB1R) is required for survival and neuroprotection in rats exposed to the organophosphate nerve agent soman

Authors: *S. O'BRIEN, B. WINNER, S. WOLFE, K. KELLY, C. PHUNG, K. PAGARIGAN, M. EISEN, P. BODNER, M. NELSON, P. MCNUTT;
MRICD, Gunpowder, MD

Abstract: The endocannabinoid (eCB) system is one of the most important and least understood endogenous on-demand neuroprotective pathways. Overstimulation of glutamatergic, cholinergic, or GABAergic receptors results in rapid biosynthesis of eCBs in the postsynaptic neuron, resulting in their retrograde transport to activate presynaptic cannabinoid receptor type 1 (CB1R) in neurons and astrocytes and reduce presynaptic release probability. Exposure to the organophosphate nerve agent soman overstimulates central muscarinic acetylcholine receptors, causing status epilepticus (SE) and eliciting excitotoxicity in several brain regions. We have previously shown in hippocampal slices that perfusion with organophosphate nerve agents elicits long-term depression at Schaffer collateral synapses that is dependent on group 1 muscarinic receptors and CB1R activation, suggesting that eCB signaling may reduce excitatory neurotransmission under conditions of cholinergic overstimulation. Here we tested the clinically used CB1R antagonist SR141716A (Rimonabant) in a rat survival model of soman exposure to determine the systemic effects of CB1R inhibition on soman-induced neuropathology and survival. In contrast to vehicle controls, which exhibited 100% survival through 10 d after soman exposure, only 25% of rats treated with Rimonabant survived through the course of the study ($p = 0.0039$). Furthermore, neuropathological scoring revealed significant increases in neuronal loss and gliosis in the hippocampus of Rimonabant-treated rats versus vehicle controls. Taken together, these data demonstrate that endogenous CB1R signaling decreases neurotoxicity and improves survival following exposure to organophosphate nerve agents. We are currently determining if positive modulation of CB1R can enhance neuroprotection in response to lethal organophosphate nerve agent exposure.

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Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.11/B67

Topic: B.10. Epilepsy

Support: Savoy Foundation
Toronto General and Western Hospital

Title: Zebrafish model of post-traumatic epilepsy

Authors: *S.-J. CHO[1], E. PARK[2], A. BAKER[2], A. REID[1];
[1]Univ. Hlth. Network, Toronto, ON, Canada; [2]St. Michael's Hosp., Toronto, ON, Canada

Abstract: Background: Post-traumatic epilepsy (PTE) is a complication from traumatic brain injury (TBI). PTE is defined as recurrent and unprovoked seizures occurring more than one week after TBI. Animal studies of PTE are lengthy and expensive. Zebrafish are an emerging model organism for studying disease and development due to their ease of use and require less maintenance than rodents. In this study, we developed a cost-effective PTE model using zebrafish to bridge the gap between *in vitro* studies and low-throughput animal studies.
Methods: Severe closed-head TBI was induced in AB strain wild-type zebrafish (6-12 months old) using pulsed high-intensity focused ultrasound, with naïve zebrafish as controls. We used an automated behavioral tracking system to evaluate locomotor/psychological deficits, and spontaneous behavioral seizure activity was manually scored for 21 days post-injury (DPI). A behavioral seizure susceptibility test was also performed using a sub-convulsive dose of 2.5 mM pentylenetetrazole (PTZ) on day 7, 14, and 21. In addition, we recorded forebrain electrophysiological signals to confirm seizure activity.
Results: The severe closed-head TBI model resulted in mortality in 25% of the injured zebrafish. Locomotor activity was disrupted post-injury and never fully recovered by 21 DPI. Also, the TBI group had heightened anxiety for 21 days. 100% of the TBI group showed spontaneous myoclonic-like jerking behavior for 21 days. 44% of the TBI group developed clonic-like prolonged jerking behavior at 3 DPI (n=15), which increased to 80% at 21 DPI (n=15). Such activities were not detected in the naïve group (n=10). After the administration of 2.5 mM PTZ, 90% of injured ZF had clonic-like seizures at 7 DPI (n=10), increasing to 100% at 14 DPI and 21 DPI (n=10), versus 30% of the naïve group. Of those progressing to clonic seizures, the average seizure onset time was significantly longer in the naïve group at 750±50s versus 258±46.5s in the TBI group at 7 DPI, 217±41.2s at 14 DPI and 298±45.2s at 21 DPI. Lastly, we demonstrated interictal epileptiform discharges and electrographic seizure activity in the TBI group, which were not detected in the naïve controls.
Conclusion: We have demonstrated increased PTZ-induced seizure susceptibility as well as spontaneous behavioral and electrographic seizure activity, after TBI in zebrafish. These changes endured for at least 21 DPI, suggesting this may be a useful model that can accelerate research in PTE.

Disclosures: S. Cho: None. **E. Park:** None. **A. Baker:** None. **A. Reid:** None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

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Topic: B.10. Epilepsy

Support: NIH NINDS K08 NS097633
NIH NINDS R01 NS110869
Burroughs Wellcome Fund Career Award for Medical Scientists to E.M.G

Title: Vasoactive intestinal peptide-expressing interneurons are impaired in a mouse model of Dravet syndrome

Authors: *K. M. GOFF[1], E. M. GOLDBERG[2];
[1]MSTP, Univ. of Pennsylvania, Philadelphia, PA; [2]Neurol., The Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: Dravet syndrome (DS) is the most common early infantile epileptic encephalopathy, caused primarily by *de novo* mutations in *SCN1A* which codes for the voltage gated sodium (Na+) channel alpha subunit Nav1.1. This channel is prominently expressed in GABAergic interneurons, and it is therefore hypothesized that selective dysfunction of interneurons leads to impaired inhibition in the developing brain, which in turn underlies the epilepsy and other cognitive comorbidities found in DS. Both parvalbumin (PV) and somatostatin (SST) expressing interneurons have been shown to be impaired in DS; however, the function of the third major group of interneurons - the vasoactive intestinal peptide (VIP) expressing interneurons - have not been specifically investigated. Here, we used *Scn1a*$^{+/-}$ mice crossed to VIP-Cre.tdTomato reporter mice to perform targeted whole cell recordings from VIP interneurons in layer 2/3 primary somatosensory and visual cortex of acute brain slices prepared from male and female mice across development. We demonstrated that VIP interneurons have impaired excitability, with depolarized action potential thresholds, reduced steady state firing frequencies, and prominent spike height attenuation in *Scn1a*$^{+/-}$ mice at both post-natal day (P) 18-21 and P35-56 age groups relative to age-matched wildtype littermate controls. Immunohistochemistry confirmed expression of Nav1.1 on VIP interneuron axons, and selectively activating Nav1.1 with the toxin Hm1a was able to rescue the cellular phenotype of VIP cells in *Scn1a*$^{+/-}$ mice. These deficits were found to primarily affect a large (50%) subgroup of VIP interneurons which show a prominent irregular spiking (IS) firing pattern. We then showed that, while IS VIP interneurons do not colocalize with other putative VIP subtype markers such as calretinin and cholecystokinin, the presence of M current in VIP interneurons largely accounts for their IS phenotype. We further explored the interaction between loss of Nav1.1 and the presence of M current with detailed biophysical modelling. Our results indicate that VIP-positive interneurons

express Nav1.1 and, along with PV and SST interneurons, are dysfunctional in DS. As the canonical VIP circuit is disinhibitory rather than inhibitory, these findings suggest that VIP cell dysfunction could relate to non-epilepsy comorbid conditions in DS. This work was supported by NIH NINDS K08 NS097633, NIH NINDS R01 NS110869, and the Burroughs Wellcome Fund Career Award for Medical Scientists to E.M.G.

Disclosures: K.M. Goff: None. **E.M. Goldberg:** None.

Poster

555. Animal Models of Epilepsy II

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Program #/Poster #: 555.13/B69

Topic: B.10. Epilepsy

Support: Associação Iluminando A Vida Grant AIV 2019

Title: Compensatory contralateral hippocampal neurogênesis in the absence of cognitive impairment following experimental hippocampectomy in adult rats

Authors: *W. GOMES-LEAL[1], G. T. M. CARDOSO[2], E. C. S. FRANCO[3], A. PEREIRA[4], F. L. GOMES[5], A. F. BRINO[6], S. M. A. LIMA[7];
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Abstract: Temporal lobe epilepsy (TLE) is the most common type of focal epilepsy in adult humans and hippocampal sclerosis (HE) is its main pathological finding. In TLE refractory cases, patients are indicated for unilateral resection surgery of the affected hippocampus (hippocampectomy), which generally does not cause any additional cognitive impairment in patients. Adult hippocampus is a region of endogenous neurogenesis even in elderly people. We have hypothesized that a compensatory increase in hippocampal neurogenesis might occur in the remaining hippocampus after surgery to treat TLE. To test this hypothesis, we performed hippocampectomy in adult Wistar rats to investigate possible compensatory neurogenic events in the contralateral hippocampus as well as whether the surgical procedures induce any kind of cognitive impairment. Animals (n=6 per group) were randomically allocated to the following experimental groups: control (no surgery), G15 and G30. Animals were deeply anesthetized with a mixture of ketamine (80 mg / kg) and xylazine (10 mg / kg) until complete absence of corneal

and paw withdraw reflexes. Adjacent cortex and hippocampus of the left hemisphere were completely removed. The G15 and G30 animals were perfused at 15 and 30 days, respectively, post-surgery. Behavioral tests were undertaken to address possible cognitive impairments using eight arms radial maze for 7 days. After this period, animals were perfused with 0.9% saline and 4% paraformaldehyde in 0.1M phosphate buffer and processed for histological analysis. Gross histopathology was performed using cresyl violet staining. Cell bodies of mature neurons and migratory neuroblasts were immunolabeled using anti-NeuN and anti-double courtin (DCX) antibodies, respectively. There was no cognitive impairment in the animals after hippocampal removal. The remaining hippocampus presented a higher number of DCX positive cells compared to control. The results suggest that unilateral hippocampectomy did not cause any cognitive impairment and there is a compensatory increase in endogenous neurogenesis in the contralateral hippocampus at both 15 and 30 days post-surgery. Further studies must test this hypothesis in hippocampectomized TLE patients using high-resolution magnetic resonance imaging.

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Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.14/B70

Topic: B.10. Epilepsy

Title: Validation of a single-channel murine seizure and interictal event detection algorithm in multi-channel rat and human EEG

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Abstract: Seizures and interictal events in humans and rodents share the same fundamental cellular basis, but analysis of electroencephalogram (EEG) signals across the species require different but equally time-consuming considerations for analysis. A seizure- and interictal event-detection algorithm originally validated in murine intracranial EEG may not, therefore, be easily applied to human or rat EEG. Here we analyze and optimize the performance of a published murine wavelet- and line-length-based EEG analysis algorithm (Bergstrom et al. 2013) on human data. This algorithm can identify and quantify ictal and interictal epileptiform EEG signal using a single algorithm. We obtained multi-channel human intracranial EEG data from ieeg.org and multi-channel rat EEG from a traumatic brain injury model and analyzed the signals to establish seizure onset and locus and to identify relevant interictal events such as spikes. We compared the algorithm output to visual scoring to determine algorithm performance. Using

published algorithm parameters optimized for murine seizure detection does not reliably quantify seizure activity in human intracranial EEG or rat EEG, even though the EEG signals of humans, rats, and mice share similar characteristics under seizure conditions. However, with slight modifications to event thresholding and definitions, we found that the algorithm was able to correctly identify and quantify seizure, spike, and other abnormal content in human and rat records with high reliability. That the algorithm is flexible for use in multiple patient and species settings suggests that the combination of line length and wavelet analysis is a robust method for seizure identification and quantification in basic and translational research and clinical settings. Further, the multi-event detection capabilities of this algorithm provide the opportunity to consider the relationships among ictal and interictal events as a part of a unified workflow.

Disclosures: R.A. Bergstrom: None. **R.J. Kotloski:** None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.15/B71

Topic: B.10. Epilepsy

Support: NIH Grant NINDS R01NS070159
NIH Grant NINDS R01NS090645

Title: Changes in neural activity associated with different gad gene mutations in larval zebrafish

Authors: *J. D. LAUDERDALE[1], Y. LIU[2], J. B. BYERS[1], H. C. SCHRIEVER[1], A. J. VANLEUVEN[1], J. M. CARPENTER[3], C. E. GUNDERSON[1], N. M. FILIPOV[4], S. QUINN[5], P. KNER[2];
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Abstract: Our group is investigating how GABAergic interneurons act to maintain homeostasis between excitation and inhibition in the intact live vertebrate brain. Under normal conditions, an increase in excitatory activity results in an increase in inhibitory activity. A focal imbalance of this response causes aberrant levels of excitation, which can be held in check by the feedforward inhibitory surround. Failure of the inhibitory surround allows coherent excitation to propagate to adjacent neural tissue. The underlying basis of this phenomenon has been difficult to study *in vivo*. We hypothesize that altered synaptic depression in interneuron populations will be a significant contributing factor to the generation and propagation of runaway coherent excitation. As a test of this hypothesis, we have generated using CRISPR-cas9 a series of zebrafish lines null for glutamic acid decarboxylase (gad) genes, *gad1a*, *gad1b*, or *gad2*. In the central nervous system, *gad1a* and *gad1b* typically exhibit differential expression, but both co-express with

gad2. Zebrafish homozygous mutant for each gad gene are viable, but exhibit seizure behavior. Loss-of-function mutations in the different gad genes differentially reduce the overall amount of GABA in the brains of larval and adult zebrafish as measured by HPLC. Electrographic recordings obtained from the tecta of larvae (5 to 7 dpf) harboring mutations in *gad1a* or *gad1b* exhibited an increase in high frequency, low-amplitude discharges compared to wild-type fish. Optical imaging of calcium activity in the tecta of larvae (5 to 7 dpf) harboring mutations in the *gad* genes revealed a spatiotemporal pattern of neural activity that was distinguishable from wild-type fish or wild-type fish exposed to the GABAA receptor antagonist pentylenetetrazol. Optical imaging experiments were performed using a custom-built, high speed light sheet microscope and wild-type or *gad* mutant zebrafish transgenic for *elavl3:GCaMP5g* on a *mitfa*$^{w2/w2}$ background. For some experiments, zebrafish also harbored a *gad1b:RFP* reporter transgene. Our results indicate that zebrafish harboring mutations in *gad1a*, *gad1b*, and *gad2* are useful animal models for understanding the impact of genetically reduced inhibition on overall network activity in the brain.

Disclosures: **J.D. Lauderdale:** None. **Y. Liu:** None. **J.B. Byers:** None. **H.C. Schriever:** None. **A.J. VanLeuven:** None. **J.M. Carpenter:** None. **C.E. Gunderson:** None. **N.M. Filipov:** None. **S. Quinn:** None. **P. Kner:** None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.16/B72

Topic: B.10. Epilepsy

Support: Grant PRODEP CVM1498

Title: Behavioral characterization of a new temporal lobe epilepsy model induced by 4-aminopyridine in rats

Authors: B. NUÑEZ-IBARRA, A. X. LÓPEZ, ***C. VENTURA**, L. MEDINA-CEJA;
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Abstract: Epilepsy is a syndrome of cerebral dysfunction characterized by the abnormal synchronic discharge of a group of cerebral neurons. The Temporal Lobe Epilepsy (ELT) is the most frequent and resistant to drugs. To study the basic mechanism of induction, maintenance and extinction of seizures and epilepsy, animal models are greatly used to simulate some of the characteristics of the TLE. These models are acute or chronic and 4-aminopyridine (4-AP) is a drug that when is administrated by intraperitoneal (i.p.) or intracerebral (i.c.) routes is capable of inducing convulsive seizures in different animal species. The pattern of convulsive seizures induced by the administration i.p. of 4-AP in the rat, is very similar to that produced by the

administration i.c. of kainic acid. For this reasons, in the present work 4-AP was used to induce a new model of TLE and some parameters such as latency to the first spontaneous seizure and severity of the convulsive behavior according the Racine scale were analyzed. For that purpose, male rats were used from the Wistar strain (200-250 g), which were divided in five groups, two groups were injected with 4-AP i.c. with doses of 10 and 20 mM and the rest of the groups were injected with 4-AP i.p. with doses of 5, 7 and 9 mg/kg of weight. The results showed that animals injected with a dose of 20 mM (i.c.) presented spontaneous and recurrent seizures between 15 to 112 days after 4-AP administration (2/3 animals) with a scale of 4 and 5 which are the most severe; it is important to point out that once administrated the 4-AP the *status epilepticus* of the animals was not blocked by any other drug and the animals did not receive special care. We conclude that 4-AP administration by i.c. route at a dose of 20 mM induced spontaneous and recurrent seizures associated with scales 4 and 5 with the advantages of no other pharmacological intervention was used and special take care of animals was not necessary.

Disclosures: B. Nuñez-Ibarra: None. **A.X. López:** None. **C. Ventura:** None. **L. Medina-Ceja:** None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.17/B73

Topic: B.10. Epilepsy

Support: NIH R01NS069861

Title: Characterization of interictal spike (IIS) morphologies important in the mouse kainate and rat pilocarpine models of epilepsy

Authors: R. A. BERGSTROM[1], J. A. PFAMMATTER[2], D. SUBRAMANIAN[3], V. SANTHAKUMAR[3], ***M. V. JONES**[2];
[1]Biol., Beloit Col., Beloit, WI; [2]Neurosci., Univ. of Wisconsin Madison, Madison, WI; [3]Molecular, Cell and Systems Biol., Univ. of California Riverside, Riverside, CA

Abstract: Interictal spikes are a potential clinical biomarker for epilepsy, but their detection, quantification, and classification in EEG is overly time-intensive and subject to significant interobserver variability. We have developed a probability-based algorithm for the detection and classification of interictal spikes (IIS) from long (24-hour) EEG records to differentiate mice with kainate (KA) model of epilepsy from saline-treated (SA) controls. (Pfammatter et al. 2018). Briefly, our algorithm detects potential spike-like events from EEG. These event waveforms are projected into principal components (PC) space using only the first three PCs and then are clustered using a Gaussian mixture model. A probability score (P(e)) based on the odds-ratio of

observing events from KA versus SA animals within that cluster is assigned to each of the resultant event clusters. We create an index that predicts risk of epilepsy by assigning each event in an EEG record its cluster-based prediction score, summing these values, then dividing by the record duration to yield an index with units of "epileptiform spikes per second". This score effectively predicts whether an animal received an epileptogenic insult even in the absence of ever observing either convulsive or electrographic seizures. Here we test and validate the utility of our algorithm to differentiate between epileptic and control EEG in the rat pilocarpine model of epilepsy. We also characterize the frequency and temporal relationships between the individual IIS morphologies and convulsive seizures in the kainate and pilocarpine models of epilepsy, which indicate that some IIS morphologies and not others may be predictive of seizure activity. Finally, we investigate the utility of a wavelet-based event detection method for spikes and other interictal events as an alternative to our previous two-threshold event detection method and find in our preliminary results that wavelet-based event detection methods provide a unique and important view of IISs regarding their potential contribution to epileptogenesis.

Disclosures: R.A. Bergstrom: None. **J.A. Pfammatter:** None. **D. Subramanian:** None. **V. Santhakumar:** None. **M.V. Jones:** None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.18/B74

Topic: B.10. Epilepsy

Title: Neurochemical changes in the hippocampus of a prenatal model of epilepsy

Authors: *S. T. PERUZZARO, N. MORISOT, L. YU, A. MALIK, S. HSIEH, H. B. JANSSENS, A. RASSOULPOUR;
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Abstract: Abnormalities in brain development have been associated with epilepsy. Yet, little is known about the functional underpinnings of epileptic episodes in patients with abnormal brain development. Recent research has shown that toxic exposure to the DNA alkylating agent, methylazoxymethanol (MAM), in pregnant rats disrupts brain formation in the offspring, resulting in abnormalities that resemble the human condition, including epileptic spasms. The aim of the present study was to investigate the neurochemical changes in the hippocampus of prenatally MAM-exposed rats. To produce malformation in brain development, dams were administered with MAM during gestation. Control dams received saline administration. Adult rats were all administered pilocarpine to induce seizures. Adult animals that were prenatally exposed to MAM or saline underwent microdialysis in the hippocampus. Spontaneous epileptic spasms were observed in MAM-exposed rats during the course of the experiment. Microdialysis

samples were analyzed by LC/MS-MS for levels of up to 14 neurotransmitters, neuromodulators and metabolites. Results revealed drastic changes in hippocampal neurochemistry in MAM-exposed rats. We observed increased levels of tryptophan, kynurenine, 3-hydroxy kynurenine, kynurenic and anthranilic acid in the MAM model compared to the control group. MAM-exposed rats also displayed elevated glutamate, dopamine, serotonin and glycine levels compared to controls. In contrast, GABA and acetylcholine concentrations were lower in MAM- compared to saline-exposed animals. Our set of data suggests that upregulation in kynurenine pathway and excitatory signaling together with GABA downregulation in the MAM-exposed rats may contribute to their epileptic phenotype. The prenatal MAM model may help understanding the neuronal mechanisms underlying epilepsy associated with abnormal brain development. In addition, the prenatal MAM model could be used to advance drug development for the treatment of epilepsy.

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Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.19/B75

Topic: B.10. Epilepsy

Support: TTUHSC Start-Up Funds to JL

Title: Impaired GABAergic inhibition and seizure susceptibility in a mouse model of SLC13A5 deficiency

Authors: *J. J. LAWRENCE[1,2,3], R. WANG[1], F. SELINA[1], T. ANDERSON[1], X. LIU[1], M. HAYES[1], S. RAMCHANDRAN[4], V. GANAPATHY[4,2];
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Abstract: SLC13A5 loss-of-function mutations cause Early-onset Infantile Epileptic Encephalopathy type 25 (EIEE-25), a condition where seizures are refractory to treatment. Human SLC13A5 and mouse Slc13a5 encode the sodium-dependent plasma membrane citrate transporter. In neurons, cytoplasmic citrate is a substrate for synthesis of ATP and the neurotransmitters GABA, glutamate, and acetylcholine. Although the precise mechanisms by which SLC13A5 deficiency causes EIEE-25 remain poorly understood, growing evidence implicates GABAergic dysfunction. Reduced cytoplasmic citrate availability could impair downstream metabolic pathways, leading to impaired synaptic function and excitation/inhibition imbalance by weakening GABAergic function. In this study, using an acute low-dosing

paradigm of consecutive intraperitoneal (IP) injections on Slc13a5 knockout (KO) and wild-type (WT) mice, we tested the hypothesis that SLC13A5 KO mice exhibit a lower seizure threshold to the chemoconvulsants pilocarpine **(**PILO) and pentylenetetrazole **(**PTZ). Seizures were scored manually using a Racine scale (RS, 0-7 index of seizure severity). In PILO experiments (1 mg/kg atropine applied 30 min preceding a sequence of 50 mg/kg PILO every 10 min), KO mice exhibited more time in RS2 (KO: 441.8 ± 24.9 sec vs. WT: 144.4 ± 45.9 sec, n=4, $p<0.001$) over the course of the first 10 min. In PTZ experiments (15 mg/kg PTZ IP every 10 min), PTZ KO mice exhibited shorter latency to seizure onset than age-matched WT mice (KO: 24.8 ± 1.4 min (n=3), WT: 44.6 ± 6.6 min (n=3), $p<0.05$). KO mice also exhibited increased seizure severity to PTZ at earlier time points relative to WT mice (time in RS3; KO:13.3 ± 2.9 sec vs. WT:0.4 ± 0.4 sec, $p<0.05$). Because cFos permits the visualization of neuronal excitability, seizure location was investigated using cFos immunocytochemistry on KO and WT mice that had undergone PILO and PTZ-induced seizures. Preliminary results indicate that high cFos activation was present in the hippocampus, cortex and hypothalamus of both WT and KO mice. However, cFos activation was highest in the hippocampal dentate gyrus (DG) of KO mice that had undergone PTZ-induced seizures, suggesting that the DG was the seizure focus in SLC13A5 KO mice. Our preliminary results from both PTZ and PILO experiments converge on the finding that KO mice have lower seizure threshold compared to WT mice. In conclusion, these results are consistent with the hypothesis that SLC13A5 deficiency impairs GABAergic signaling.

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Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.20/B76

Topic: B.10. Epilepsy

Support: The Cornell University Ithaca-WCMC seed grant
the Daedalus Fund for Innovation

Title: *In vivo* unanesthetized mapping of glutamate neurotransmission during acute interictal spikes in the mouse neocortex using a genetically encoded sensor

Authors: *M. Z. ZHAO[1,2], J. LI[1,3], F. YANG[1,3], J. NIEMEYER[1], H. MA[1,2,3], T. H. SCHWARTZ[1,2];
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Abstract: Epilepsy is a neurological disorder characterized by aberrant neuronal excitability. Glutamate is the major excitatory neurotransmitter in the brain and plays an important role in the initiation and spread of epileptic activity. However, little data exists on the utility of in vivo real-time glutamate neurotransmission mapping of epileptic activity and the impact of anesthesia on glutamate concentration and release. Furthermore, glutamate has been hypothesized to play a role in neurovascular coupling. We performed in vivo real time imaging of interictal spikes using local field potential, glutamate, blood flow and oxygenation imaging in unanaesthetized and anesthetized transgenic mice. We generated Emx-CaMKII-iGluSnFR transgenic mice to produce expression of iGluSnFR within all excitatory neurons across all layers of the cortex, but not in GABAergic neurons. For the anesthetized experiments, 1.5% isoflurane was used. We induced acute focal interictal discharges in the neocortex by injection of bicuculline methiodide (BMI, 5mM, 0.5µl). Glutamate fluorescence imaging and intrinsic optical imaging including 530nm and 617nm wavelengths were used to measure glutamate transmission and hemodynamic signals. The local field potential was recorded to identify the epileptic discharges. Single interictal spike induced a strong change in iGlu fluorescence in the area of the interictal spike focus. The maximum amplitudes of fluorescence changes in anesthetized and awake mice were 17.1±5.7% (n=178 spikes, n=3 animals) and 42.7±9.9% (n=284 spikes, n=3 animals; p=0.044) at 0.033±0.010s and 0.027±0.006s (p=0.322), respectively. The intrinsic optical imaging showed that Hbt concentration increase peaks at 0.57±0.13 µm and 1.56±0.45µm (p=0.049) with latencies of 1.95±0.32 s and 1.21±0.02s (p=0.042) in anesthetized and awake mice, respectively, whilst Hbr concentration decreases by 0.37±0.15 µm and 0.51±0.19 µm (p=0.304) and at 0.37±0.31 s and 1.07±0.63 s (p=0.148). Our data suggests that genetically encoded glutamate sensor imaging might provide a powerful tool to map neuronal activity in neocortical epilepsy. The glutamate neurotransmission and hemodynamic responses measured in awake mice are substantially different from anaesthetized animals. These results may have important implications for the neuroimaging research in awake epileptic humans and animals.

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Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.21/B77

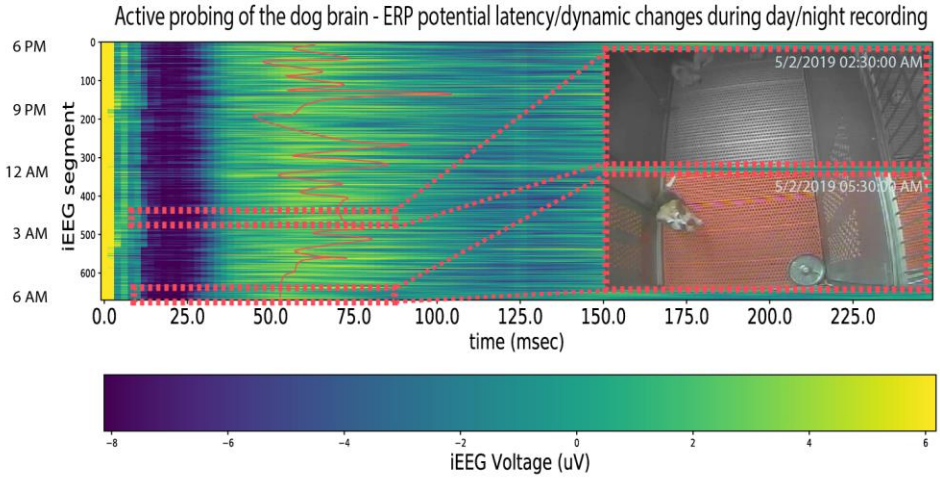
Topic: B.09. Network interactions

Support: NIH Grant R01 - NS092882
NIH Grant UH2/UH3 - NS95495
Institutional Resources of Czech Technical University in Prague, Czech Republic

Title: Behavioral state tracking using intracranial electrophysiology in an implantable system

Authors: *V. KREMEN, Jr[1], V. SLADKY[2], P. NEJEDLY[2], I. KIM[1], T. PAL ATTIA[1], B. H. BRINKMANN[1], B. K. STURGES[3], C. M. CROWE[4], G. A. WORRELL[2];
[1]Neurol., [2]Mayo Clin., Rochester, MN; [3]Dept. of Surgical and Radiological Sci., [4]Vet. Med. Teaching Hosp., Univ. of California at Davis, Davis, CA

Abstract: Electrical brain stimulation (EBS) is an emerging therapeutic option for patients with neurological and psychiatric diseases. The FDA approved indications include epilepsy, obsessive compulsive disorder, Parkinson's disease, and tremor. Sleep disorders are common comorbidities of brain disease and accurate automated sleep staging is needed for long-term objective assessment of sleep and to help guide chronic EBS therapy.
We developed a system for the automated sleep scoring using machine learning and narrow artificial intelligence applied to intracranial EEG recordings acquired from a chronic brain implant. The investigational Medtronic Summit RC+S system (bilateral hippocampus & anterior thalamic nucleus (ATN) or cortical electrodes) was implanted in canines with naturally occurring epilepsy. The system provides streaming iEEG and bi-directional connectivity between the implant and a tablet computer enabling large-scale data management and analytics for real-time, remote tracking of behavioral state and adaptive stimulation. We developed classifiers for different behavioral states with both passive and active probing paradigms using hippocampal iEEG and evoked potentials during ATN stimulation.
We verified the automated system for real-time, remote behavioral state tracking using a single hippocampal electrode and one electrode pair (bilateral hippocampus). Our results suggest that the observed iEEG dynamics in hippocampal electrodes can be used to assess the brain state of subjects receiving chronic EBS. The iEEG-based behavioral state classification developed here is efficient and could feasibly be incorporated into implantable devices for quantifying patient sleep patterns, administering behavioral state-specific therapies, and adjust other iEEG-based classifiers.



Disclosures: **V. Kremen:** None. **V. Sladky:** None. **P. Nejedly:** None. **G.A. Worrell:** None. **I. Kim:** None. **T. Pal Attia:** None. **B.H. Brinkmann:** None. **C.M. Crowe:** None. **B.K. Sturges:** None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.22/B78

Topic: B.10. Epilepsy

Support: ERC grant 682345

Title: A novel epileptic mouse model to better understand pathogenic mechanisms: mTOR-repressor DEPDC5 deficient mouse

Authors: *A. BACQ, T. RIBIERRE, D. ROUSSEL, S. BAULAC;
Inst. Du Cerveau Et De La Moelle Epiniere (ICM), Paris, France

Abstract: *DEPDC5* gene (Dishevelled, Egl-10, and Pleckstrin Domain Containing 5) is so far the most frequently mutated gene in familial focal epilepsies. Patients often have drug-resistant seizures requiring neurosurgery. Moreover, recent observations from the clinics suggested that

DEPDC5 mutations might confer a higher risk to sudden unexplained death in epilepsy (SUDEP). DEPDC5 is part of the GATOR1 (Gap Activity Towards Rags complex 1) complex, which functions as a repressor of the recently recognized amino acid-sensing branch of the mTORC1 pathway (mechanistic Target Of Rapamycin Complex 1). To date, the specific function of DEPDC5 in the brain and how mutations leads to seizures remain unknown. We have developed a novel mouse model with both a tagged-version of Depdc5 and lox sites for subsequent deletion (unpublished data). Using the tagged mouse, we were able to describe the spatio-temporal profile of Depdc5 expression in the mouse brain. We then generated a neuronal synapsin 1 KO (Syn1cKO) and unveiled the occurrence of spontaneous seizures, premature death resembling SUDEP, and comorbid psychiatric features. We further explored the pathomechanism of SUDEP, by investigating cardiorespiratory functions and their cerebral origin. We show alterations in limbic system and their connexions to brain stem that may sustain the SUDEP phenotype. To further investigate the underlying pathogenic mechanisms, we performed RNA-sequencing from the somatosensory cortex of adult animals (before the age of seizure onset). We found ~ 600 differentially expressed genes in the cKO mice compared to WT littermates. New pathways, independent of mTORC1 signaling cascade, were altered, highlighting dysregulation of genes involved in the regulation of neuronal excitability. Investigation of the functional consequences of these molecular alterations are ongoing to better understand how Depdc5-deficiency cause epilepsy.

Disclosures: A. Bacq: None. **T. Ribierre:** None. **D. Roussel:** None. **S. Baulac:** None.

Poster

555. Animal Models of Epilepsy II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 555.23/B79

Topic: B.10. Epilepsy

Title: Morphological and physiological characterization of DEPDC5 acute and chronic deficiency models

Authors: *M. CERULLO[1,2], A. DE FUSCO[1,2], E. CASTROFLORIO[3], C. MICHETTI[1,4], S. BAULAC[5], F. BENFENATI[1,4];
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Abstract: Background In the central nervous system, the mTOR signaling cascade is involved in normal neuronal homeostasis by promoting neuronal differentiation, neurite elongation and branching, synaptic formation during development and regulation of excitability in mature

synapses. DEPDC5 protein is a member of GATOR1, a negative regulator of mTOR complex 1 (mTORC1). Recently, mutations in *DEPDC5* have been associated with various focal epileptic syndromes, both lesional and non-lesional, even within the same family. **Aims** Our aim is to characterize morphologically and physiologically the epileptogenic mutants belonging to the mammalian target of rapamycin (mTOR) pathway, in particular *Depdc5*. Since it has been demonstrated that the complete knockout is embryonically lethal in rodents, we decided to compare a constitutive condition of haploinsufficiency (*Depdc5*$^{+/-}$) with the acute silencing of *Depdc5* obtained by RNA interference, in order to unveil new aspects of GATOR1-related epileptogenesis. **Methods** We employ a combination of Real-Time PCR, Western Blot, Immunofluorescence and Patch-Clamp recordings to evaluate the effect of Depdc5 deficiency in both *Depdc5*$^{+/-}$ and *Depdc5* acutely silenced cortical primary neurons. **Results** While we do not observe a strong epileptogenic phenotype in *Depdc5*$^{+/-}$ primary cortical neurons compared to wild type neurons, *Depdc5* silenced neurons show mTOR pathway hyperactivation associated with increased soma size and dendritic arborization and coupled with increased excitatory synaptic transmission and intrinsic excitability. **Conclusions** This study shows novel aspects of GATOR1-related epileptogenesis due to Depdc5 deficiency resulting in increased excitatory synaptic connectivity and intrinsic excitability and confirming its role in epileptogenic process.

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Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.01/B80

Topic: B.11. Glial Mechanisms

Support: NIH Grant-ZIAHD000713-22

Title: Oligodendrocyte involvement in adapter-protein 4 deficient hereditary spastic paraplegia

Authors: *J. BELGRAD, E. SANTOS, R. DE PACE, J. BONIFACINO, R. FIELDS;
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Abstract: Hereditary spastic paraplegia (HSP) is a rare genetic disorder characterized by lower extremity weakness and stiffness, with symptoms arising in children as early as the first year of life. With over 80 genetic subtypes, one of the more severe forms of HSP is adaptor protein 4 (AP-4)-deficient HSP. In addition to the typical features of spastic paraplegia, children with AP-4-deficient HSP present additional symptoms, including thinning of the corpus callosum, nonspecific periventricular white matter loss, impaired speech development and early onset seizures. AP-4 is a heterotetrameric complex that sorts the autophagy-related protein 9A

(ATG9A) from the trans-Golgi network (TGN) to pre-autophagosomal structures to promote autophagosome formation. Autophagy has recently emerged as an essential process in many cells, particularly neurons, but the role of autophagy in myelinating glia, particularly in oligodendrocytes, remains largely unknown. Our studies show that components of the autophagy machinery are expressed in oligodendrocytes across development and are activated during hypoxia and starvation. Using an AP-4-epsilon (*AP4E1*) knockout mouse, we characterize the spinal cord white matter, and test the hypotheses that autophagy is necessary for white matter maturation and that oligodendrocytes contribute to the motor and cellular phenotypes that hallmark the pathophysiology of AP-4-deficient HSP.

Disclosures: J. Belgrad: None. **E. Santos:** None. **R. de Pace:** None. **J. Bonifacino:** None. **R. Fields:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.02/DP02/B81

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: B.11. Glial Mechanisms

Support: NIH Grant NS082203

Title: The function of tuberous sclerosis complex in oligodendrocytes and myelin

Authors: *A. V. EVANGELOU[1], J. N. BOURNE[2], W. B. MACKLIN[2], T. L. WOOD[1];
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Abstract: A number of investigators have provided evidence that the mechanistic target of rapamycin (mTOR) has an important role in oligodendrocyte development and CNS myelination. Our prior studies demonstrated that deleting mTOR from the oligodendrocyte lineage leads to hypomyelination in the spinal cord (Wahl et al., 2014). In contrast, other groups have reported results from experiments designed to upregulate mTOR signaling in oligodendroglia through disrupting tuberous sclerosis complex (TSC), a negative upstream regulator of the mTOR complex 1 (mTORC1). Surprisingly, these studies showed that mice with constitutive activation of the mTORC1 pathway displayed a hypomyelination phenotype, instead of hypermyelination as originally predicted (Lebrun-Julien et al., 2014; Carson et al., 2015; Jiang et al., 2016). However, in these prior reports, the deletion of *Tsc1* or *Tsc2* was introduced early in development, during specification or differentiation of the oligodendrocyte lineage. These early deletions led to decreased number of oligodendrocytes and thus, myelination independent of

differentiation was not evaluated.
The goal of this study is to assess how myelin production is altered when mTORC1 signaling is upregulated exclusively in mature oligodendrocytes so that the differentiation process remains unperturbed. We have generated an inducible conditional knock-out mouse model carrying Tsc1 floxed alleles and the tamoxifen inducible proteolipid protein promoter (*Tsc1* cKO). We induced *Tsc1* deletion in premyelinating oligodendrocytes at postnatal day (PND) 7-10, at the peak of oligodendrocyte differentiation in spinal cord. Our data suggest that loss of TSC in maturing oligodendrocytes in spinal cord has no effect on oligodendrocyte survival or differentiation as assessed at PND17 and PND49. Interestingly, electron microscopy analysis at PND25 showed normal myelin thickness indicating no effect of *Tsc1* loss on developmental myelination in spinal cord. Surprisingly, myelin thickness was significantly decreased at PND49, supporting a cell intrinsic function for TSC in myelin maintenance. Very unexpectedly, we also observed that Tsc1 cKO mice had epileptic episodes beginning at 3-4 months of age. Myelin in the corpus callosum of these mice showed normal thickness. This seizure phenotype is likely due to a subset of neurons showing recombination, in line with previous reports of PLP promoter activity in areas outside the white matter in the early postnatal brain. Follow up studies are designed to further investigate this unexpected brain phenotype, as well as to define the mechanism underlying the defect in myelin maintenance in the *Tsc1* cKO spinal cord.

Disclosures: **A.V. Evangelou:** None. **T.L. Wood:** None. **J.N. Bourne:** None. **W.B. Macklin:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.03/B82

Topic: B.11. Glial Mechanisms

Support: NIMH R56MH104593
NIH R01 grant 5R01MH11048
MDBR-15-108-PH
NARSAD Young investigator grant #20653
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Title: Defects of myelination are common pathophysiology in autism spectrum disorder

Authors: B. PHAN[1], ***J. BOHLEN**[2], B. A. DAVIS[2], Z. ZE[2], H.-Y. CHEN[2], B. MAYFIELD[2], S. C. PAGE[2], M. CAMPBELL[2], H. L. SMITH[2], D. GALLOP[2], C. L. THAXTON[3], J. M. SIMON[3], E. E. BURKE[2], J. SHIN[2], A. J. KENNEDY[4], D. SWEATT[5], B. D. PHILPOT[3], A. E. JAFFE[2], B. J. MAHER[2];

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Abstract: Autism Spectrum Disorder (ASD) is genetically heterogeneous in nature with convergent symptomatology, suggesting dysregulation of common molecular pathways. We analyzed transcriptional changes in the brains of five independent mouse models of Pitt-Hopkins Syndrome (PTHS), a syndromic ASD caused by autosomal dominant mutation in *TCF4*, and identified considerable overlap in differentially expressed genes (DEGs). Gene and cell-type enrichment analyses of these DEGs highlighted oligodendrocyte dysregulation and we confirmed the myelin-associated transcriptional signature in two additional mouse models of syndromic ASD (*Pten*$^{m3m4/m3m4}$, *Mecp2*$^{tm1.1Bird}$). We subsequently validated oligodendrocyte deficits in our *Tcf4* mouse model which showed inefficient oligodendrocyte maturation in both an isolated oligodendrocyte *in vitro* cell culture system and *ex vivo* at day 24 (P24) and day 42 (P42). Furthermore, we used transmission electron microscopy (TEM) to visualize myelination in the corpus callosum (CC) of *Tcf4*$^{+/tr}$ and *Tcf4*$^{+/+}$ littermates, observing a significant decrease in the proportion of myelinated axons in the CC of *Tcf4*$^{+/tr}$ mice compared to *Tcf4*$^{+/+}$ littermates. Similar to our *ex vivo* IHC results, we observed a significant reduction in the number of CNP-positive oligodendrocytes in primary cultures derived from *Tcf4*$^{+/tr}$ mice compared to *Tcf4*$^{+/+}$ littermates. When comparing compound action potentials (CAP) using electrophysiology, we show the ratio of N1/N2 is significantly reduced in the *Tcf4*$^{+/tr}$ mice compared to *Tcf4*$^{+/+}$ littermates, indicative of a greater proportion of CAP traveling down unmyelinated axons. Moreover, we integrated syndromic PTHS mouse model DEGs with human ASD genes (SFARI) and human idiopathic ASD postmortem brain RNA-seq, and found significant enrichment of overlapping DEGs and common biological pathways associated with myelination. Remarkably, we show that DEGs from syndromic ASD mouse models can be used to identify human idiopathic ASD cases from controls. These results from seven independent mouse models of ASD are validated in human brain, implicating disruptions in oligodendrocyte biology as shared mechanisms in ASD pathology.

Disclosures: J. Bohlen: None. **B.A. Davis:** None. **Z. Ze:** None. **H. Chen:** None. **B. Mayfield:** None. **S.C. Page:** None. **M. Campbell:** None. **H.L. Smith:** None. **D. Gallop:** None. **C.L. Thaxton:** None. **J.M. Simon:** None. **E.E. Burke:** None. **J. Shin:** None. **A.J. Kennedy:** None. **D. Sweatt:** None. **B.D. Philpot:** None. **A.E. Jaffe:** None. **B.J. Maher:** None. **B. Phan:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.04/B83

Topic: B.11. Glial Mechanisms

Support: NSF (RII Track 1ASSET III, #1457888)

Title: Nanostructured surfaces for oligodendrocyte differentiation

Authors: *K. D. SHARMA[1], K. M. ALGHAZALI[2], A. B. RANGUMAGAR[3], J. TRINGALI[4], A. GHOSH[3], A. S. BIRIS[2], J. Y. XIE[4];
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Abstract: In regenerative medicine, replenishing lesioned cells through the implantation of differentiated cells has been proposed to reduce the tumorigenic risk of stem cells. “On-demand” generation of functional oligodendrocytes (ODCs) represents a better therapeutic option in restoration of the signal transduction and axonal functions in demyelinating diseases than the undifferentiated stem cells. However, current methods used to create ODCs from neural stem cells (NSCs) fail to result in sufficient differentiations. Mounting evidence suggests that rigidity and composition of the extracellular matrix (ECM) play a pivotal role in determining the fate of the stem cells. Advances in biocompatible material development provide several options for fabrication of ECM to promote NSCs differentiated to the desired cell types. Nanostructured surfaces have been shown to best mimic the cell-environment interactions and facilitate cell adhesion, migration and differentiation. In this study, we have tested the efficiency of a couple of fabricated surfaces, i.e., (i) covalently modified crystalline nanocellulose with lysine molecule (CNC-Ly) and (ii) gold nanorods (AuNRs) functionalized with amine (NH_2^+) group, on the differentiation of NSCs to ODCs. Both materials are biocompatible and have been used as novel and advanced nanomaterials in biomedical sciences. Lysine and amine molecules confer positive charges to the nanomaterials and thus promotes the attachment of NSCs, which have negatively charged plasma membranes. Cortical NSCs from E14 rat embryos were differentiated on CNC-Ly or AuNRs substrate for one week. The differentiation of NSCs on these surfaces were compared to that of traditional poly-D-lysine (PDL) surface. Markers of ODCs (Rip) and astrocytes (GFAP) were identified by immunocytochemical methods and the quantification was done via Gen5 3.05 program. Our results showed that by one week 55±1.82% and 33±2.76% of cells were Rip^+ ODCs on AuNR and nanocellulose substrates, respectively, compared to 21±5.36% on PDL. While 66±9.33% (PDL) and 50±1.86% (CNC-Ly) of NSCs remained undifferentiated, such cells were very few on AuNR substrate. 18±0.45% and 45±2.32% of differentiated NSCs were $GFAP^+$ astrocytes on CNC-Ly and AuNR substrates, respectively, compared to 15.68±4.6% on PDL. Additionally, the survival rate and the morphology of the ODCs differentiated on AuNR and CNC-Ly substrates were better than those on PDL. The results from CNC-Ly and AuNR surfaces indicate that the design and properties of the plasmonic surfaces are advantageous for tissue engineering in respect to neural regeneration.

Disclosures: K.D. Sharma: None. **K.M. Alghazali:** None. **A.B. RanguMagar:** None. **A. Ghosh:** None. **A.S. Biris:** None. **J.Y. Xie:** None. **J. Tringali:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.05/B84

Topic: B.11. Glial Mechanisms

Support: NIH NS082203

Title: mTOR regulation of differentiation, myelination, and maintenance in brain and spinal cord oligodendroglia

Authors: *L. KHANDKER[1], M. A. JEFFRIES[1], T. L. WOOD[2];
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Abstract: Myelin deficits during development can result in diseases such as leukodystrophies, and loss of myelin after development leads to demyelinating diseases such as Multiple Sclerosis. The process of myelination is highly regulated through multiple signaling pathways, including the PI3K/Akt/mTOR pathway. Disruption of this pathway in mice compromises developmental myelination and may affect long-term myelin integrity. Loss of mTOR in the oligodendrocyte lineage by CNP-Cre deletion of mTOR floxed alleles (mTOR cKO) results in a delay in oligodendrocyte differentiation and initiation of myelination as well as long-term hypomyelination of the spinal cord. In contrast, these mice exhibit normal developmental myelination of the brain up until 8 weeks of age, suggesting heterogeneity in cellular response to loss of mTOR. By flow cytometry, we have determined that at postnatal day 10 there is an increase in PDGFRα+ early-stage precursors in mTOR cKO spinal cords, and a decrease in O4+ late-stage progenitors/immature oligodendrocytes, suggesting an accumulation of early precursors that are unable to or delayed in progress to the O4+ stage when mTOR is deleted. In contrast, oligodendroglia from mTOR cKO brains exhibit normal proportions of early and late-stage OPCs. In order to define molecular pathways downstream of mTOR that promote myelination, we have undertaken single-cell mRNA transcriptome analysis of oligodendroglia from mTOR cKO animals. We isolated O4+ oligodendroglia from mTOR cKO and control animals and used 10x Genomics to simultaneously analyze mRNA transcripts of thousands of individually identifiable cells. Sequencing data reveal alterations in several key cellular pathways, including oxidative phosphorylation which is the most significantly downregulated pathway in mTOR cKO. Interestingly, analysis of O4+ OPCs from mTOR cKO brains reveal that despite the lack of a developmental phenotype, mTOR cKO brain oligodendroglia also exhibit a downregulation of mitochondrial function and oxidative phosphorylation. We measured mitochondrial function in isolated O4+ cells and confirmed that loss of mTOR results in a deficit in oxidative phosphorylation in both the brain and spinal cord. Consistent with these findings, we

observe hypomyelination in the brains of mTOR cKO mice at 12 weeks of age, suggesting compromised myelin maintenance. As the mice age, this myelin deficit persists in both the spinal cord and brain. Understanding the molecular regulators of myelination and oligodendrocyte stability, along with heterogeneity, will promote better understanding of human myelin diseases and potential therapeutic targets.

Disclosures: L. Khandker: None. **M.A. Jeffries:** None. **T.L. Wood:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.06/B85

Topic: B.11. Glial Mechanisms

Support: NINDS K12NS079414 (CME)
Child Neurology Society Dodge Young Investigator Award (CME)
Baby Alex Foundation Grant (CME)
NIH EY024481 (PAR)
NIH EY027881 (PAR)
NIH P50 HD 018655
NIH GM067169 (CJF)

Title: Zinc storage proteins and zinc transporters are developmentally regulated in oligodendrocytes

Authors: *C. M. ELITT[1,2], C. E. R. RICHARDSON[3], J. WANG[1], S. J. LIPPARD[4], M. D. SHOULDERS[3], P. A. ROSENBERG[1,2];
[1]Neurol., Boston Children's Hosp., Boston, MA; [2]Harvard Med. Sch., Boston, MA; [3]Chem., [4]MIT, Cambridge, MA

Abstract: Zinc is abundant in the central nervous system and required for proper function of a variety of enzymes, proteins and transcription factors, including many important in myelination. Increases in free ionic zinc (Zn^{2+}) play a critical role in neuronal and oligodendrocyte (OL) injury. Little is known about mechanisms of zinc regulation in developing or mature OLs. We have previously shown that concentrations of free zinc are downregulated as OLs mature using Chromis-1, a novel Zn(II)-selective ratiometric fluorescent probe optimized for two-photon excitation fluorescence microscopy (TPEM) (Bourassa and Elitt et al., *ACS Sensors,* 2018). The objective of the current study was to understand molecular mechanisms that might contribute to these developmental changes in intracellular free zinc concentrations. Mixed glia cultures were isolated from postnatal day 2 (P2) rat forebrains and grown for 10-17 days. Developing OLs were separated from microglia and astrocytes using selective detachment. Cells were maintained

in the presence of platelet-derived growth factor (PDGF) and basic fibroblast growth factor (FGF) for 6 days prior to harvesting RNA or protein for analysis. To produce mature OLs, PDGF and FGF were replaced by triiodothyronine (T3) and ciliary neurotrophic factor (CNTF) and harvested at 16 days. We used qPCR to evaluate mRNA expression of metallothioneins, the metal regulatory transcription factor 1 (MTF-1) as well as zinc influx proteins (ZIPs) and zinc exporters (ZnTs). MT-1, MT-2 and MTF-1 were all increased 4-6 fold in mature OLs compared to developing OLs. Initial evaluation of zinc transporters by qPCR and immunoblot have shown similar increases as OLs differentiate. Taken together, these results raise the possibility that a zinc influx is required for OL differentiation to proceed. To study zinc transport across oligodendrocyte cell membranes, we measured $^{65}Zn^{2+}$ uptake in the two cells types and both robustly take up zinc. We are currently correlating changes in uptake with changes in zinc storage proteins and transporters. With an improved understanding of zinc homeostasis in oligodendrocytes, additional studies into zinc dyshomeostasis in white matter disorders will be warranted.

Disclosures: **C.M. Elitt:** None. **C.E.R. Richardson:** None. **J. Wang:** None. **S.J. Lippard:** None. **M.D. Shoulders:** None. **P.A. Rosenberg:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.07/B86

Topic: B.11. Glial Mechanisms

Support: the Grants-in-Aid for Sasakawa Scientific Research (No. 28-411)

Title: Oligodendrocyte progenitor cells during development and upon sensory loss in mouse visual cortex

Authors: *H. SHIN[1], H. D. KAWAI[2];
[1]Dept. of Bioinformatics, [2]Dept. of Sci. and Engin. for Sustainable Innovation, Soka Univ., Tokyo, Japan

Abstract: Oligodendrocyte progenitor cells (OPCs) are widely distributed as the principal proliferative cells in the postnatal cortex and continue to proliferate to produce newly myelinating cells throughout the lifetime. It is unclear how OPCs self-renew or differentiate into oligodendrocytes (OLs) and how sensory deprivation affects them in primary visual cortex (V1). We examined developmental changes in the distribution of OPCs and the effects of binocular enucleation (BE) starting at postnatal day (P) 15. 3-day BrdU injection from P22 to P25 (i.e., around the onset of the critical period for ocular dominance plasticity, ODP), but not from P19 to P22 nor from P25 to P28, resulted in increased proliferative cells. BE notably increased

proliferative cycling OPCs particularly in lower layer 6 at P25. The visual deprivation increased OPC progeny in the lower layer due mainly to the shift of the symmetric cell division from the differentiated to the undifferentiated states. We then examined possible signaling mechanism underlying the BE-induced shift and found that sonic hedgehog (Shh) signaling pathway is involved. At P30, most, if not all, of P22-25 BrdU-labeled proliferated cells exited the cell cycle and mostly became differentiated cells in control mice. Meanwhile, BE increased the formation of quiescent OPCs rather than the formation of differentiated cells. The difference in the elevated undifferentiated cells at P25 between BE and control mice was maintained at P30. Further, many of the BrdU-labeled proliferated OPCs differentiated into mature OLs at P50. At this age, BE mice had an elevated number of mature OLs and an increased expression of CNPase particularly near the white matter. Overall, our study suggests that V1 has a sensitive period of OPC proliferation and differentiation around the ODP critical period, in which sensory loss promotes undifferentiation via a shift in symmetric cell division in lower layer 6, but later resulting in an increase in quiescent OPCs and the subsequent formation of mature OLs.

Disclosures: H. Shin: None. **H.D. Kawai:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.08/B87

Topic: B.11. Glial Mechanisms

Title: Myelinating glial connexin deficiency within the central nervous system results in an increased inflammatory response and decreased oligodendrocyte development

Authors: *S. KEIL[1], M. FREIDIN[2], C. K. ABRAMS[3];
[1]Neurol. and Rehabil., Univ. of Illinois Chicago, Chicago, IL; [2]Neurol. & Rehabil., [3]Dept of Neurol. & Rehabil., Univ. of Illinois at Chicago, Chicago, IL

Abstract: Central nervous system (CNS) glia rely on a dynamic network of communication to maintain effective function and homeostasis throughout the brain. Their interactions are dependent, in part, on several transmembrane proteins called connexins (Cxs). Through the formation of low resistance gap junctions or hemichannels, Cxs provide a pathway for small signaling molecules and ions between the cells or the external environment. These channels transmit the signals necessary for a variety of functions involved in cellular development, synchronization, and immune response. Alterations in Cx function hinders this communication, causing a wide range of cell and tissue-specific disease states in the brain and throughout the body. In the CNS, the role of oligodendritic connexins in overall glial function is highlighted by human diseases; mutation of oligodendrocyte Cx32 causes X-linked Charcot-Marie-Tooth disease (CMT1X) while mutation in Cx47 causes Pelizaeus-Merzbacher-Like disease 1

(PMLD1). Using mixed glial cultures and tissue sections from Cx32KO, Cx47KO and WT mice, we evaluated the effect of Cx loss on the CNS glia. In both KO models, there is a significantly lower presence of $O4^+$ cells, with a decrease in proliferation in both mature oligodendrocytes and oligo progenitor cells. There is a significant increase in activation and presence of $Iba1^+$ cells, and a significant increase in proliferation and fluorescence intensity in $GFAP^+$ cells, suggesting an increased inflammatory state at baseline. This baseline inflammatory state within mutant CNS tissue could make it difficult to manage additional neurologic stress, resulting in the inability to remyelinate injured nervous tissue, as has been seen in previous experiments.

Disclosures: S. Keil: None. **M. Freidin:** None. **C.K. Abrams:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.09/B88

Topic: B.11. Glial Mechanisms

Support: NIH R37 NS102185

Title: Oligodendrocyte progenitor cell fate after white matter stroke

Authors: *N. M. SHIH[1], I. L. LLORENTE[2], M. MACHNICKI[2], S. T. CARMICHAEL[3]; [2]Neurol., [1]UCLA, Los Angeles, CA; [3]UCLA Sch. Med., Los Angeles, CA

Abstract: White matter stroke is a progressive vascular disease that leads to neurological deficits and accumulates to cause dementia. It accounts for approximately 30% of all stroke subtypes and damages the cellular constituents of subcortical white matter: oligodendrocytes, myelinated and unmyelinated axons, astrocytes, microglia and blood vessels. In clinical studies, new white matter strokes develop within pre-existing lesions and also generate adjacent lesions in 70% of cases. This indicates a vulnerable peri-infarct region which can progress to further damage and disrupt neuronal connections to cause substantial disability. Sozmen *et. al* previously showed that an oligodendrocyte progenitor cell (OPC) response is triggered after a focal lesion is induced in white matter of mice. OPC proliferation occurs acutely after stroke but an OPC differentiation block prevents OPCs from maturing into myelinating oligodendrocytes. Additionally, other studies have demonstrated that OPCs have the ability to become other glial cells (Zhang L *et. al*, 2016). To understand how OPCs in the white matter respond to later stages of white matter stroke and initiate a process of repair, we are utilizing a model of white matter stroke that mimics more advanced stages of white matter stroke and vascular dementia. To study cell fate changes of proliferating OPCs after stroke, we are labeling proliferating OPCs by brief pulses of the S phase marker 5-ethynyl-2′-deoxyuridine (EdU) given at multiple timepoints after stroke. EdU is administered at acute and chronic timepoints to compare levels of OPC proliferation post-stroke

as well as cell identity changes of these labeled OPCs at later timepoints. We are examining if proliferating OPCs induced after injury remain as OPCs, differentiate into oligodendrocytes and/or other cell types, or dying at a later time. By understanding OPC cell fate following white matter stroke, we can investigate what repair mechanisms exist to remyelinate damaged axons at different phases post-stroke and what disease mechanisms are preventing the brain from undergoing full recovery.

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Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.10/B89

Topic: B.11. Glial Mechanisms

Title: Oxygen tension regulates the phenotype of oligodendrocyte precursor cells

Authors: *K. YASUDA, T. MAKI, H. KINOSHITA, R. TAKAHASHI;
Neurol., Kyoto Univ. Grad. Sch. of Med., Kyoto, Japan

Abstract: Background: Oligodendrocyte precursor cells (OPCs) regulate the neuronal system in various ways, and play crucial roles in brain homeostasis besides their well-known role as a major reservoir for mature oligodendrocytes (OLGs). Recent studies have reported that some OPCs exposed to severe hypoxia gain ability of promoting angiogenesis during developmental stage[1] and post-stroke[2] at the expense of OPC differentiation arrest. However, how different oxygen tension affects the phenotype of OPCs remains unclear.
Object: The purpose of present study was to investigate the phenotypic changes of OPCs under different levels of oxygen concentration.
Methods: For *in vitro* experiments, we prepared primary culture of oligodendrocyte lineage cells obtained from neonatal rats. During OPC differentiation induction, cultured OPCs were maintained under normoxic (FiO_2=21%) or different levels of hypoxic (FiO_2=3, 5, 7 and 10%) conditions in a multi-gas incubator. Six days after differentiation induction, immunocytochemistry, western blot analysis, and quantitative RT-PCR analysis were performed to examine the effects of different oxygen tension on the phenotype of OPCs.
Results: Immunocytochemistry demonstrated that the number of myelin basic protein (MBP) positive cells was significantly increased under mild hypoxic condition (FiO_2=5%) compared to normoxic condition. Western blot analysis confirmed that the expression of MBP level was significantly increased under different levels of hypoxic conditions (FiO2=3, 5, 7 and 10%) compared to normoxic condition. Quantitative RT-PCR analysis revealed the gene expressions of OPC differentiation-related factors such as *Sox10*, *Olig2*, and *Myrf* were higher in

oligodendrocyte lineage cells under mild hypoxic condition (FiO_2=5%).
Conclusion: The present study indicated that mild hypoxia promotes OPC differentiation and different oxygen tension may regulate the phenotype of OPCs.
Reference: 1. Yuen TJ, Silbereis JC, Griveau A, Chang SM, et al. Oligodendrocyte-encoded HIF function couples postnatal myelination and white matter angiogenesis. Cell. 2014;158:383-396. 2. Kishida N, Maki T, Takagi Y, Yasuda K, et al. Role of Perivascular Oligodendrocyte Precursor Cells in Angiogenesis After Brain Ischemia. J Am Heart Assoc. 2019;8(9):e011824.

Disclosures: K. Yasuda: None. **T. Maki:** None. **H. Kinoshita:** None. **R. Takahashi:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.11/B90

Topic: B.11. Glial Mechanisms

Support: Ministry of Education, Taiwan 107L7837

Title: The role of neuron-derived connective tissue growth factor in cuprizone-induced intoxication of mature oligodendrocytes

Authors: *L.-J. LEE, C.-Y. CHEN;
Anat. and Cell Biol., Natl. Taiwan Univ., Taipei, Taiwan

Abstract: Connective tissue growth factor (CTGF) is a matricellular protein which is involved in many physiological processes. In the nervous system, CTGF is expressed in some distinct brain areas, such as the cortical subplate, a layer just above the white matter which contain great amount of oligodendrocytes. In the present study, we aimed to evaluate the role of subplate neuron-derived CTGF in the maturation of oligodendrocytes using a cuprizone (CPZ) intoxication paradigm. Eight-week old female forebrain-specific *Ctgf* knockout (Fb*Ctgf* KO) and control mice were fed with CPZ-containing chow (0.25% w/w) for 4 weeks. Afterwards, some mice were returned to normal chow for another 1 or 2 weeks. Mature oligodendrocytes were labeled by GST-pi immunohistochemistry and quantified in six brain regions, including the genu of corpus callosum, the upper (layer II/III), lower (layer V) and subplate (layer VIb) regions of the somatosensory cortex, the underneath external capsule and the striatum. After 4 weeks of CPZ treatment, compared with controls, greater number of GST-pi-positive mature oligodendrocytes was noted in the cortical subplate as well as the two regions in close proximity, the external capsule and lower cortex in Fb*Ctgf* KO mice. In the rest of examined regions, the numbers were comparable between genotypes. In the genu of corpus callosum, interestingly, greater number of mature oligodendrocyte was counted in CPZ-treated Fb*Ctgf* KO mice after 1

week of normal chow compared with CPZ-treated controls. Our results suggested a suppressive role of CTGF in the maturation of oligodendrocyte.

Disclosures: L. Lee: None. **C. Chen:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.12/B91

Topic: B.11. Glial Mechanisms

Support: NSF Graduate Research Fellowship
Adelson Medical Research Foundation
NMSS Postdoctoral Fellowship
Hilton Foundation Bridging Grant

Title: Remyelination leads to new myelination patterns in the cerebral cortex

Authors: *C. L. CALL[1], J. L. ORTHMANN-MURPHY[2], G. C. MOLINA-CASTRO[1], Y.-C. HSIEH[3], M. N. RASBAND[4], P. A. CALABRESI[1], D. E. BERGLES[1];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Neurol., Perelman Sch. of Medicine, Univ. of Pennsyl, Philadelphia, PA; [3]Harvard Univ., Boston, MA; [4]Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Myelination patterns in the cerebral cortex are highly variable, with sheath number and length varying among different types of neurons and even along individual axons. Although discontinuous, we find that myelin is allocated preferentially to a small subset of the diverse array of axons available. This sparse, but specific, pattern of cortical myelination has been shown in recent *in vivo* imaging studies to be remarkably stable, suggesting that maintaining sheath placement is important for cortical function. In people with multiple sclerosis, and the cuprizone model of toxic demyelination in mice, the cortex is capable of spontaneous remyelination after demyelination. However, it is unknown whether precise myelination patterns or overall myelin coverage of particular axons are restored following oligodendrocyte regeneration. To determine the specificity of myelin repair in the cortex, we performed longitudinal *in vivo* two-photon microscopy to follow individual oligodendrocytes and their myelin sheaths through de- and remyelination in MOBP-EGFP mice fed 0.2% cuprizone diet for 3 weeks. This protocol sufficiently induced near-complete loss of oligodendrocytes within the cortex, with complete restoration of layer I oligodendrocytes by 5 weeks recovery. Regenerated oligodendrocytes were formed in different locations, but had similar overall morphologies and comparable sheath production, despite the larger axonal territory available, suggesting oligodendrocyte size is primarily determined by cell-autonomous mechanisms. Unexpectedly, myelin sheaths from regenerated oligodendrocytes overlapped weakly with the territories of previous

oligodendrocytes, suggesting that inhibitory factors may prevent new oligodendrocytes from differentiating within the territories of degenerated cells. As a result, just over half of baseline sheaths were restored and many novel sheaths were formed along previously unmyelinated axon segments. For instances where sheaths were replaced, their position along axons was remarkably conserved, suggesting that demyelinated axons retain molecular marks that dictate sheath location. Indeed, in prolonged cuprizone experiments, nodal structural proteins persisted even after complete demyelination, indicating that axonal nodal molecular architecture may serve as a guidepost for remyelinating sheaths. These studies suggest that despite efficient oligodendrocyte regeneration, overall myelination patterns are not preserved during remyelination, which may have consequences for sensory processing and cognitive function.

Disclosures: C.L. Call: None. **J.L. Orthmann-Murphy:** None. **G.C. Molina-Castro:** None. **Y. Hsieh:** None. **M.N. Rasband:** None. **P.A. Calabresi:** None. **D.E. Bergles:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.13/B92

Topic: B.11. Glial Mechanisms

Support: 2UL1TR000433 (NCATS / MICHR)
Dystonia Medical Research Foundation
RO1NS077730 (NINDS)

Title: The DYT6 dystonia protein THAP1 regulates glycosaminoglycan metabolism during oligodendrocyte maturation

Authors: *D. YELLAJOSHYULA[1], M. R. COOKSON[2], W. DAUER[1];
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Abstract: Dystonia is a common neurological movement disorder characterized by debilitating prolonged involuntary movements. The neuropathology of one form of inherited dystonia (DYT6), caused by loss-of-function mutations in the THAP1 gene encoding the transcription factor THAP1 appears to stem from myelination deficits in the CNS. Our prior studies demonstrate that THAP1 plays a critical role in myelination during CNS maturation in a cell autonomous manner. Conditional deletion of THAP1 in the CNS retards maturation of the oligodendrocyte (OL) lineage, delaying myelination and causing persistent motor deficits. To develop mechanistic insight into the THAP1-regulated OL lineage progression we conducted RNA-seq analyses in differentiating OL from control and THAP1 null OPCs. Glycosaminoglycan (GAG) metabolism and extracellular matrix (ECM) signaling pathways

were the most-represented and significant THAP1 dependent biological pathways that are persistently dysregulated in differentiating OL. Consistent with gene expression studies, we observed abnormal accumulation of GAGs in differentiating THAP1 null OL and CNS, resulting from deficits in their catabolism. We present a model where THAP1 loss-of-function impedes OL lineage maturation by disrupting GAG metabolism. GAGs have significant influence on the development of OL lineage, however mechanisms regulating GAG metabolism and biology in various cell types of CNS are complex and poorly understood. Our studies on THAP1 function in the CNS illuminates the cell-autonomous role and regulation of GAG in the OL lineage.

Disclosures: D. Yellajoshyula: None. **M.R. Cookson:** None. **W. Dauer:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.14/B93

Topic: B.11. Glial Mechanisms

Support: MDA Development grant 381190

Title: Loss of oligodendrocyte monocarboxylate transporter 1 expression causes late onset axonal degeneration

Authors: *T. PHILIPS[1], Y. MIRONOVA[1], Y. JOUROUKHIN[3], M. V. PLETNIKOV[4], D. E. BERGLES[5], J. D. ROTHSTEIN[2];
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Abstract: In the CNS neuronal energy homeostasis is highly dependent on the metabolic support by glia. Apart from forming the myelin that ensheats the axons, oligodendrocytes play an essential role in fueling neuronal energy metabolism. Our earlier work has identified the lactate/pyruvate transporter monocarboxylate transporter 1 (MCT1) as a key mediator of oligodendrocyte metabolic support: acute oligodendroglial knock-down of MCT1 by virally delivered MCT1shRNAs causes neuronal degeneration. Still unexplored to date is the developmental and long-term consequences of loss of MCT1 metabolic support in oligodendrocytes. Our preliminary data has indicated that oligodendrocyte MCT1 expression is gradually decreasing with aging, which could contribute to subtle neuronal metabolic alterations in older mice. In order to understand the full importance of oligodendrocyte MCT1, we have recently generated MCT1 conditional null mice that allow for Cre mediated deletion of MCT1 expression in specific cell types. We crossed our conditional MCT1 null mice with Cre mice targeting either mature oligodendrocytes only (MogiCre) or both oligodendrocytes as well as

oligodendrocyte progenitor cells (Sox10Cre). We observed that mice with oligodendroglial loss of MCT1 using either Cre line develop indistinguishable from their littermate controls: P90 old oligodendrocyte conditional null mice were behaviorally normal and did not develop any signs of axonal or myelin pathology as assessed with either light or electron microscopy (EM). On the other hand, EM analysis of aged nerves of oligodendroglial MCT1 null mice (P360-P700) revealed specific pathological hallmarks of metabolic disturbances with full blown axonopathy: At P360, mitochondria in the axons had significantly increased in size and were often found to have a dysmorphic, enlarged christae structure strongly suggestive of axonal metabolic dysregulation. In addition, we observed an increase in intra-axonal mitochondrial aggregation in the null mice as compared to littermate controls. At a later time point, (~P700) the pathology had further progressed into a full-blown axonopathy with axonal swellings with intra-axonal organelle accumulations and significant myelin debris accumulation. We are now looking to further characterize these alterations either metabolically (ie changes in ATP or ROS production) as well as with electrophysiology on acutely isolated optic nerves. In summary, loss of oligodendrocyte MCT1 is well tolerated in early development and early adulthood but causes a progressive, late onset axonopathy characterized by severe metabolic alterations.

Disclosures: **T. Philips:** None. **Y. Mironova:** None. **Y. Jouroukhin:** None. **M.V. Pletnikov:** None. **D.E. Bergles:** None. **J.D. Rothstein:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.15/B94

Topic: B.11. Glial Mechanisms

Support: NIH (R01NS520340 to B.P.),
National Multiple Sclerosis Society (RG-1501-02797 to B.P.),

Title: m6A mRNA methylation is essential for oligodendrocyte maturation and CNS myelination

Authors: *H. XU[1], J. S. JONES[1], R. B. KUNJAMMA[1], Y. WENG[3], B. ELBAZ[1], Q. FEI[2], X. ZHUANG[4], G.-L. MING[3], C. HE[2], B. J. POPKO[1];
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Abstract: The exact molecular mechanisms involved in oligodendrocyte lineage progression remain unclear. Emerging studies have shown that N6-methyladenosine (m6A), the most common internal RNA modification of mammalian mRNA, plays a critical role in various

developmental processes. In this study, we demonstrate that oligodendrocyte lineage progression is accompanied by changes in m6A modification on numerous transcripts. *In vivo* conditional inactivation in oligodendrocyte lineage cells of an essential m6A writer component, METTL14, results in decreased oligodendrocyte numbers and CNS hypomyelination, although oligodendrocyte precursor cell (OPC) numbers are not altered. *In vitro* Mettl14 ablation disrupts post-mitotic oligodendrocyte maturation. In addition, Mettl14 ablation has distinct effects on OPC and oligodendrocyte transcriptomes. Together, our findings indicate that dynamic RNA methylation plays a critical regulatory role in oligodendrocyte development and CNS myelination.

Disclosures: **H. Xu:** None. **J.S. Jones:** None. **R.B. Kunjamma:** None. **Y. Weng:** None. **B. Elbaz:** None. **Q. Fei:** None. **X. Zhuang:** None. **G. Ming:** None. **C. He:** None. **B.J. Popko:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.16/B95

Topic: B.11. Glial Mechanisms

Support: NIH Grant 5250016602

Title: Developmental myelination and the nuclear progesterone receptor

Authors: *P. WINOKUR[1], B. ZHAO[2], Y. MA[2], T. VARTANIAN[2];
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Abstract: Steroid hormones synthesis within the CNS is evolutionarily conserved and thought to play important roles in development, homeostasis, and response to injury. Progesterone stimulates remyelination in experimental models of CNS demyelination through unknown molecular mechanisms. We developed an *ex vivo* mouse cerebellar explant system ideally suited to investigate both developmental myelination and remyelination. Oligodendrocyte maturation in cerebellar slices mimics physiological development in terms of temporal and cytoarchitectural patterns. To induce demyelination, cerebellar explants were treated with epsilon toxin, which induced highly specific and reproducible demyelination in a dose- and time-dependent fashion. To address the effect of progestins on myelination, cerebellar slices from P7 mouse pups were cultured for 7 or 14 days in the presence or absence of Nestorone, a potent, synthetic progesterone analog. Administration of 20 or 50 μM Nestorone significantly enhanced myelination as assessed by fluorescent staining intensity of the mature myelin protein, myelin basic protein (MBP). The most striking effects were seen at the 7-day timepoint, with 20 and 50

uM Nestorone treatment resulting in 96% and 81% increases in MBP fluorescence intensity, respectively, compared to that in vehicle-treated control slices. This trend was more modest at the 14-day timepoint, with 20 uM Nestorone treatment leading to a 35% increase in MBP fluorescence intensity. Interestingly, no effect was apparent with 50 uM treatment. This data suggests progesterone impacts myelination at an early postnatal age. To determine if the classical nuclear receptor is required for the effects of Nestorone on myelination, we conducted cerebellar explant experiments as described above in slices from mice carrying a germline loss-of-function mutation at the nuclear progesterone receptor locus.

Disclosures: P. Winokur: None. **B. Zhao:** None. **Y. Ma:** None. **T. Vartanian:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.17/B96

Topic: B.11. Glial Mechanisms

Support: NSERC (PGSD3-487560)
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Rachleff Family Endowment

Title: Activity-induced release of a neuropeptide promotes oligodendrocyte precursor cell differentiation and myelination

Authors: *L. A. OSSO, K. A. RANKIN, J. R. CHAN;
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Abstract: Evidence of activity-dependent myelination has been rapidly accumulating, generating substantial excitement in recent years. Yet, the mechanisms through which neuronal activity regulates myelination remain unknown. Using an unbiased screen, we previously identified a cluster of kappa opioid receptor agonists - including the neuropeptide class dynorphins - that promote oligodendrocyte precursor cell (OPC) differentiation and myelination *in vitro* and *in vivo* (Mei et al., 2016). These neuropeptides are released from neurons following high levels of neuronal activity, leading us to investigate whether the activity-dependent release of these neuropeptides is an underlying mechanism of activity-dependent myelination. Combining behavioral, genetic, pharmacological, and chemogenetic techniques to manipulate neuropeptide release in adult mice *in vivo*, we demonstrate that activity-induced neuronal release of these

neuropeptides promotes OPC differentiation and myelination. These data demonstrate a novel mechanism of activity-dependent myelination.

Disclosures: **L.A. Osso:** None. **K.A. Rankin:** None. **J.R. Chan:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.18/B97

Topic: B.11. Glial Mechanisms

Support: T32HL007446-36A1

Title: Electrophysiological and genetic profiling of single oligodendrocyte lineage cells

Authors: *E. GOULD[1], J. KIM[2];
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Abstract: The oligodendrocyte lineage consists of distinct states and subpopulations as defined by morphology, physiology, and transcriptional profile. Physiological characteristics of oligodendrocytes are shaped by their transcriptional profile. How the molecular profile of specific oligodendrocyte populations confers different physiological profiles is not known. Oligodendrocyte lineage cells have the capacity to sense neuronal activity because these cells express neurotransmitter receptors and can receive synaptic input. Our previous study showed a subpopulation of pre-myelinating oligodendrocytes display spikes in response to neuronal input. Not all oligodendrocyte lineage cells demonstrate a spiking response to neuronal input and the significance of this excitability is still undetermined. It is hypothesized that the electrophysiological properties of oligodendrocytes depend on the expression of specific voltage-gated ion channels, such as voltage-gated sodium channels. This study aims to better understand the role of electrical excitability in oligodendrocytes in the developing brain. Utilizing the whole-cell patch-clamp recording paired with single-cell transcript profiling, we identified the molecular profile of single oligodendrocytes and their distinct physiological characteristics. Following whole cell recording, oligodendrocyte was collected for single-cell quantitative polymerase chain reaction to quantify the expression of 45 key genes. All cells (n=62) isolated after electrophysiological recordings show optimal levels of housekeeping genes (e.g. *Actin*), indicating consistent and reliable collection of mRNA. Individual oligodendrocytes showed a distinct molecular profile with consistent expression of oligodendrocyte markers (e.g. *Olig1*), which differentiated them from neurons. Oligodendrocyte lineage markers (e.g. *Pdgfra*) were expressed in a gradient across the cell population and correlated with the distinct physiological characteristics. Isolated oligodendrocytes expressed multiple voltage-gated sodium channel

subunits, indicating each cell contains multiple sodium channel types. Intriguingly, *Scn2a*, encoding Nav1.2 channel, expression was restricted to oligodendrocytes with distinct spikes. This electrophysiological and genetic profile of a single oligodendrocyte strongly supports that Nav1.2 is expressed in a unique subpopulation of excitable oligodendrocytes, as has been described in our previous work. Understanding the molecular diversity of oligodendrocytes will further our understanding of how the molecular profile shapes their physiology and function.

Disclosures: E. Gould: None. **J. Kim:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.19/B98

Topic: B.11. Glial Mechanisms

Title: Using patient-derived hiPSCs to model white matter changes in autism spectrum disorder

Authors: *J. LI, S. CHETTY;
Stanford Univ., Stanford, CA

Abstract: Autism Spectrum Disorder (ASD) is defined as a group of neurodevelopmental disorders associated with impaired social communication, repetitive behaviors, and intellectual deficits. However, early diagnosis of ASD remains challenging due to its complexity and heterogeneity. In some subtypes of ASD, an increase in brain size precedes the first clinical signs, suggesting that understanding the mechanisms leading to brain overgrowth could provide important insights in disease onset. Here, we use human induced pluripotent stem cell (hiPSC) technology to model ASD associated with disproportionate megalencephaly (ASD-DM) and investigate the cellular and molecular mechanisms involved. While an overall enlargement in brain size has been shown through brain imaging of autistic children with megalencephaly, the iPSC models to date have primarily focused on modeling neurons in ASD. In this study, we investigate changes in glial cells by differentiating hiPSCs to brain-derived glia from control subjects and ASD-DM subjects. Changes in morphology, including the cell body size and the number of processes, and proliferation rates were compared across control and patient-derived hiPSCs. Preliminary data shows that the ASD-DM-derived glia have more processes. Also, increases in proliferation could be observed in glia from ASD-DM compared to the controls. We also investigate and compare changes in gene expression associated with the cell cycle. Overall, these data indicate that ASD with megalencephaly is possibly a result of enhanced proliferation. While prior studies have focused on changes in neurons, this study is the first to systematically investigate changes in glial cells in ASD-DM.

Disclosures: J. Li: None. **S. Chetty:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 556.20/B99

Topic: B.11. Glial Mechanisms

Support: NSF CAREER 1845603
National Multiple Sclerosis Society 5274A1/T
National Multiple Sclerosis Society PP-1706-29071
Winona State University Foundation Special Projects Award 251.0327

Title: Regulation of oligodendrocyte exploratory behavior and sampling of axons by neural activity

Authors: J. R. GRONSETH[1], T. A. MALLON[1], M. R. MARTELL[1], B. B. DUXBURY[1], A. J. TREICHEL[1], J. T. HENKE[1], E. S. MENGES[1], H. N. NELSON[1], T. L. HOBBS[2], *J. H. HINES[1]; [1]Dept. of Biol., [2]Winona State Univ., Winona, MN

Abstract: Oligodendrocytes (OLs), the myelinating cell type of the CNS, interact with a plethora of diverse neuronal subtypes but only wrap a select subset with myelin sheaths. Prior to initiating axon wrapping, OLs dynamically extend and retract membrane processes in order to contact and sample numerous axons. Whether neural activity-dependent mechanisms regulate exploratory axon sampling, target axon recognition, and stabilization of OL-axon interactions prior to initial axon wrapping is unknown. To test this, we directly observed interactions between pre-myelinating OL processes and individually labeled target axons in larval zebrafish using time-lapse confocal microscopy. In control larvae anesthetized with the neuromuscular blocker pancuronium bromide, we observed dynamic axon sampling characterized by frequent formation and turnover of OL-axon interactions. In contrast, treatment with the neural activity blocker tricaine methanesulfonate (MS-222) caused reduced frequency of new interaction formation, increased interaction duration, and reduced frequency of interaction retraction. Time-lapse imaging revealed differential effects on OL-axon interactions at axon varicosities and thin, intervening segments. Specifically, the destabilizing effects of neural activity on OL-axon interactions were heightened at axon varicosities. MS-222 increased contact durations at varicosities but not at neighboring intervening segments. Neural activity manipulations also influenced the dynamics of axon varicosity formation, lifetime, and turnover, raising the possibility that changes to axon morphology or local properties could direct OL-axon interactions and subsequent myelination. Taken together, we conclude that neural activity negatively regulates the duration of OL-axon interactions prior to initial axon wrapping and myelination. These findings support a mechanism whereby neural activity plays opposing roles on OL-axon interactions before and after initial myelin ensheathment. Prior to ensheathment,

neural activity destabilizes interactions, which may serve to facilitate increased overall sampling of potential wrapping sites. After successful ensheathment, neural activity stabilizes OL-axon adhesion in order to promote continued growth and maturation of the myelin sheath. Current and future studies aim to understand the reciprocal effects between OL processes and axon morphology, and the effects of synaptic vesicle release during initial OL-axon interactions.

Disclosures: J.R. Gronseth: None. **T.A. Mallon:** None. **M.R. Martell:** None. **B.B. Duxbury:** None. **A.J. Treichel:** None. **J.T. Henke:** None. **E.S. Menges:** None. **H.N. Nelson:** None. **J.H. Hines:** None.

Poster

556. Central and Peripheral Myelinating Cells I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

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Topic: B.11. Glial Mechanisms

Support: NSF Grant 1845603
National Multiple Sclerosis Society 527481-T
National Multiple Sclerosis Society PP-1706-29071
Winona State University Foundation/Special Projects Award 21.0327

Title: Axon determination of subtype specific myelin ensheathment and pruning

Authors: *H. N. NELSON, A. J. TREICHEL, E. DANKERT, M. MARTELL, A. KAISER, A. TRUDEL, J. R. GRONSETH, S. LANG, J. H. HINES;
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Abstract: In the developing central nervous system, pre-myelinating oligodendrocytes contact and sample candidate nerve axons by extending and retracting process extensions. Some contacts stabilize and mature, leading to the initiation of axon wrapping, myelin sheath formation, and sheath elongation by oligodendrocytes. Although axonal signals influence the overall process of myelination, which precise steps and oligodendrocyte cell behaviors require signaling from axons is incompletely understood. In this study, we investigated whether cell behaviors during the early events of myelination involve input from axons or are mediated by an oligodendrocyte-autonomous myelination program. To address this, we utilized *in vivo* time-lapse imaging in embryonic and larval zebrafish during the initial hours and days of axon wrapping and myelination. Transgenic reporter lines marked individual axon subtypes or oligodendrocyte membranes. In the larval zebrafish spinal cord, individual axon subtypes supported distinct nascent sheath growth rates and pruning frequencies. Oligodendrocytes ensheathed individual axon subtypes at different rates during a two-day period after initial axon wrapping. When the ratio of oligodendrocytes to target axons was increased by ablating spinal projection axons, local

spinal neuron axons supported a constant ensheathment rate despite the increased ratio of oligodendrocytes to target axons. We conclude that properties of individual axon subtypes instruct oligodendrocyte behaviors during initial stages of myelination by differentially controlling nascent sheath growth and stabilization.

Disclosures: H.N. Nelson: None. **A.J. Treichel:** None. **E. Dankert:** None. **M. Martell:** None. **A. Kaiser:** None. **A. Trudel:** None. **J.R. Gronseth:** None. **S. Lang:** None. **J.H. Hines:** None.

Poster

557. Neuro-Oncology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 557.01/B101

Topic: B.13. Neuro-Oncology

Support: Aga Khan University Research Council (URC Project ID 181007 SUR)

Title: Magnetic resonance imaging guided study of regional variations in glioblastoma multiforme pathology and gene expression

Authors: *F. M. ARAIN[1], A. SHAIKH[1], M. WAQAS[2], M. U. TARIQ[3], M. F. RAGHIB[2], G. HAIDER[1], M. S. SHAMIM[2], F. MUBARAK[4], S. H. HASSAN[3], S. A. ENAM[2], *A. A. JABBAR[5];
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Abstract: Glioblastoma multiforme (GBM) is the most malignant, aggressive and common form of gliomas. Despite extensive research this situation has not changed significantly during the past decade. Currently, GBM is considered to be a homogenous mass histologically and all its margins are treated equally at the time of resection. However, it is not known whether radiologically distinct regions of GBM are also distinct at cellular level? We conducted this study to see if 4 radiologically distinct regions of 20 GBM patients, identified using MRI Apparent Diffusion Coefficient (ADC) and Contrast Enhancement (CE), i.e. 1) high ADC and high CE, 2) high ADC and low CE, 3) low ADC and low CE and 4) low ADC and high CE were also different at cellular level. Hematoxylin and Eosin staining showed markedly increased nuclear pleomorphism, cellularity, vascularity and necrosis in Region 2. Oncogene IDH was expressed in all regions, however, it was highest in Region 4. Stem cell marker, CD44 expression was highest in Region 1 and lowest in Region 4. Interestingly, expression of another stem cell marker, CD133, was highest in Region 4. This study shows that MRI characteristics of an area within GBM can indicate the type cells that populate it.

Disclosures: **F.M. Arain:** None. **A. Shaikh:** None. **M. Waqas:** None. **M.U. Tariq:** None. **M.F. Raghib:** None. **G. Haider:** None. **M.S. Shamim:** None. **F. Mubarak:** None. **S.H. Hassan:** None. **S.A. Enam:** None. **A.A. Jabbar:** None.

Poster

557. Neuro-Oncology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 557.02/B102

Topic: B.13. Neuro-Oncology

Title: From tumor growth to invasiveness: Morpho-molecular dynamics of the glial-immune-vascular unit in the GL261-C57/Bl6J mouse model of glioblastoma

Authors: A. VIRTUOSO[1,2], G. CIRILLO[1], M. RIVA[2,3], A. BENTIVEGNA[2], C. GIUSSANI[2], M. LAVITRANO[2], *M. PAPA[1], R. GIOVANNONI[4];
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Abstract: Glioblastoma multiforme (GBM) is the most aggressive brain tumor with ineffective treatments, bad prognosis, and poor survival. Recent studies have attributed the tumor growth and invasiveness to the ability of the GBM in converting the activity of the brain elements to its benefits. Moreover, the broad genetic-epigenetic heterogeneity of the GBM and the lack of suitable experimental models have limited the translation of the results to humans. Hence, targeting both the tumor and the microenvironment in a reliable model represents a more valuable approach for translational studies. In the present work, we aimed to describe the kinetics of the tumor progression in parallel with its landscape using an immuno-competent mouse model of primary GBM. GL261 glioma cells were implanted in the right striatum of syngeneic C57Bl6J mice and animals were sacrificed at 7, 14 and 21 days (7D, 14D, 21D) after the cell implants. Brains were then processed for immunohistochemistry, immunofluorescence and western blotting analyses. Our preliminary results showed a definite tumoral bulk at 14D, with no expression of the glial fibrillary acidic protein (GFAP) by GL261 cells and fibrous GFAP+ astrocytes surrounding the malignancy. GBM invasiveness prevailed at 21D: we observed a partially necrotic GBM-lesion in most of the tumor-injected hemispheres, causing tissue compression while a secondary cancerous mass developed in the contralateral hemisphere. We found that the "growth to go" decision of the malignancy was associated to an inhibition of the tumor immuno-escape as observed from the microglia/macrophages (Iba1+, Ionized calcium binding adaptor molecule 1) dynamic. The resident immune system exploited only in the late stage of the disease while peritumoral astrocytes density gradually increased with time. Changes in the extracellular matrix (tenascin-C; metalloproteases) as well as in the vascular pericytes

(platelet-derived growth factor receptor-β, PDGFR-β+) and in the antigen presenting functions were correlated to the GBM switch towards the invasive mode. By combining morpho-molecular features, our study offers a picture of the alterations in the glial-immune-vascular unit leading the GBM from the growth to the invasiveness, gaining hints for the development of novel multi-targeted therapies in an experimental model expected to be analogous to the human system.

Disclosures: A. Virtuoso: None. **G. Cirillo:** None. **M. Riva:** None. **A. Bentivegna:** None. **C. Giussani:** None. **M. Lavitrano:** None. **M. Papa:** None. **R. Giovannoni:** None.

Poster

557. Neuro-Oncology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 557.03/C1

Topic: B.13. Neuro-Oncology

Title: Translational imaging findings in a pediatric patient-derived orthotopic xenograft brain tumor model

Authors: J. SCHUELER[1], J. RYTKÖNEN[2], D. LÖTSCH[3], D. LENHARD[1], A. SHATILLO[2], K. LEHTIMÄKI[2], P. POUTIAINEN[4], D. MISZCZUK[2], J. GOJOL[3], W. BERGER[3], ***T. HUHTALA**[2];
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Abstract: Malignant brain tumors are the most common cause of solid cancer death in children. Innovative therapies are vital to improve treatment outcomes, but must be developed to enable trafficking across the blood brain barrier (BBB). For this advent, animal models provide important information prior to clinical studies. Among the different in vivo models orthotopic patient-derived xenograft (PDX) models represent the diversity seen in patient tumors and hence replicate response rates in the clinical trials better as compared to other more simplistic models. Especially in the brain tumor field, imaging has a central role in clinical diagnosis and as a prognostic factor to monitor therapy response. It enables longitudinal patient monitoring in a fully translational manner. Magnetic resonance imaging (MRI) and positron emission tomography (PET) are widely used for clinical diagnosis and disease follow up. Choosing the most suitable imaging application depends of the target of interest or mechanism of action. MRI offers unprecedented soft tissue contrast, high spatial resolution and non-invasive nature renders MRI in rodents a perfect tool for preclinical work in oncological applications. In case of orthotopic brain tumor models, MRI offers the state-of-the-art quantitative volumetric tumor size analysis over disease progression. PET is an excellent tool to study tumor proliferation, metabolism, metastasis as well biodistribution of novel antibodies.

The purpose of this work was to analyze volumetric, metabolic and functional changes in orthotopic PDX brain tumor model using MRI, MRS and PET imaging. During the course of the experiment, volume, perfusion within the tumor as well proliferation and metastasis were monitored. Perfusion measurement indicates angiogenesis in tumor, one hallmark of most malignant gliomas. Also, alterations in glucose and amino acid metabolism between tumor and healthy tissue has been previously identified. By direct comparison of the imaging data derived from the preclinical mouse model with similar data-sets from the donor patient the translational value of the model as well as the read-out system will be achieved.
As a conclusion, translational in vivo imaging techniques were applied to study orthotopic tumor progression. These readouts provide a powerful and translational research tool together with oncological disease animal models allowing comprehensive evaluation of disease progression and treatment interventions for in vivo studies.

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Poster

557. Neuro-Oncology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 557.04/C2

Topic: F.08. Biological Rhythms and Sleep

Support: Deutsche Forschungsgemeinschaft (SFB 1089, FOR 2715)
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BONFOR
We thank Dr. David Jones for providing the DNA encoding BRAFV600E

Title: Comparative RNA-seq analyses of mouse IUE-induced gangliogliomas and human counterparts

Authors: ***S. CASES-CUNILLERA**[1], H. VATTER[2], S. SIVALINGAM[3], S. SCHOCH[4], A. J. BECKER[1];
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Abstract: Gangliogliomas are the most common entity in the glioneuronal neoplasm spectrum. Their pathogenetic basis is only insufficiently understood and their neuropathological phenotype

composed from an admixture of dysplastic neuronal and neoplastic glial cells appears peculiar. Recently, frequent $BRAF^{V600E}$ mutations and increased mTOR pathway signaling were observed in ganglioglioma biopsy tissue obtained from patients generally undergoing epilepsy surgery for seizure relief. Neoplasms reflecting key ganglioglioma features have been recently induced by intraventricular in-utero electroporation of the murine equivalent of $BRAF^{V600E}$ to mice. Here, we aimed to scrutinize whether $BRAF^{V600E}$ mutations and mTOR pathway activation may act synergistically to induce ganglioglioma like tumors. Ethical approval was obtained for animal experiments (Nr. 84.02.04.2013.A307). We induced gangliogliomas by IUE of $BRAF^{V600E}$ (n = 5) as well as co-IUE of a piggyBac vector containing the sequence encoding $BRAF^{V600E}$ and constitutively active Akt kinase (*p*Akt) under the control of the ubiquitous (CAG-) promoter at the embryonic day 14 (E14) in CD1/ C57BL6 mice (n = 4). Both experimental approaches resulted in brain lesions with a glioneuronal phenotype resembling neuropathological features of gangliogliomas. With respect to survival, we did not find any statistical difference between the both groups of mice with gangliogliomas and long-term survival. We performed mRNA sequencing in order to analyze the transcript signatures of mouse ganglioglioma-like tumors compared to human GGs (n = 4), from patients of whom informed written consent was obtained for these experiments. GO enrichment analysis of abundant RNAs revealed growth related transcripts, whereas low expression of mRNAs was related to synaptic transmission, nervous system development and ion transport. Overall, our data indicate that $BRAF^{V600E}$ and active mTOR pathway signaling elicits tumor in mice recapitulating all characteristic features of GGs.

Disclosures: **S. Cases-Cunillera:** None. **H. Vatter:** None. **S. Sivalingam:** None. **S. Schoch:** None. **A.J. Becker:** None.

Poster

557. Neuro-Oncology

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Program #/Poster #: 557.05/C3

Topic: B.13. Neuro-Oncology

Support: ONACYT Fronteras 2015-2 1256.

Title: Androgens stimulate glioblastoma derived U87 cell metabolism and proliferation while steroid enzymes inhibitors and androgen antagonists reduced their metabolic capacity

Authors: M. A. OROZCO[1], R. A. VALDEZ[2], J. V. SEGOVIA-VILA[3], *M. C. ROMANO[4]; [2]Fisiología, Biofísica y Neurociencias, [1]Cinvestav IPN, Ciudad de México, Mexico; [3]Cinvestav-IPN, Mexico 07300 DF, Mexico; [4]Fisiología, Biofísica y Neurociencias, Ctr. De Investigación Y De Estudios Avanzados De, Ciudad de México, Mexico

Abstract: Glioblastoma (GBM) is the most frequent and aggressive primary brain tumor in adult humans. Therapeutic resistance and tumor recurrence after surgical resection results in poor prognosis. The incidence of GBM in the adult population is 50% higher in men than in women, which suggest a significant role of steroid hormones in its development. It has been shown that U87 cells synthesize a number of androgens, express several steroidogenic enzymes involved in androgen synthesis, and have androgen receptors. These data strongly suggest that androgens may have a role in tumor pathogenesis. The aims of this study were to investigate: 1.The effect of three androgens on U87 metabolism and proliferation. 2. The consequence of 5α-reductase inhibitors and androgen receptor antagonists in the growth and survival of GBM derived cells. To perform the experiments U87 human glioma derived cells were cultured in DMEM plus antibiotics in the absence or presence of different doses of androstenedione (A4), testosterone (T4), or dehydrotestosterone (DHT). The competitive inhibitor of 5α-reductase, dutasteride, or the androgen receptor antagonist's ciproterone and flutamide, alone or in combination with androgens, were also assayed with different concentrations and periods in culture. Cells were processed to investigate metabolism by MTT and proliferation by BrdU. Results showed that T4 and DHT, but not A4 increased U87 cell metabolism and proliferation. DHT was more efficient than T4. The 5α-reductase inhibitor dutasteride significantly decreased the cell metabolism. In addition, ciproterone and flutamide significantly reduced the metabolism of U87 cells after 72h of exposure to the drugs. These results showed that testosterone ad DHT enhance glioblastoma derived cells metabolism and proliferation, and that a 5α-reductase inhibitor that interferes with androgen synthesis significantly reduced their metabolic activity. Furthermore, drugs that inhibit androgen binding to the receptor also affected their metabolism. Therefore, the use of drugs related to androgen synthesis or receptors could be an adjuvant tool for the treatment of glioblastoma.

Disclosures: M.A. Orozco: None. **R.A. Valdez:** None. **J.V. Segovia-Vila:** None. **M.C. Romano:** None.

Poster

557. Neuro-Oncology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 557.06/C4

Topic: B.13. Neuro-Oncology

Support: CIHR
UK Brain Tumor Charity

Title: Osmr controls cellular respiration and resistance to stress in glioma stem cells and post mitotic neurons

Authors: *A. JAHANI-ASL, A. SHARANEK, A. BURBAN;
McGill Univ., Montreal, QC, Canada

Abstract: Cytokines and their receptors play important roles in the regulation of cell fate, inflammation and immunity. Oncostatin M receptor (OSMR) is a plasma membrane receptor that is activated by Oncostatin M (OSM) ligand. OSM/OSMR signaling (OSMR) plays important roles in the nervous system. For example, OSM confers neuroprotection against ischemic stroke and protects against demyelination via modifying microglia function. On the other hand, OSMR promotes the self-renewal of brain tumour stem cells (BTSCs), a rare population of multipotent stem cells in the bulk of the tumor, that are responsible for the tumor growth and exhibit resistance to therapy. BTSCs possess a unique metabolic phonotype, with a distinct upregulation of oxidative phosphorylation (OXPHOS) and a low glycolytic rate. Thus, BTSCs more closely resemble neurons as opposed to the majority of cells in the bulk of the tumor relying on aerobic glycolysis. Here we report a novel role for OSMR in the control of cellular respiration in BTSCs and primary neurons. OSMR promotes mitochondrial biogenesis via MAPK/PGC1 signaling. Knockdown of OSMR in BTSCs sensitizes BTSCs and patient derived xenografts to DNA damage-induced ionizing radiation. OSMR knockout mice exhibit metabolic defects and a decrease in oxygen consumption rate (OCR). Furthermore, OSMR and its ligand OSM, upregulate maximal respiration in primary neurons, induce mitochondrial fusion, and protect against camptothecin induced DNA damage. Our data suggests that OSMR is targeted to peroxisomes to induce conversion of long fatty acid to provide substrates to the mitochondria to enhance oxidative phosphorylation. Thus, we have identified a novel mechanism by which OSMR regulates respiration and confers resistance to DNA-damage induced cell death.

Disclosures: A. Jahani-asl: None. **A. Sharanek:** None. **A. Burban:** None.

Poster

557. Neuro-Oncology

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Program #/Poster #: 557.07/C5

Topic: B.13. Neuro-Oncology

Support: HHMI Medical Fellowship
Alex's Lemonade Stand Foundation
Stanford MedScholars Program

Title: Diffuse intrinsic pontine glioma invasion mediated by the Nogo pathway

Authors: *R. AZIZ-BOSE, K. R. TAYLOR, A. C. HUI, H. ZHANG, A. PONNUSWAMI, M. MONJE;
Stanford Univ., Stanford, CA

Abstract: Diffuse intrinsic pontine glioma (DIPG) is a devastating childhood brain cancer, in part due to its characteristic diffuse infiltration of brain that prevents the option of surgical resection. DIPG is thought to arise from early oligodendrocyte precursor cells (OPCs or pre-OPCs) and peaks in incidence during a specific developmental timepoint in mid-childhood, suggesting that the tumor may be influenced by dysregulated signaling cues in the environment of the developing childhood brain. However, the microenvironmental signaling that regulates DIPG invasion and migration is incompletely understood. An emerging principle is that signaling pathways classically involved in axon guidance during neural development are repurposed in malignancy to regulate cancer invasion. Early studies in adult glioblastoma indicate that inhibition of the Nogo receptor (NgR), important for axon pathfinding and neurite outgrowth, may increase tumor cell migration *in vitro*. Our RNA sequencing studies of patient-derived DIPG samples demonstrate that NgR is also expressed in pediatric DIPG tumors. To evaluate the role of NgR in DIPG migration, CRISPR/Cas9 technology was used to delete NgR from a patient-derived DIPG culture derived from a frontal lobe DIPG metastasis, SU-DIPGXIII-FL. Loss of NgR, confirmed by qPCR and by Western blot, significantly enhanced DIPG tumor cell migration at 72 hours in a 2D spheroid migration assay ($p < 0.05$). NSG mice xenografted with SU-DIPGXIII NgR-null cells exhibited a 33% increased extent of tumor invasion through the brain at 8 weeks compared to mice xenografted with wild-type SU-DIPGXIII control cells ($p < 0.05$). Additionally, the endogenous Nogo pathway antagonist Crtac1 is sufficient to promote tumor cell migration at 72 hours in the 2D spheroid migration assay ($p < 0.005$). Ongoing DIPG pontine xenografts into a newly established Crtac1 knock-out mouse line will demonstrate the contribution of Crtac1 to tumor spread *in vivo*. This work elucidates the importance of Nogo pathway signaling in diffuse intrinsic pontine glioma, which may be targeted therapeutically to limit tumor spread.

Disclosures: R. Aziz-Bose: None. **K.R. Taylor:** None. **A.C. Hui:** None. **H. Zhang:** None. **A. Ponnuswami:** None. **M. Monje:** None.

Poster

557. Neuro-Oncology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 557.08/C6

Topic: B.13. Neuro-Oncology

Support: NSF AMP
NMSU Foundation

Title: Capsaicin effects on glioma cell cultures

Authors: A. SANGAMI, A. TORRES, T. GRAY, *E. E. SERRANO;
New Mexico State University, Biol., Las Cruces, NM

Abstract: The high cost and prolonged time frame of the drug discovery pipeline have fueled interest in drug repositioning. Capsaicinoids have emerged as a class of alkaloid compounds with potential therapeutic effects that extend beyond analgesia to include neuroprotective and antineoplastic activity. Previous reports have suggested that capsaicin can serve as an inhibitor of the survival of human glioma cells in culture, a finding we seek to confirm as a prelude to mechanistic studies of capsaicinoid action on cells of the nervous system. In this pilot study we compared the effect of capsaicin exposure on the proliferation of the CCF-STTG1 glioblastoma cell line (RRID:CVCL_1118) with that of the antimalarial drug, chloroquine. Cells were purchased from a vendor (ATCC CRL-1718) and used within the first five passages of cell line stock preparation. A blinded-experimental design was undertaken by preparing and anonymizing treatment and control solutions and unmasking treatment identity after completion of all data analysis. Cultures were continuously exposed to chloroquine (Sigma 12084-10MG-F; Lot #: BCBS7557V) and capsaicin (Sigma C6628-25G; Lot#: 085M4098V) for 96 hours. Drug effects were evaluated by using Hoechst 33342 (Invitrogen H3570; Lot#: 1387197) to label nuclei, then capturing images, and quantifying cells per unit with the open access program, ImageJ. Analysis from replicate experiments uncovered that chloroquine was effective at preventing cell survival ($p < .01$; 200 uM) but capsaicin showed modest potential to reduce glioma proliferation ($p < 0.10$; 200 uM). These outcomes underscore the need to evaluate drug action on multiple cell lines and suggest that capsaicin may be useful in conjunction with other antineoplastic agents. Future experiments will extend the analysis to include additional cell lines and evaluate the potential of other capsaicinoids to serve as antineoplastic agents.

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Poster

557. Neuro-Oncology

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Program #/Poster #: 557.09/C7

Topic: B.13. Neuro-Oncology

Support: FOMIX-JAL-2014-01-250508
CONACYT Scholarship No. 488270

Title: Evaluation of the *in-vitro* effect of coumaric derivatives against the aggressiveness of glioblastoma multiforme cells

Authors: *L. J. RESÉNDIZ-CASTILLO[1], Y. K. GUTIÉRREZ-MERCADO[3], J. C. MATEOS-DIAZ[2], A. A. CANALES-AGUIRRE[1];
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for Res. and Assistance in Technol. and Design of the State of Jalisco A.C., Zapopan, Mexico; [3]Univ. of the Valley of Mexico, Guadalajara, Mexico

Abstract: Glioblastoma multiforme (GBM) are tumors composed of several types of cells, such as: progenitor cells, glial cells, neurons & GBM tumor stem cells (GSC); In addition, tumors of the central nervous system are most aggressive & have a worse prognosis, being the type of primary brain tumor more common in adults, with a survival rate of 15 months. Temozolomide (TMZ) is currently administered as a chemotherapeutic treatment; however, some tumors have drug-resistance mechanisms against the cytotoxic effects of TMZ; Although, the main cause of this drug resistance is not yet clear, it can be pointed out to the GSC as possible culprits of this characteristic. It has been proven that coumaric compounds have the potential to attack tumor stem cells, reducing their capacity for proliferation, self-renewal & resistance in gliomas. The objective of this work is to evaluate the therapeutic potential of coumaric derivatives such as propyl, iso-butyl & ethyl-o-coumaric, since they have cytotoxic & antiproliferative capacity in GBM cells, in addition to reducing self-renewal & inhibiting the expression of stem markers in GSC. The GBM U-87 cell line, was used as a study model; In previous studies in our laboratory the LC50 was determined by MTT, for each compound, covering a range between 200μM & 300μM. Spheroid formation assay & Clonogenic assay were performed to determine the decrease in the proliferative capacity & self-renewal of the GSC, for which the neurospheres generated in the culture were collected & cultured with the LC50 of each compound for 24 hours, for 15 days; A decrease was observed not only in the capacity of formation of secondary spheroids, but also in the number of spheres & the number of colonies generated by individual cells in culture. The cells were also exposed to the compounds for 3 days, to determine the inhibition of the stem & induction of neuronal & astrocyte differentiation by immunofluorescence, using the antibodies CD133, GFAP, NeuN & Nestin; where we observed the constant expression of differentiation markers such as GFAP & NeuN, & the inhibition of stem markers such as CD133 & Nestin. This can allow the development of joint therapies with coumaric derivatives for cases of chemoresistant GBM, having the faculty to act on the GSC & the malignant properties that confer to the tumors of GBM.

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Poster

557. Neuro-Oncology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 557.10/C8

Topic: B.13. Neuro-Oncology

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Leah's Happy Hearts
University of Michigan Comprehensive Cancer Center
Chad Tough Foundation
The Phase One Foundation (to M.G. Castro and P.R. Lowenstein)

Title: The chemokine receptor CXCR7 modulates numerous signaling pathways in glioblastoma stem cells

Authors: *G. F. TAPSALL[1], A. CALINESCU[3], S. AKULA[2];
[1]Dept. of Neurosurg., [2]Univ. of Michigan Med. Sch., Ann Arbor, MI; [3]Neurosurg., Univ. of Michigan, Ann Arbor, MI

Abstract: Glioblastoma is one of the deadliest and most common forms of primary malignant brain cancer. The resilience of glioblastoma stem cells (GSCs) may account for resistance to treatment of GBM. Studies demonstrate that the chemokine CXCL12 promotes the growth of GSCs, resistance to hypoxia and disease progression. CXCL12 and its signaling receptor CXCR4 have been the focus of much interest, due to important roles in cancer biology. CXCR7 is an alternate receptor for CXCL12, that binds CXCL12 with higher affinity than CXCR4, targets the chemokine for degradation and prevents signaling through CXCR4. Studies of CXCR7 in various cancers present conflicting results; CXCR7 appears to either promote or inhibit cancer progression. Previous studies have demonstrated that blocking CXCR4 decreases viability of GSCs, suggesting that CXCL12 is necessary for continued growth of GSCs. We reasoned that overexpression of CXCR7 will decrease CXCL12 and render GSCs more sensitive to CXCR4 blockade. Surprisingly, we found decreased sensitivity of CXCR7-GSCs to AMD3100 and AMD070. To test if the presence of CXCR7 on alternate cells in the environment alter viability of GSCs, these were cultured with neural stem cells (NSCS) overexpressing or not CXCR7. No change in GSC viability was observed. Interestingly, the tumor cells decreased viability of NSCs and this decrease was less pronounced in the presence of CXCR7-GSCs. Analysis of CXCL12 in GSCs and NSCs revealed increased expression in CXCR7 cells, accompanied by a decrease in expression of CXCR4. This suggested that CXCR7 modulates transcriptional activity in GSCs to adapt to the surrounding environment. RNA-Seq analysis identified 706 differentially expressed genes between GSCs and CXCR7-GSCs, majority of the genes (555) being downregulated, among them numerous growth factors and cytokines, such as FGF1, FGF21, TGFb2, TGFbi, VEGFa, VEGFb, PGF, PTN, GDF15, CXCL1 and CXCL10. Pathway analysis revealed 58 significantly impacted pathways, with decreased MAPK, cAMP, and TNF pathways and activation of the Wnt and Hippo pathways. Current experiments are dissecting the contribution of these genotypic alterations on the malignant phenotype of GSCs using *in vitro* assays and an *in vivo* orthotopic mouse model of GBM.

Disclosures: G.F. Tapsall: None. **A. Calinescu:** None. **S. Akula:** None.

Poster

557. Neuro-Oncology

Location: Hall A

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Topic: B.13. Neuro-Oncology

Support: Damon Runyon Sohn Postdoctoral Fellowship
Abbie's Army Grant
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The Cure Starts Now Grant
McKenna Claire Foundation Grant

Title: Neuronal-activity regulated BDNF secretion promotes pediatric glioma growth

Authors: *K. TAYLOR, R. AZIZ-BOSE, H. ZHANG, A. HUI, A. BLANK, A. C. GERAGHTY, M. MONJE;
Stanford Univ., Stanford, CA

Abstract: Pediatric high-grade gliomas (pHGG) are a devastating group of diseases that critically require novel therapeutic options. We have previously demonstrated that pHGGs hijack mechanisms of brain development and plasticity to their advantage. One key process, neuronal activity, robustly drives proliferation of pHGG via the secretion of the synaptic protein neuroligin-3 (NLGN3) and the neurotrophin brain-derived neurotrophic factor (BDNF) into the tumor microenvironment. The relative contribution of BDNF signaling to pHGG progression and therapeutic utility of targeting the BDNF receptor remains to be defined. Here, we investigated the role of microenvironmental BDNF on pediatric gliomas, independent of the NTRK fusion events commonly identified in infant HGG. We found spatio-temporal patterns of BDNF expression in normal brain during the postnatal developmental period that highlight this growth factor as particularly relevant to childhood gliomas. Primary pediatric glioma single-cell RNA-Seq confirms expression of the canonical BDNF receptor TrkB, without expression of the BDNF ligand. Conditioned media (CM) collected from optogenetically stimulated acute cortical slices robustly increases patient-derived DIPG cell proliferation, an effect that is abrogated with CM collected from mice deficient of activity-regulated BDNF expression. The BDNF ligand increases patient-derived pediatric glioma cell proliferation and activates the canonical downstream MAPK signaling pathway. CRISPR deletion of the TrkB receptor, *NTRK2*,in glioma cells abrogates the proliferative response to BDNF ligand exposure, subsequent p42/44 MAPK pathway activation and increases survival in an orthotopic cortical GBM xenograft model (SU-pcGBM2, p=0.0032). Small molecule pan-TrkB antagonists, entrectinib and LOXO-101, abrogate the tumor cell proliferative response to BDNF ligand stimulation. Entrectinib treatment reduces *in vivo* tumor proliferation of a brainstem glioma xenograft model (SU-DIPGXIIIFL,

p<0.05). Disrupting pediatric glioma responses to microenvironmental cues such as BDNF may contribute to effective therapeutic strategies for these lethal childhood brain cancers.Funding: Abbie's Army Foundation

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Poster

557. Neuro-Oncology

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Topic: B.13. Neuro-Oncology

Support: Sardegna Ricerche-Progetto IBERNAT-NBL-P.O.R. Sardegna 2014-2020, CUP F21B17000730005

Title: Altered neurotrophin receptor expression and signalling by histone deacetylase inhibitors in human neuroblastoma cells

Authors: S. DEDONI[1], L. MARRAS[2], M. C. OLIANAS[3], A. INGIANNI[2], *P. ONALI[2]; [1]Univ. of Cagliari, Dept Biomed. Sci., Cagliari, Italy; [2]Univ. of Cagliari, Dept.Biomedical Sci., Cagliari, Italy; [3]Biomed. Sciences, Sect. Neurosci., Univ. of Cagliari, Monserrato, Italy

Abstract: Neurotrophin receptors, including TrkA, TrkB, TrkC and p75NTR, have been shown to play a critical role in the biology of human neuroblastoma. Preclinical and clinical studies have demonstrated that the expression of TrkB, the receptor of brain-derived neurotrophic factor (BDNF), is associated with tumour aggressiveness and resistance to chemotherapy. On the other hand, enhanced expression of the common neurotrophin receptor p75NTR has been reported to induce neuroblastoma cell apoptosis. In the present study we investigated the effects of various histone deacetylase (HDAC) inhibitors on the expression and functional activity of Trk and p75NTR receptors in human neuroblastoma cell lines. We found that in retinoic acid (RA)-differentiated SH-SY5Y cells the HDAC inhibitor valproic acid reduced the expression of TrkB at the protein and mRNA levels, and inhibited the intracellular signalling, neurotrophic activity, and pro-survival function of BDNF. VPA down-regulated TrkB and curtailed BDNF-induced signalling also in RA-differentiated MYCN-amplified LAN-1 and Kelly cells. The class I HDAC inhibitors entinostat and romidepsin mimicked the VPA effect, whereas the class II HDAC inhibitor MC1568, the HDAC 6 inhibitor tubacin and the HDAC 8 inhibitor PCI 34051 were inactive. VPA and entinostat increased the cellular levels of the transcription factor RUNX3, a suppressor of TrkB gene expression. Exposure to VPA enhanced the protein and transcript levels of p75NTR and its co-receptor sortilin in SH-SY5Y and LAN-1 cells. In both cell lines, this

effect was associated with a potentiation of VPA-induced apoptosis in response to proNGF. Collectively, these data indicate that some HDAC inhibitors alter neurotrophin receptor expression to promote apoptotic cell death and suggest that this action may contribute to the anti-neuroblastoma activity of these agents.

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Poster

557. Neuro-Oncology

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Topic: B.13. Neuro-Oncology

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Title: Evaluation of combinations of PI3K / AKT and Sonic Hedgehog (SHH) inhibitors against glioblastoma

Authors: *R. MEJÍA-RODRÍGUEZ[1], D. ROMERO-TREJO[1], R. O. GONZALEZ[2], J. V. SEGOVIA-VILA[3];
[1]CINVESTAV, CDMX, Mexico; [2]Univ. Autónoma Metropolitana-Iztapalapa, Mexico City, Mexico; [3]Cinvestav-IPN, Mexico 07300 DF, Mexico

Abstract: Glioblastoma (GBM), a grade IV glioma, is a very aggressive tumor, that promotes vascularization, necrosis and is resistant to chemotherapy and radiotherapy. There is currently no effective therapy for its treatment. This means that new therapeutic approaches are needed. AZD5363 is an inhibitor of AKT and its isoforms; AZD8542 is a SMO inhibitor (AstraZeneca) and both have antitumor activity *in vivo* and *in vitro* in breast, prostate and pancreatic cancer cells. Curcumin (CCR) is a polyphenolic compound extracted from the root of the turmeric plant, native to Asia, it is used as a spice and dye in the food industry. CCR decreases the activity of PI3K / AKT and SHH signaling pathways in human GBM cells. Resveratrol (RV) is a phytoalexin, an antimicrobial agent that accumulates in some plants and is also a molecule with anticancer and chemoprotective effects. RV decreases AKT phosphorylation and activates p53 in human GBM cells, moreover it decreases the activity for the SHH pathway in pancreatic, colon and gastric cancers. A current experimental approach for the treatment of GBM is to use combined therapies that affect different signaling pathways, to increase their efficacy and decrease secondary effects. In this work, we propose the use four anticancer agents (AZD5363, AZD8542, RV and CCR) to develop an alternative or adjuvant combination therapy against

GBM. For these experiments we employed human GBM cells lines U87-MG and A-172. Each of the agents tested was shown to have a cytotoxic effect. Using the IC50 of each agent, 10 combinations were tried in each cell line and MTT and Trypan Blue cell viability assays were performed. We found that the combination of AZD8542 and CCR is the most effective to decrease the growth of human GBM cell lines, presumably by inhibiting both the PI3K/AKT and SHH signaling pathways. The action of this combined therapy reduces cellular metabolic activity, induces plasma membrane damage and produces 70%-80% cell death in the lines tested.

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Poster

557. Neuro-Oncology

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Topic: B.13. Neuro-Oncology

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PRIN 2017, MIUR. 2017WJZ9W9

Title: Identification and characterization of the role played by the neuronal Na^{+}/Ca^{2+} exchanger in glioblastoma progression and malignity

Authors: L. CALABRESE[1], ***P. MOLINARO**[1], A. SERANI[1], B. SEVERINO[2], S. NATALE[1], F. FRECENTESE[2], F. FIORINO[2], G. DI RENZO[1], L. ANNUNZIATO[3];
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Abstract: Glioblastoma multiforme (GBM) is the most lethal and recidivist brain tumor in adults and it is characterized by an aggressive phenotype, with a progressive invasion of brain parenchyma, that is resistant to chemo- and radio-therapy. Furthermore, GBM shows the alteration of several transcription factors involved in genetic and epigenetic mechanisms of control a large number of target genes including *Slc8a2*, encoding for Sodium Calcium Exchanger 2 (NCX2). In fact, NCX2 is physiologically expressed in neuronal and glial cells of CNS, but it is selectively silenced in all glioma subtypes, including GBM, suggesting that this gene might represent a tumor suppressor gene for this disease. To explore the genetic and epigenetic mechanisms leading to NCX2 downregulation, we identified and cloned both rat and human *slc8a2* promoters. Furthermore, we analyzed the promoter regions and the binding sites involved in the regulation of NCX2 transcription. The transfection of several transcription factors, whose expression is altered in a GBM cell line (U87), modified the promoter activity and the mRNA expression of NCX2 in PC12 cells, whereas they were ineffective in U87 cell line suggesting the presence of an epigenetic upstream mechanism that turns off *Slc8a2* gene in

GBM. Indeed, we found that the genomic DNA demethylation of U87 cell line, induced by 5-aza-2′-deoxycytidine treatment, increased NCX2 mRNA expression levels. In addition, the stably transfection of NCX2, or the other isoform NCX1, in U87 cells hampered cell growth. In a prospective therapeutic approach, we also analyzed the effect of two compounds, namely neurounina-1 and CN-PYB2, on the vitality and cell growth of U87 cell line. Neurounina-1 is a stimulator of NCX1 and NCX2 activity, whereas CN-PYB2 is a selective stimulator of NCX1 activity. Results showed that these compounds hampered in a concentration- and time-dependent manner cell growth of U87 cell line, whereas they were ineffective in BHK, SH-SH5Y and PC12 cell lines. Altogether, these data suggest that NCX1 and NCX2 expression/activity slows-down glioblastoma cell growth and thus might exert a tumor suppressor effect in glioblastoma.

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Poster

557. Neuro-Oncology

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Title: Adora2a inhibition as novel therapeutic target for cisplatin-induced cognitive dysfunction

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Abstract: Cisplatin chemotherapy, although efficacious in positive resolution of cancer, adversely potentiates off-target cognitive dysfunction and affects approximately 14 million cancer survivors in the United States alone. Despite the high prevalence of chemotherapy induced cognitive impairments (referred to as chemobrain), there is little information on how memory and learning are impaired and no known cure. In order to elucidate the mechanisms by which chemobrain impairs cognition, we implement a novel experimental mouse model resembling clinical cisplatin-chemotherapy. Our results reveal that repeated cisplatin administration impairs hippocampal neuronal functional morphology, while inducing significant emotional and memory deficits. Although the molecular targets and pathways vulnerable to

cisplatin in the central nervous system (CNS) are currently unknown, RNA-sequencing derived from mice administered cisplatin or vehicle revealed the adenosine A_{2A} receptor (Adora2a), a G-protein coupled receptor critical for synaptic plasticity and memory, as a promising therapeutic target for chemobrain. Bioinformatic analysis and qRT-PCR validation revealed significant induction of Adora2a mRNA expression by cisplatin in the adult hippocampus, a brain structure critical for learning and memory. Interestingly, while Adora2a is known to be expressed by various CNS cell types, including neurons and astrocytes, confocal microscopy analysis demonstrates that cisplatin specifically increases Adora2a expression in hippocampal neurons without affecting astrocytes in this structure, indicating that Adora2a expressing neurons are particularly vulnerable to cisplatin. To mechanistically determine whether elevated neuronal Adora2a functionality are implicated in cisplatin-induced chemobrain, we assessed the efficacy of Istradefylline (KW-6002), a selective Adora2a inhibitor, in preventing cisplatin-induced chemobrain. Our results indicate that selective pharmacological inhibition of Adora2a prevented cisplatin induced anxiety and cognitive impairments in the elevated plus maze, the Morris water maze and novel object recognition test. Therefore, our results suggest a critical role for Adora2a in cisplatin-induced cognitive dysfunction. Given that Adora2a antagonists are proven to be safe and neuroprotective in neurodegeneration as well as in enhancing anti-tumor activity, inhibiting Adora2a may have far-reaching synergistic effects on cancer treatment and chemobrain.

Disclosures: **A. Oliveros:** None. **K. Yoo:** None. **A.M. Corujo:** None. **J. Tang:** None. **D. Brogren:** None. **M. Jang:** None.

Poster

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Title: Harnessing redox homeostasis as a therapeutic modality in glioblastoma

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Abstract: A potential clinical application of targeting cancer metabolic reprogramming (i.e. the Warburg effect) is the ability to capitalize on the differences in oxidative stress levels; with specific disruption in cancer cells without damaging (or perhaps even benefitting) non-tumor cells. Coenzyme Q_{10} (CoQ_{10}) represents a prototypical agent for this approach due to its primary role in electron transfer reactions in mitochondria and its capacity to form toxic free radicals

when present in high concentrations, leading to generation of oxidative stress. BPM31510 is a novel ubidecarenone (oxidized CoQ_{10}) - lipid formulation that facilitates delivery of supraphysiologic concentrations of this quinone to cells and their mitochondria. In this study, we assessed the effects of BPM31510 on comparative viability and redox homeostasis in rodent and human derived *in vitro* cocultures of glioma and non-cancerous cells (rodent C6 glioma and NIH3T3 cells or human U251 glioma and primary human astrocytes, respectively). Sensitivity to increasing doses of BPM31510 was initially assessed in the rodent coculture model. After 6 days of treatment, the percentage of C6 relative to NIH3T3 cells within the coculture was lowest at doses of BPM31510 between 115 and 230 μM, providing evidence of greater sensitivity to BPM31510-induced cytotoxicity in the C6 glioma cells in this dose range. The differential effects on cell viability were less evident at higher doses of BPM31510. Interestingly, the peak effect of differences in superoxide levels and cell growth occurred at the same dosage (230 μM). A similar differential (glioma selective) sensitivity to BPM31510 was observed in a human derived model. Basal superoxide levels for U251 cells were 1.5-fold higher compared to the astrocytes, and this difference increased to over 4-fold upon treatment with BPM31510, suggesting BPM31510 exploits differential redox vulnerabilities between U251 and astrocytes to mediate its anti-cancer activity. In summary, the data indicate that cellular delivery of ubidecarenone differentially affects cell growth via increasing intramitochondrial superoxide in tumor cells, when compared to non-transformed cells. The results also suggest that dosing of agents inducing oxidative stress is crucial to enhance cancer-selective effects and that clinical application will be bolstered by the development of a measurement tool for real-time, *in situ* measures of oxidative stress.

Disclosures: **J. Sun:** A. Employment/Salary (full or part-time):; Stanford Medicine. **S. Gesta:** A. Employment/Salary (full or part-time):; BERG LLC. **S. Nagpal:** A. Employment/Salary (full or part-time):; Stanford Medicine. **C. Patel:** A. Employment/Salary (full or part-time):; Stanford Medicine. **M. Merchant:** A. Employment/Salary (full or part-time):; Stanford Medicine. **T. Jang:** A. Employment/Salary (full or part-time):; Stanford Medicine. **A.R. Diers:** A. Employment/Salary (full or part-time):; BERG LLC. **S. Kazerounian:** A. Employment/Salary (full or part-time):; BERG LLC. **N.R. Narain:** A. Employment/Salary (full or part-time):; BERG LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG LLC. **R. Sarangarajan:** A. Employment/Salary (full or part-time):; BERG LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BERG LLC. **L. Recht:** A. Employment/Salary (full or part-time):; Stanford Medicine.

Poster

557. Neuro-Oncology

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CMA BIO-BIO PIA-Conicyt ECM-12

Title: Vitamin C induces glioblastoma invasiveness by increasing perivascular satellitosis and bystander effect

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Abstract: Introduction: Glioblastoma, a highly aggressive astrocytic tumor, expresses both vitamin C transporters, SVCT2 and GLUT1/3, but preferentially uptakes oxidized dehydroascorbic acid (DHA) by GLUT1. It is well accepted that reduced ascorbic acid (AA) plays an important role in the biosynthesis of collagen, which is essential for tumor progression; its disruption reduces invasiveness. We propose that DHA confers antioxidant protection to glioblastoma cells by its reduction to AA and increasing collagen deposition. **Materials and Methods:** U87MG, HSVT-C3, and RAV27 human glioblastoma cells were used to characterize SVCT2, GLUT1, and GLUT3 expression. Cell viability was evaluated by the XTT-method. Migration assays were performed using *in vitro* and *in situ* (Organotypic Brain Slice Culture, OBSC) spheroid strategies. A guinea pig orthotopic xenograft model and human tumor samples were analyzed by immunohistochemistry. Picrosirius-Red staining (PRS) and second harmonic generation (SHG) were used to analyze collagen deposition.**Results:** Glioblastoma cells express intracellular SVCT2 while GLUT1 is found in the cell membrane. Radiolabeled assays confirm functional DHA uptake. XTT experiments show that DHA protects glioblastoma cells against H_2O_2-induced oxidative stress. AA and DHA increase *in vitro* RAV27 cell migration. *In situ* analysis using the OBSC assay confirms that migration was associated with collagen IV. U87MG xenografts and human tumor samples express collagens. Xenografts also show augmented blood vessel invasion that is reduced during scurvy.**Conclusions:** Glioblastoma cells functionally uptake DHA, which protects them against oxidative stress. Vitamin C could enhance perivascular satellitosis associated with collagen deposition.

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Poster

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Title: A new class of inhibitors of HuR multimerization is identified

Authors: *N. FILIPPOVA[1], J. A. CALANO[1], X. YANG[1], S. ANANTHAN[2], E. OFORI[2], P. VIBHA[2], L. B. NABORS[1];
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Abstract: HuR is an mRNA binding protein (ELAV family), and it is overexpressed in different types of cancer, including brain tumors. In normal non-proliferating cells, HuR exhibits mostly nuclear localization; however, in proliferating and tumor cells, HuR localizes in both the nucleus and cytoplasm. HuR strong cytoplasmic localization and multimerization are associated with a rise of the tumor grade and poor patient outcome. We identified a new class of inhibitors of HuR multimerization and evaluated the outcome of the disruption of HuR multimerization on HuR function and glioma progression. We utilized a split Firefly Luciferase-HuR assay (HuR molecules were attached to the N and C parts of Firefly Luciferase in living glioma cells) to search for new compounds, which interfere with HuR multimerization. The cell lines expressing a full-length luciferase without HuR or co-expressing N and C parts of luciferase were utilized as a control. New inhibitors of HuR multimerization (with IC50s ranging from 0.3 uM to 5 uM in glioma cells) were identified. We observed a significant reduction of the expression of the anti-apoptotic Bcl-2 family molecules on mRNA and protein levels after cell treatment with newly identified inhibitors of HuR. The average decreases of Bcl2/18S and Mcl1/18S mRNA ratios were 96$\pm$2% and 95$\pm$3%, 95$\pm$2% and 86$\pm$7%, 95$\pm$2% and 87$\pm$8%, 96$\pm$2% and 90$\pm$9% based on three experiments for the established U251, U87, LN229, and the primary XD456 cell lines, respectively, after cell treatment with compound #2 compared to the control. We confirmed that the identified inhibitors of HuR multimerization reduce proliferation and evoke cell cycle arrest with significant cell accumulation in the G1 phase and a dramatic reduction in the S phase of the cell cycle. The spheroid viability of primary GBMs was decreased by compound #2 with the IC50s ranging from 1.5 to 8 uM (48 hours of treatment). The global Illumina RNA-Sequencing workflow and proteomic analysis are on the way for the identification of the pathways involved in the tumor spheroids' sensitivity to the compound #2. In the intracranial athymic mice glioma model, we observed a decrease of primary XD456 tumor growth by an average of 5-7 folds after treatment with compound #2 compared to the control. The mice were treated with compound #2

by intraperitoneal injection (15mg/kg, twice a day for 15 days) or with the corresponding vehicle as a control. We conclude that the disruption of HuR multimerization in glioma cells by a new class of HuR inhibitors results in a decrease of anti-apoptotic Bcl2 family molecules in mRNA and protein levels, the arrest of cell cycle progression, and, therefore, reduces tumor cell viability and proliferation.

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Poster

557. Neuro-Oncology

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Topic: B.13. Neuro-Oncology

Title: Identifying small molecules that specifically inhibit glioma stem cells

Authors: S. E. LAYE[1], R. SPINA[2], A. SLOAN[2], D. M. VOSS[2], *B. J. HOFFER[3], E. E. BAR[2]; [1]Hathaway Brown Sch., Shaker Heights, OH; [2]Case Western Reserve Univ., Cleveland, OH; [3]Scientist Emeritus, NIDA/NIH, Lyndhurst, OH

Abstract: Glioblastoma (GBM) are a highly malignant form of brain tumor which proliferate rapidly throughout the brain and are incredibly difficult to treat. The median survival time is approximately 15 months with the combined treatment of maximal surgical resection followed by concomitant radiation and temozolomide (TMZ) chemotherapy. Glioblastoma stem cells (GSC) are shown to play a role in tumor growth and survival due to their tumor initiation and propagation abilities as well as their link to GBM resistance to current treatment. Due to these poor clinical outcomes and resistance to current treatments, more potent and preferably more specific pharmacological therapies are needed in order to target cellular-molecular pathways to eradicate GSCs and effectively treat GBM. Small-molecule drug library including over 3,000 compounds was screened in an effort to identify agents that effectively and specifically target GBM patient derived neurospheres. HSR020913 patient derived neurospheres were treated for 72 hours with library agents at a concentration of 10 µM and cell growth was observed for a period of 5 days. We identified twelve highly potent compounds in the primary screen that inhibited the growth of HSR020913 neurospheres by over 50%. Subsequently, the potency of these compounds was tested on five additional GBM patient derived neurosphere lines (HSR040622, HSR040822, CCF3691, CCF3832, and CCF08-387), immortalized human neural stem cells (v-Myc hNSCs) and normal human astrocytes (NHA) at concentrations ranging from 10 µM to 0.001 µM. Collectively, these efforts yielded three drugs: AGSC9, AGSC11, and AGSC12 all capable of inhibiting GBM cells but show no effect against normal neural stem cells (NSC and NHA). The respective half maximal inhibitory concentration (IC50) was determined

for all the neurosphere lines utilized. Future studies will help to determine the effect of these drugs on self-renewal *in vitro*, to elucidate the molecular mechanisms involved and also to shed light on the effect on tumorigenicity and survival *in vivo*.

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Poster

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Title: Identifying safe and effective pharmacologic agents for use with neural stem cell therapy in glioblastoma

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Abstract: There is no known cure for glioblastoma multiforme (GBM), the deadliest and most common form of malignant brain tumor in adults. Although current therapies slow progression, the median survival for patients with GBM is less than two years. Glioma stem cells (GSCs), which are resistant to chemo- and radiotherapy, are a main contributor to treatment failure and recurrence of GBM. Neural Stem Cells (NSCs) can naturally migrate towards the tumor and represent a promising new alternative as vehicles for GBM targeted therapy. No single therapy has been shown effective in the treatment of GBM. To identify pharmacological agents effective in killing tumor cells, but safe to use in combination with NSC therapy, we first tested a panel of chemotherapeutics commonly used in the treatment of GBM, in murine NSCs and in GSCs derived from an aggressive model of mouse GBM. Results so far indicate that all tested drugs severely affect the viability of both GSCs and NSCs, with NSCs being more sensitive to Temozolomide, Cisplatin and Erlotinib and less sensitive to Imatinib and SU-6668 than GSCs. To identify specific molecules to target GSCs we compared gene expression between NSCs and GSCs using high throughput RNA-Seq. This analysis identified 2951 differentially expressed genes. Among these, SIX1, a transcription factor member of the PAX-SIX-EYA-DACH developmental transcriptionally regulatory network had a 64-fold higher expression in GSCs than in NSCs (2^{nd} hit on the list). Overexpression of SIX1 has been documented to correlate with increased aggressiveness and poor prognosis in multiple human cancers, including GBM. It has been shown that SIX1 increases cancer stem cell numbers and promotes malignancy by regulation of cell proliferation, apoptosis, genome stability, and energy metabolism. Current

experiments are focused on testing strategies to inhibit SIX1 expression and activity with specific siRNAs and/or phosphatase inhibitors targeting its EYA cofactors and activators. Results from this study will enhance our understanding of glioma stem cell biology and may identify strategies for optimal use of therapeutic NSCs in combined treatment strategies for GBM.

Disclosures: **M. Kauss:** None. **A. Calinescu:** None.

Poster

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Title: Lateral ventricle infiltrating glioblastoma disrupts the ventricular-subventricular zone neurogenic niche

Authors: *E. S. NORTON[1], C. DE LA ROSA PRIETO[3], S. JEANNERET[4,2], K. BELTRAN[2], N. ZARCO[2], M. A. LARA VELAZQUEZ[2,5], A. CARRANO[2], A. QUINONES-HINOJOSA[2], J. GARCIA-VERDUGO[6], H. GUERRERO CAZARES[2];
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Abstract: Glioblastoma (GBM) is the most common and devastating primary brain tumor in adults, with an average survival of only 15 months and a recurrence rate of nearly 100%. This is largely due to the high invasive capacity of GBM cells into distal regions of the brain parenchyma, leading to recurrence despite standard of care therapy of combinatorial surgical resection, chemotherapy, and radiation. Tumor location has a strong effect on patient outcome, as association of GBM with the lateral ventricles (LV) results in a lower survival rate and an increased rate of distal tumor recurrence. Although the reason for this worse prognosis is unknown, it may be due in part to the interaction of tumor cells with the neurogenic niche in the ventricular-subventricular zone (V-SVZ). This niche is highly organized, with characteristic

pinwheel structures of ependymal cells and neural stem cell process centers. This organization forms a barrier on the LV surface that separates the cerebrospinal fluid (CSF) from the rest of the brain parenchyma. Disruption of the V-SVZ may lead to the interaction of GBM with growth factors and chemokines contained in the CSF. Using patient-derived primary lines of GBM brain tumor initiating cells (BTICs), we evaluated the effect of tumor proximity on the integrity of the V-SVZ niche and survival using immunosuppressed mice. GFP-labeled BTICs were implanted into immunosuppressed mice at locations proximal and distal to the LV. The organization of the V-SVZ was evaluated by wholemount preparations of the V-SVZ, as well as coronal sections followed by immunofluorescence or transmission electron microscopy. In agreement with patient retrospective studies, mice with LV-proximal GBM displayed a more proliferative tumor phenotype and shorter survival rate than mice with LV-distal tumors. We observed that LV-proximal GBM interrupts the characteristic pinwheel cytoarchitecture of the V-SVZ. GFP+ tumor cells disrupt the ependymal barrier and integrate into the LV surface. By electron microscopy, we found that LV-proximal GBM induces an accumulation of lipid droplets in ependymal cells and that V-SVZ fractones are smaller and less dense when compared to controls. Our observations demonstrate that the typically organized V-SVZ becomes severely disrupted by invading GBM, potentially implicating the normal function of this niche. The mechanisms utilized by GBM cells to disrupt the neurogenic niche as well as the effect on neurogenic function remain to be studied.

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Poster

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Title: *In vivo* circadian rhythms in glioblastoma multiforme presents opportunities for chronotherapy and personalized medicine

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Abstract: Glioblastoma multiforme (GBM) is the most common primary adult brain tumor diagnosed, with a 15-month prognosis using current standard of care treatment which includes chemotherapy with Temozolomide (Temodar, TMZ). Previous work on a cultured murine mesenchymal GBM cell line showed a time-of-day dependent maximum in DNA double-strand breaks, activation of the apoptotic pathway, and cell death corresponding with the peak of *Bmal1* and trough of *Per2* expression, two core clock genes. However, tumor circadian rhythms *in vivo* have not been shown to exist. We hypothesized that circadian rhythms exist in GBM tumors *in vivo* and that TMZ treatment would reduce tumor size in our GBM mouse model. We implanted murine GBM expressing a real-time luciferase reporter of either *Bmal1* or *Per2* transcription into the basal ganglia of 10 ten-week-old male nude (CrTac:NCr-*Foxn1*^{nu}) mice and recorded bioluminescence for 6 weeks, as well as locomotor data. Mice were maintained in a light-dark cycle and imaged in darkness. We found that GBM tumors had daily rhythms in gene expression with high *Per2* and low *Bmal1* at ZT9. The phase of expression corresponded to host daily rhythms as measured by locomotor activity, showing a two-fold change between peak and trough, which decreased to no change in amplitude by week 6 when the experiment was concluded. In a second group of 10 mice, tumor size was measured over 10 weeks via a fluorescent reporter. At 6 weeks post-implant, mice were treated with the standard dose of 21mg/kg/day TMZ for 5 days at either ZT2 or ZT9. Tumor fluorescent intensity was reduced following treatment with TMZ in both groups. Follow-up histology confirms successful implantation and proliferation of the xenograft. The time of day difference in clock gene expression in GBM cells, which corresponds to daily onset and offset of activity in mice, indicates that GBM tumors have circadian rhythms that synchronize to the host *in vivo*. The decrease in amplitude of bioluminescent signal could be due to the development of a hypoxic environment in the solid tumor mass, which can disrupt clock gene function. The decrease in fluorescence intensity following TMZ treatment indicates that TMZ is effective in killing tumor cells in this xenograft mouse model of GBM. This work establishes a foundation for testing whether chemotherapy timed according to circadian time in the host and tumor could be used to maximize tumor killing and minimize side effects.

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Poster

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Topic: B.13. Neuro-Oncology

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Title: Treatment of glioblastoma using superparamagnetic iron oxide nanoparticles with modified surface

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Abstract: Glioblastoma multiforme (GBM) is a frequent brain tumor, representing 80% of malignant primary central nervous system tumors. The life span of patients with treatment is about 12 months. The aim of our study was to develop multifunctional superparamagnetic iron oxide (SPIO) nanoparticles suitable for magnetic resonance imaging (MRI), hyperthermia in high frequency electromagnetic field and drug delivery [carrying poly[*N*-(2-hydroxypropyl)methacrylamide-*co*-*N*-(2-hydrazinyl-2-oxoethyl)methacrylamide] [P(HP-MAH)] with conjugated doxorubicin (Dox)].
We used human glioblastoma line (GAMG), and primary cultures isolated from solid patient GBM tumors, which were characterized by flow cytometry. As a model of healthy cells, human mesenchymal cells (hMSC) were utilized. To evaluate the therapeutic effect, SPIO- P(HP-MAH)-Dox nanoparticles were incubated with all types of used cells and cell growth was assessed using real time proliferation assay (XCELigence). SPIO nanoparticles alone did not affect the viability of any of the tested cells and transmission electron microscopy confirmed the uptake of SPIO nanoparticles into the cell cytoplasm. SPIO nanoparticle-labeled cells were visualized by MRI. Due to hydrolysis of the hydrazone bond in acid milieu of tumor cells and Dox release, the SPIO-P(HP-MAH)-Dox nanoparticles significantly decreased the GAMG and GBM cell growth compared to free Dox and P(HP-MAH)-Dox in low concentration (10 nM), whereas free Dox was effective only up to 50 nM. Moreover, SPIO P(HP-MAH)-Dox nanoparticles did not affect growth of hMSC. Hypothermia was effective only in cells mixed with SPIO nanoparticles in concentration of 16-32mM, in which temperature reached 50°C. On contrary, the exposure to high frequency magnetic field did not affect cells that contained SPIO nanoparticles only in the cytoplasm. The temperature of these samples did not exceed 30°C. In conclusion, SPIO-P(HP-MAH)-dox nanoparticles can offer enhanced cell permeation, increased cell death and reduced nonspecific toxicity, however, their hyperthermic effect has to be enhanced.

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Poster

557. Neuro-Oncology

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Topic: B.13. Neuro-Oncology

Title: Interactions between immune microenvironment, stem cells, and cell proliferation in pediatric embryonal central nervous system [CNS] tumors

Authors: *K. T. SCHAFERNAK[1], E. C. UTAGAWA[2], S. V. MEHTA[2], T. DI MODICA[1], E. J. MUFSON[3], S. E. PEREZ[4];
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Abstract: Mounting evidence suggests that the brain's own immune cells, microglia, and perivascular macrophages play important roles in immune surveillance/inflammation and response to injury, but also support proliferation and growth of gliomas, possibly through interactions with tumor stem cells. Immune cells are increasingly regarded as potential targets for cancer therapy, however, the immune microenvironment has not been well studied in embryonal CNS tumors [i.e., medulloblastomas (MBLs), primitive neuroectodermal tumors (PNETs) and atypical teratoid-rhabdoid tumors (ATRTs)], the most common malignant pediatric brain tumors. To characterize the tumor-associated immune microenvironment of a series of pediatric brain tumors (13 MBLs, 7 PNETs and 6 ATRTs) we quantified the number of cells immunopositive for macrophage/microglia Ionizing calcium binding adaptor molecule 1 [Iba1], CD68 (expressed on both "M1" antitumor/proinflammatory macrophages and "M2" protumor/anti-inflammatory macrophages), CD163 ("M2" macrophages), CD3 (T-cell marker), CD4 (helper T cell), CD8 (cytotoxic T cell) and CD20 (B-cell marker) and correlated these findings with the stem-cell marker nestin and the Ki67/MIB1 proliferation index. Significant results were as follows: Across groups, CD68 showed a strong Spearman rank-order correlation with both CD163 (r=0.610, p=0.0007) and nestin (r=0.577, p=0.0017), while CD3 correlated strongly with CD8 (r=0.601, p=0.004), CD4 (r=0.526, p=0.005) and CD20 (r=0.499, p=0.008). Between groups, the number of CD163-positive cells was significantly higher in PNETs compared to MBLs (p=0.035). Within the MBL group, CD68 showed a significant relationship with nestin (r=0.595, p=0.0387) and Ki67 (r=0.606, p=0.0333), and there was a robust correlation between CD4 and CD8 values (r=0.846, p=0.0000002), less so with CD20 and CD3 (r=0.793, p=0.001) and CD20 and CD4 (r=0.756, p=0.003). Within the PNETs, there was a strong negative correlation between CD163 and nestin (r=-0.883, p=0.0000002), while CD68 correlated with CD4 (r=0.803, p=0.006). Within ATRTs, nestin and Ki67 were strongly correlated (r=1.000, p=0.0028) as were CD68 and CD163 (r=0.943, p=0.017). These data suggest a role for blocking embryonal CNS tumor-associated macrophages by inhibiting the CSF1R pathway (perhaps in conjunction with CD8-positive T cells which could antagonize the immunosuppressive function of tumor-associated macrophages) or reprogramming them from an M2 to an M1 phenotype (particularly in PNETs, which had the highest number of CD163-positive cells).

Disclosures: **K.T. Schafernak:** None. **E.C. Utagawa:** None. **S.V. Mehta:** None. **T. Di Modica:** None. **E.J. Mufson:** None. **S.E. Perez:** None.

Poster

557. Neuro-Oncology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 557.25/C23

Topic: B.13. Neuro-Oncology

Support: NS092466
AR070547

Title: Gliobalstoma invades by co-opting healthy astrocytes via gap junctional communication

Authors: S. MCCUTCHEON, ***D. C. SPRAY**;
Neurosci., Albert Einstein Col. Med., Bronx, NY, NY

Abstract: Glioblastoma multiforme (GBM) is the deadliest CNS cancer. Its dismal prognosis is due to difficulty of resection, chemotherapeutic resistance, and invasion along vasculature. Elucidating how GBM invades is critical for development of effective resection and adjuvant therapies. GBM invasion involves change of non-cancerous cells, including astrocytes, in the tumor microenvironment toward a cancer-friendly phenotype. Evidence suggests post-transcriptional regulation by miRNAs may be the culprit. Past studies have highlighted transfer of miRNAs from GBM to astrocytes by means of Cx43 channels, however it is known that gap junctions have a size exclusion of 1 kDa, and miRNAs are about 14 kDa. We seek to address how gap junctions are implicated in the expression or transfer of miRNAs whether by direct passage through Cx43 junctions or other pathways. Invasion assays were done using coated transwell inserts, using 10% fetal bovine serum as the chemoattractant. Invasion index was quantified for GL261, U87, primary astrocytes, immortalized astrocytes, and Cx43 knockout astrocytes individually, in cocultures, and treated with 100µM carbenoxolone. An ex vivo slice culture invasion model was used to measure invasion in a pseudo-3D environment with native astrocytes. 350µm whole brain coronal slices were injected with 250 µm diameter U87 spheroids (150-200 Cells), cultured for 0-3 days, then quantified for tumor outgrowth. miRNA sequencing on cocultures of U87 cells with immortalized wild type or Cx43 knockout astrocytes, utilizing genetic GFP labeling, FACS, and small RNA isolation identified targets for miRNA trafficking studies. Functional Cx43 homotypic gap junctions form between GBM and astrocytes *in vitro*. Presence and functionality of astrocyte-GBM Cx43 channels alter the invasion potential of GBM *in vitro* and *ex vivo*. GBM-GBM Cx43 junctions limit invasion and promote tumor cohesion, while astrocyte-GBM junctions promote invasion and of GBM along vascular tracts. Presence of GBM-astrocyte Cx43 junctions causes a shift in miRNA profile for cells cocultured with the GBM cell line U87-MG, such that miRNA found in GBM pre-coculture appeared in wild type but not Cx43 knockout astrocytes post-coculture. Future work seeks to pursue the mechanism for miRNA transfer.

Disclosures: D.C. Spray: None. **S. McCutcheon:** None.

Poster

557. Neuro-Oncology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 557.26/C24

Topic: F.08. Biological Rhythms and Sleep

Support: Vice-rectory of Research Universidad de los Andes

Title: Xenotransplantation of human glioblastoma y neuroblastoma in zebrafish larvae: *In vivo* imaging and proliferation assessment

Authors: *V. AKLE[1], J. A. VENEGAS[1], M. A. FORERO-SHELTON[2], J. M. GONZALEZ[1]; [1]Sch. of Med., [2]Fac. of Sci., Univ. de los Andes, Bogota, Colombia

Abstract: Neuroblastoma (NBM) and glioblastoma (GBM) have completely different backgrounds with respect to their ontogeny. Treatment options include maximal surgical resection and drug-radiotherapy combination for GBM, while there are many more treatment options for NBM. However, chemotherapy continues to be an important option treatment with significant side effects, prompting the search for new models for drug discovery and testing, especially those that allow assessment of *in vivo* responses to treatment. Here, it is introduced an *in vivo* imaging and proliferation assessment method of human NBM and GBM xenograft in zebrafish larvae. Zebrafish larvae microinjected with fluorescently labeled human tumor cells were screened daily using a stereomicroscope and imaged by Light Sheet Fluorescence Microscopy (LSFM); volumetric modeling and composite reconstructions was done in single individuals. Larvae containing tumors were enzymatically dissociated, and the proliferation of human cancer cells was measured using dye dilution by flow cytometry. GBM microtumors formed mainly in the zebrafish yolk sac and perivitelline space following injection in the yolk sac. Daily image analysis suggested cellular division, as microtumors progressively grew with differentiated fluorescence intensity signals. At least three division cycles for human GBM cells were identified in the dye dilution assay by flow cytometry. Human cancer cells proliferate in zebrafish larvae, making it possible to assess cell divisions and tumor growth, and the interference by chemotherapy agents. With this approach, it should be possible to better predict the clinical efficacy of different anticancer treatments and contribute to individualize patient treatment.

Disclosures: V. Akle: None. **J.A. Venegas:** None. **M.A. Forero-Shelton:** None. **J.M. Gonzalez:** None.

Poster

557. Neuro-Oncology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 557.27/C25

Topic: B.13. Neuro-Oncology

Title: Intratumoral modulation therapy enhances multi-modality treatment platforms for pediatric and adult high grade gliomas

Authors: *A. DEWEYERT[1], E. IREDALE[2], H. XU[3], E. WONG[2], S. SCHMID[2], M. HEBB[2]; [1]Univ. of Western Ontario, London, ON, Canada; [2]Western Univ., London, ON, Canada; [3]London Hlth. Sci. Ctr., London, ON, Canada

Abstract: Introduction: Intratumoral modulation therapy (IMT) is a putative new treatment modality that delivers non-ablative electrical stimulation directly into tumor-affected brain regions to induce tumor cell death. We have previously shown that low amplitude, intermediate frequency IMT reduces glioblastoma burden [Di Sebastiano et al 2018] and now aim to assess IMTs therapeutic potential for the pediatric brain tumor diffuse intrinsic pontine glioma (DIPG).
Hypothesis: We hypothesize that targeted IMT in combination with chemoradiotherapy will provide an effective means to increase drug sensitivity and reduce viability of patient-derived high grade-gliomas in monolayer and spheroid cultures.
Methods: Spheroids were generated by implanting $1x10^4$ patient-derived cells into extracellular matrices and allowed to grow for 3 days. DIPG cells or spheroids were treated with either 72 hours IMT using a continuous sinusoidal waveform (200 kHz, ±2V), temozolomide (TMZ), radiation (RT) or the combination of IMT, TMZ, and RT. DIPG cell monolayer viability was assessed with the MTT assay, and flow cytometry with Annexin V and zombie red detection. Spheroid viability was evaluated with bioluminescence imaging (BLI), confocal microscopy and stereology. Computer-generated electric field modeling was performed using COMSOL software to predict field strength and dimensions and to reconstruct IMT treatment fields using various electrode configurations. To validate mathematical predictions, *in vitro* measurements within our IMT models were taken using an oscilloscope.
Results: MTT revealed a significant loss of metabolic viability in DIPG cells treated with IMT compared to sham conditions *in vitro* (<40% vs. sham; n=4, p<0.01). TMZ and RT revealed a modest 19% and 28% reduction in cell viability respectively but increased significantly to 80% with concomitant IMT (<80% vs. sham; n=3, p<0.001). BLI revealed a significant loss of metabolic viability in spheroids treated with IMT compared to sham conditions. To date measurements within our IMT models have corroborated mathematical predictions of field intensity by COMSOL allowing for accurate mapping of electric fields and determination of IMT therapeutic coverage.
Conclusion: This study provides first-time evidence of DIPG cell susceptibility to a non-ablative

electrical therapy and demonstrates the potential of IMT to effectively enhance multi-modality treatment platforms for high grade-glioma both in 2D and 3D model systems. Continued advances in this technology, has the potential to facilitate clinical translation of IMT as a critically-needed therapy for these devastating brain cancers.

Disclosures: A. Deweyert: None. **E. Iredale:** None. **H. Xu:** None. **E. Wong:** None. **S. Schmid:** None. **M. Hebb:** None.

Poster

557. Neuro-Oncology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 557.28/C26

Topic: B.13. Neuro-Oncology

Support: Swedish Research Council 01641
Barncancerfonden PR2017-0105

Title: Predisposition for neoplasia in progenitors for horizontal and cone photoreceptor cells in the developing chicken retina

Authors: *D. KONJUSHA, M. BLIXT, M. HELLSAND, F. HALLBÖÖK;
Dept. of Neurosci., Uppsala Univ., Uppsala, Sweden

Abstract: The intra-ocular child tumor retinoblastoma originates in the neural retina. The tumors arise mainly as a result of biallelic RB1 gene loss-of-function mutations, although other mutations such as MYCN amplification have been found in a subset of cases. The cell-of-origin in human retinoblastoma is mainly from the horizontal cells (HC)/cone photoreceptors (PR) cell type lineage. The variation in mutations causing the tumor, together with previous studies indicating a p53-insensitivty in the HC/cone PR progenitors in the developing chicken retina, indicate a cell type-specific predisposition for neoplastic growth.
PiggyBac genome-integrating over expression vectors with variants of MYC (MYCN, MYCN T58A, cMYC or cMYC T58A) and a GFP reporter were injected subretinally in embryonic day 3.5 (E3.5)/Hamburger & Hamilton stage 22 (st22) White-Leghorn chicken embryos and electroporated *in ovo*. Expression was driven from the ubiquitous actin promotor. Eyes were analyzed at ages E8-P43 by immunohistochemistry. Cells from GFP+ regions were dissected, dissociated, cultured and were orthotopically transplanted to E18 eyes for analysis of tumor formation.
Initially GFP (MYC) expression was observed in all retinal cell types. By E14, GFP+ clusters with HC and cone PR markers were observed while cells with amacrine and ganglion cell markers had disappeared (by E10-12). A similar result was seen by E18 and in post-hatch chickens. Similar results were obtained regardless of the MYC-construct used. Transformed cells

were grown *in vitro* for 6 months while maintaining this phenotype. Orthotopic transplantation of these GFP+ cells to E18 embryo eyes generated clusters of proliferating cells in various parts of the eye with maintained phenotype. Cells had increased expression of Ki67 and decreased expression of p21.
We show that MYCN over expression is sufficient to transform the chicken HC/cone PR progenitor cells, while the amacrine and ganglion cells die. This effect was observed regardless of the MYC variant, implying a cell type and developmental stage-specific intrinsic predisposition for neoplastic transformation. Tentatively, the low p21 expression indicates that the tumor suppressor protein p53 may be involved and urge for further investigation of the mechanistic basis. This potential chicken model for neoplastic transformation in retina shows similarity to the human cancer and allows for further investigation of early carcinogenesis both *in vitro* and *in vivo*.

Disclosures: D. Konjusha: None. **M. Hellsand:** None. **F. Hallböök:** None. **M. Blixt:** None.

Poster

557. Neuro-Oncology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 557.29/C27

Topic: B.13. Neuro-Oncology

Support: Translational Neuroscience Core

Title: Generation of a porcine experimental model of spinal cord glioma

Authors: *M. S. TORA, P. TEXAKALIDIS, J. WETZEL, N. HARDCASTLE, T. FEDERICI, N. M. BOULIS;
Neurosurg., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Background: SC Glioma (SCG) is an orphan disease which accounts for 8-10% of all primary SC (SC) tumors. High-grade lesions result in survival as low as 11% and a clinical picture of untenable morbidity and mortality. The failure of numerous therapeutic strategies has highlighted the importance of novel disease models in rodents and large animals as pre-clinical platforms. In the interest of developing putative novel-models in the spinal cord for pre-clinical study, our group utilized orthotopic, thoracolumbar, intraparenchymal injections of retroviral vectors expressing combinations of Platelet-Derived Growth Factor Beta (PDGF-B), HRASG12V, and shRNA-P53. Here we report our initial behavioral, immunohistochemical, and histologic data in 12 Sprague Dawley rats and 3 Göttingen-Minipigs.**Methods**: Sprague Dawley Rats and Göttingen Mini-pigs received thoracolumbar laminectomies followed by stereotactic injection targeting the lateral white matter. Retroviral vectors expressing oncogenic transgenes were infused at a volume of 2ul in rats and 25 ul in pigs. Animals underwent were monitored for

motor deficits until IACUC defined endpoint with subsequent imaging and histology.**Results:** Our results demonstrate the growth of high-grade gliomas in wild-type rats within 60 days of inoculation with PDGF-B (11 of 12 rats, 91%), resulting in complete hind-limb paralysis. H&E staining demonstrated infiltrative lesions consistent with high-grade gliomas (N = 11/12). 1 pilot pig inoculated with PDGFB-IRES-DsRED (N = 1) resulted in a hypercellular region with immunohistochemical findings consistent with glioma markers (GFAP-, NG2+, Olig2+, Nestin+, N= 5/5 sections). Most notably, 2/2 pigs receiving retroviral PDGF-B, HRASG12V, and shRNA-P53 developed market motor deficits and mass forming lesions on MRI consistent with high-grade gliomas in 21 days. **Conclusion:** Oncogenic transgene expression generates high-grade SCGs in the spinal cord of rats and pigs, warranting further study as putative candidates for immunocompetent, orthotopic, and reproducible models of SCG.

Disclosures: M.S. Tora: None. **P. Texakalidis:** None. **J. Wetzel:** None. **N. Hardcastle:** None. **T. Federici:** None. **N.M. Boulis:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.01/C28

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Sex-specific effects of maternal separation on cognition and LPS-induced accumulation of amyloid beta in adult C57BL6/J mice

Authors: *J. L. PETERMAN, J. D. WHITE, S. LOPEZ, M. JOHNSON, M. CHUMLEY, G. BOEHM;
Texas Christian Univ., Fort Worth, TX

Abstract: Alzheimer’s Disease (AD) is the most common form of dementia, with an incidence expected to drastically increase as our population grows older. AD is characterized by the accumulation of amyloid-beta (AB) plaques and neurofibrillary tangles. Our laboratory has previously demonstrated that 7 consecutive daily injections of LPS (250 ug/kg; i.p.) result in increased inflammation and significant elevation of amyloid-beta within the hippocampus of C57BL6/J mice. Given the relationship between stress, inflammation, and AD pathology, we sought to explore how an early life stressor, maternal separation, could impact AD-like markers in adulthood. Mouse pups were separated from their mothers for three hours daily from post-natal day 2 (PND2) to PND21 and then were allowed to age in standard housing conditions into adulthood. At 4-6 months of age, mice received LPS or Saline injections and cognition was assessed utilizing a contextual fear conditioning (CFC) paradigm. Tissue was collected and hippocampal AB levels were quantified via ELISA, while western blotting was utilized to explore potential mechanisms behind AB alterations. Maternal separation significantly impaired

cognitive function, and exacerbated LPS-induced accumulation of AB in a sex-specific manner. Maternal separation also resulted in decreased hippocampal BDNF expression in males and females. Overall, the results suggest that early-life stress can exacerbate inflammation-induced AD-like pathologies in adulthood. Understanding how the interaction of stress and immune function may increase one's potential risk for AD, as well as impact AD pathologenesis, are some of the first steps in developing effective interventions.

Disclosures: J.L. Peterman: None. **J.D. White:** None. **S. Lopez:** None. **M. Johnson:** None. **M. Chumley:** None. **G. Boehm:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.02/C29

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NSFC 81571046

Title: Cystatin F derived from blood borne monocyte ameliorates cognitive impairment of APP/PS1 transgenic mice

Authors: *K. ZHANG, Y.-H. CHEN, X. CHEN;
Developmental Cell Biol., China Med. Univ., Shenyang, China

Abstract: Alzheimer's disease (AD) is the most common form of age-related dementia. One important pathological hallmarks of AD is the activated microglia. Two different types microglia exist in the brain, the resident and newly differentiated microglia originates in part from hematopoietic cells, and more particularly from monocytes, called bone marrow-derived microglia (BMDM). BMDM are more efficient in restricting amyloid burden and preventing the formation or eliminating amyloid beta (Aβ) plaques deposition than resident counterparts. In an attempt to identify the determinants that associated with AD in BMDM, we first performed microarray analysis of mRNA isolated from monocytes of AD patients. Compared with aged-matched controls, the transcription of cystatin F were up-regulated significantly, which was then verified by qRT-PCR. In order to investigate the function of cystatin F in AD monocytes, we knocked down the level of cystatin F in U937 cells by using a lentiviral-based RNAi technique. Results showed that RNAi-cystatin F U937 cells had an impaired ability to degrade exogenous Aβ. In contrast, cystatin F-overexpressing monocytic THP-1 cells line displayed enhanced ability in degradation of Aβ. Furthermore, over-expressing of cystatin F in THP-1 cells markedly increased the clearance of Aβ plaque in the APP/PS1 mouse brain slices. These data indicated that cystatin F in monocytes was associated with the metabolism of Aβ. We tried to explore the molecular mechanism on cystatin F-related degradation of Aβ in monocytes. We found that

cystatin F could bind Aβ directly in vitro. Furthermore, GST-pull down assay showed that endogenous cystatin F interacted with GST-Aβ 1-40, GST-Aβ 1-42,or GST-C99 in U937 cells. To further detect how cystatin F worked in vivo, we generated a monocyte-derived human cystatin F transgenic mouse which was then crossed with the APP/PS1 transgenic mouse. Immunofluorescence staining images showed that cystatin F^+/APP^+ double transgenic mice had decreased Aβ plaques in brain. In additional, cystatin F^+/APP^+ mice had an increased cognitive function than APP/PS1 mice in morris water maze test. These data suggested that cystatin F exhibited a protective role in AD through increasing the degradation of Aβ and ameliorating cognitive impairment of APP/PS1 transgenic mice. Further study will focus on determine whether cystatin F promotes degradation of Aβ through a lysosomal-dependent pathway in monocytes and analyzing the binding sites between cystatin F and Aβ. Our study will provide a potential therapeutic strategy by adjusting the level of cystatin F in monocyte and promoting the clearance of Aβ by BMDM.

Disclosures: K. Zhang: None. **Y. Chen:** None. **X. Chen:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.03/C30

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JSPS KAKENHI Grant Number JP18K05342

Title: Effect of humanin on streptozotocin-induced cognitive deficit in mice

Authors: T. TANAKA[1], *Y. KITA[2], T. NIIKURA[1];
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Abstract: Humanin (HN) is a 24-residue neuroprotective peptide. HN with a substitution of glycine for serine 14 (HNG) is a highly potent HN derivative and protects neurons from amyloid beta-induced cell death at nano M levels in vitro. In a mouse model of Alzheimer's disease (AD), HNG suppressed cognitive impairment and reduced amyloid burden. HNG also ameliorated amnesia induced by a muscarinic receptor antagonist and a $GABA_A$receptor agonist in normal mice. In addition, HNG reduced gliosis and cognitive deficit induced by short-period treatment of cuprizone, a copper chelator, suggesting that HN has anti-inflammatory function. To further understand the effects of HN on cognitive deficit related to AD, we used an AD-like mouse model using streptozotocin (STZ). STZ is a glucosamine-nitrosourea and the systemic administration of STZ is commonly used to induce long-lasting model of diabetes mellitus. Intraventricular (icv) injection of STZ triggers some features of sporadic AD, such as disturbance in learning and memory, neuroinflammation, and dysregulation of insulin signal. As a model of

early stage of AD, we used lower dose of STZ and longer treatment period comparing with a frequently used model (3 mg/kg STZ, 3 weeks treatment). To test the effect of HNG, we injected HNG intraperitoneally. After 9 weeks of treatment, we performed a series of behavioral tests to evaluate cognitive function. We found that STZ induced cognitive deficit in object recognition memory and social recognition memory. HNG attenuated the effects of STZ. These findings suggest that HN can rescue memory impairment in a sporadic AD model.

Disclosures: **T. Tanaka:** None. **Y. Kita:** None. **T. Niikura:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.04/C31

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH grant R01-AG044404

Title: Effects of docosahexaenoic acid and its peroxidation product on amyloid-β peptide-stimulated microglia

Authors: ***X. GENG**[1], B. YANG[2], R. LI[3], M. LADU[4], G. Y. SUN[3], C. GREENLIEF[2], J. C. LEE[1];
[1]Bioengineering, Univ. of Illinois at Chicago, Chicago, IL; [2]Chem., [3]Biochem., Univ. of Missouri-Columbia, Columbia, MO; [4]Anat. and Cell Biol., Univ. of Illinois, Chicago, Chicago, IL

Abstract: Growing evidence suggests that docosahexaenoic acid (DHA) exerts neuroprotective effects, although the mechanism(s) underlying these beneficial effects has not been fully understood. Here we demonstrate that DHA, but not arachidonic acid (ARA), suppressed oligomeric amyloid-β peptide (oAβ)-induced reactive oxygen species (ROS) production in primary mouse microglia and immortalized mouse microglia (BV2). Similarly, DHA but not ARA suppressed oA-induced increases in phosphorylated cytosolic phospholipase A_2 (cPLA_2), inducible nitric oxide synthase (iNOS), and tumor necrosis factor-α (TNFα) in BV2 cells. LC-MS/MS assay indicated the ability for DHA to cause an increase in 4-hydroxyhexenal (4-HHE) as well as suppressing oAβ-induced increase in 4-hydroxynonenal (4-HNE). Although oAβ did not alter the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, exogenous DHA, ARA as well as low concentrations of 4-HHE and 4-HNE upregulated this pathway and increased production of heme oxygenase-1 (HO-1) in microglial cells. These results suggest that DHA modulates ARA metabolism in oAβ-stimulated microglia through its actions to suppress oxidative and inflammatory pathways, and upregulates the antioxidative stress pathway involving Nrf2/HO-1. Understanding the mechanism(s) underlying the beneficial effects of DHA

on microglia should shed light into nutraceutical therapy for the prevention and treatment of Alzheimer's disease.

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Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.05/C32

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Neonatal infection leads to increased susceptibility to amyloid-βoligomer-induced brain inflammation, synapse loss and cognitive impairment in mice

Authors: P. S. FROST[1], R. T. DA SILVA[1], A. VENANCIO[2], I. MATIAS[1], N. LYRA E SILVA[1], G. KINCHESKI[1], P. M. PIMENTEL-COELHO[1], F. G. DE FELICE[1], F. C. A. GOMES[1], S. T. FERREIRA[1], C. P. FIGUEIREDO[1], ***J. R. CLARKE**[3];
[1]Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [2]Federal Univ. of Santa Catarina, Florianopolis, Brazil; [3]Federal Univ. of Rio De Janeiro, Rio de Janeiro, Brazil

Abstract: Harmful environmental stimuli during critical stages of development can profoundly affect behavior and susceptibility to diseases. Alzheimer disease (AD) is the most frequent neurodegenerative disease, and evidence suggest that inflammatory conditions act cumulatively, contributing to disease onset. Here we investigated whether infection early in life can contribute to synapse damage and cognitive impairment induced by amyloid-β oligomers (AβOs), neurotoxins found in AD brains. To this end, wild-type mice were subjected to neonatal (post-natal day 4) infection by *Escherichia coli* (1 x 10^4 CFU/g), the main cause of infection in low-birth-weight premature infants in the US. *E. coli* infection caused a transient inflammatory response in the mouse brain starting shortly after infection. Although infected mice performed normally in behavioral tasks in adulthood, they showed increased susceptibility to synapse damage and memory impairment induced by low doses of AβOs (1 pmol; intracerebroventricular) in the novel object recognition paradigm. Using *in vitro* and *in vivo* approaches, we show that microglial cells from *E. coli*-infected mice undergo exacerbated activation when exposed to low doses of AβOs. In addition, treatment of infected pups with minocycline, an antibiotic that inhibits microglial pro-inflammatory polarization, normalized microglial response to AβOs and restored normal susceptibility of mice to oligomer-induced cognitive impairment. Interestingly, mice infected with by *E. coli* (1 x 10^4 CFU/g) during adolescence (post-natal day 21) or adulthood (post-natal day 60) showed normal cognitive performance even in the presence of AβOs (1 pmol), suggesting that only infections at critical stages of development may lead to increased susceptibility to amyloid-β-induced toxicity.

Altogether, our findings suggest that neonatal infections can modulate microglial response to AβOs into adulthood, thus contributing to amyloid-β-induced synapse damage and cognitive impairment.

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Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.06/C33

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Coordenação de Aperfeiçoamento (CAPES) de Pessoal de Nível Superior
Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)
Fundação de Amparo à pesquisa do Estado do RS (FAPERGS)
Instituto Nacional de Ciência e Tecnologia Excitotoxicidade e Neuroproteção

Title: Systemic long-term inflammation promotes spatial memory impairment

Authors: *G. H. SCHIRMBECK, C. F. DA RÉ, M. SEADY, F. FRÓES, S. G. SILVA, J. H. TADAY, C. S. GONÇALVES, M. C. LEITE;
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Abstract: Long-term inflammation is a major player in the progression of neurodegenerative diseases such as dementia, although is not its main initiator. Its been demonstrated that inflammatory activation of microglia and astrocytes promotes aggregation of amyloid plaques and tau tangles, leading to neuronal death through other mechanisms, such as excitotoxicity. Although some studies investigated the effect of systemic inflammatory insult on the progression of dementia and amyloid plaques in genetic mouse models of Alzheimer's disease, is not clear if systemic inflammation *per se* for an extended period of time can induce cognitive impairment observed in dementia models. **Methods:** 90-day Wistar rats were exposed to chronic inflammatory challenges with intraperitoneal injections of LPS in two doses (500 μg/kg and 250 μg/kg) or saline once a week, for a 16-week period. Rats were euthanasied 24 h after last LPS injection. Behavioral evaluation was conducted through Open Field (OF) and Object Location Memory-Test (OLM) for spatial memory assessment. Hippocampal S100B content was measured by ELISA, nuclear Nf-κB was measured by western blot, and L-[^{3}H] glutamate uptake was analyzed. **Results:** Both groups receiving LPS presented impaired spatial memory in the 24 h OLM, which is characteristic of hippocampal degeneration in animal models of dementia, while OF shown no locomotor impairment. S100B protein remained unchanged between groups,

and glutamate uptake was reduced only in LPS 500 μ/kg group. Nuclear fraction of Nf-κB was increased in both LPS groups. Discussion: Here, we demonstrate that chronic peripheral inflammatory stimuli promote cognitive impairment in the absence of other underlying neurodegenerative causes, such as genetic background. Increased Nf-κB in nucleus indicates hippocampal neuroinflammation, despite LPS challenge being peripheral. Besides, glutamate uptake was reduced in the higher dose of LPS, indicating a possible excitotoxic damage. Conversely, S100B content, which is an important biomolecule in inflammatory signaling, was not affected by LPS.

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Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.07/C34

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Metabolic dysregulation induces early-onset Alzheimer's disease in a high-fat diet mouse model

Authors: *M.-H. JO[1], R. ULLAH[1], M.-W. KIM[1], B. P. F. RUTTEN[2], *M.-O. KIM[1]; [1]Gyeongsang Natl. Univ., Jinju, Korea, Republic of; [2]Maastricht Univ. Med. Ctr., Maastricht, Netherlands

Abstract: Obesity-related metabolic dysfunction is a risk factor for cognitive decline and is concomitant with early-onset Alzheimer’s disease. A high-fat diet induces obesity-associated microglial activation, neuroinflammation, and neuronal insulin resistance, which are considered important risk factors for neurodegeneration. However, the molecular mechanism underlying HFD-induced neuropathy remains unclear. The present study aimed to elucidate whether chronic consumption of HFD (24 weeks) can induce neuroinflammation, insulin resistance, amyloid deposition and, most importantly, plaque formation in mouse brains. HFD-fed mice showed abnormal metabolic parameters and insulin resistance compared with their age-matched littermates fed with normal chow diet. Similarly, HFD increased neuroinflammation, as indicated by an increased expression of inflammatory markers (NF K B, IL-1β and TNFα) and astrocyte and microglial activation (Iba-1 and GFAP) in the cortex and hippocampus region in the brains of HFD mice. Furthermore, HFD mouse brains exhibited early signs of amyloid pathology, as evident by the minor accumulation of deposited amyloid plaques, decreased expression of markers of synaptic plasticity (SNAP-23 and PSD95) and subsequent behavioral deficits observed in the HFD mouse brains compared with the normal chow-fed mouse brains. Taken together, our findings suggest that the consumption of an HFD has a profound impact on brain

activity, which involves the acceleration of cognitive impairment due to increased insulin resistance and neuroinflammation that ultimately leads to early-onset of Alzheimer's-like pathology.

Disclosures: M. Jo: None. **R. Ullah:** None. **M. Kim:** None. **B.P.F. Rutten:** None. **M. Kim:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.08/C35

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA/NIH Grant AG056114

Title: Human TREM2 gene dosage-mediated microglia reprogramming is impaired by the R47H variant *in vivo*

Authors: *C. LEE[1,2], A. DAGGETT[1], K. INOUYE[1], P. LANGFELDER[1,2], R. KAWAGUCHI[1,2], N. WANG[1,2], X. GU[1,2], G. COPPOLA[1,3,4], H. XU[5], X. W. YANG[1,2,3]; [1]Ctr. for Neurobehavioral Genetics, Jane and Terry Semel Inst. of Neurosci. and Human Behavior, [2]Dept. Psychiatry and Biobehavioral Science, David Geffen Sch. of Med., [3]Brain Res. Inst., [4]Dept. Neurology, David Geffen Sch. of Med., UCLA, Los Angeles, CA; [5]Neurosci. and Aging Res. Ctr., Sanford Burnham Prebys Med. Discovery Institutu, La Jolla, CA

Abstract: Whole-genome and exome sequencing studies identified a rare R47H variant of Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) linking to 2-4 fold higher risk for developing late-onset Alzheimer's disease (AD). In the brain, TREM2 is expressed exclusively by microglia. The human genetic findings led to a plethora of discoveries on the *in vivo* function of TREM2 (e.g. promoting microglia survival and enabling microglia to cluster around and remove amyloid plaques). Recently, we showed that elevated TREM2 gene-dosage exerts multiple beneficial effects in amyloid-depositing AD mouse models, which are likely due to a molecular and functional reprogramming of the microglia responsivity in the disease brains (Lee et al., Neuron 97:1032-1048, 2018). In the current study, we applied the same human TREM2 genomic transgenic model system to address whether the AD risk-associated R47H variant could alter TREM2 function *in vivo* by modifying microglia responsivity in the disease brains. We created BAC transgenic mice carrying TREM2 with R47H variant (BAC-TREM2-R47H), and crossed them to 5xFAD, an accelerated Aβ-depositing mouse model of AD. By comparing the pathology and behavioral phenotypes of 5xFAD mice with or without the BAC-TREM2 or BAC-TREM2-R47H transgenes, we found that the TREM2-R47H variant appears hypofunctional compared to the wildtype TREM2 allele in reducing the amyloid pathology, and

is minimally effective in altering the morphology of the activated, plaque-associated microglia. Moreover, RNA-sequencing studies showed the transcriptomic signatures of TREM2-mediated microglial reprogramming are also absent in the 5xFAD/TREM2-R47H mice. Finally, we were able to examine the effect of R47H SNP on the splicing of human TREM2 exons. Together, our study demonstrates the important utility of a human genomic transgenic model system to study disease-associated TREM2 variants in the mammalian brain.

Disclosures: **C. Lee:** None. **A. Daggett:** None. **K. Inouye:** None. **P. Langfelder:** None. **R. Kawaguchi:** None. **N. Wang:** None. **X. Gu:** None. **G. Coppola:** None. **H. Xu:** None. **X.W. Yang:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.09/C36

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CSIR 12FYP BSC0115

Title: Tissue inhibitor of matrix metalloproteinase-1, a cytokine secreted rapidly from amyloid-β induced reactivated astrocytes, ameliorate disease pathology and cognitive impairments in models of Alzheimer’s disease

Authors: S. SARKAR, P. SAHA, P. KUMAR, *S. C. BISWAS;
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Abstract: Reactivation of astrocytes is an integral part of Alzheimer’s disease (AD) however its role in disease pathogenesis is poorly understood. It is hypothesized that at initial stages of AD progression reactive astrocytes act in a protective manner. In this study, we aim to identify the key players in reactive astrocytes at the early phase of AD that contribute to their neuroprotective potential in disease models. We used primary cortical neuron culture from Sprague Dawley (SD) rat and performed a time-dependent cytokine array of astrocyte-conditioned medium (ACM) to find the secretion status of proteins from astrocytes in response to oligomeric Aβ1-42 (Aβ) treatment in vitro. Among the differentially expressed cytokines in response to Aβ, extracellular levels of tissue inhibitor of metalloproteinase-1 (TIMP-1) was rapidly elevated at 6h. We then tested the effect of 6h Aβ-treated ACM (Aβ-ACM) on neuronal health by a combination of immunocytochemistry and cell viability assay and found that Aβ-ACM induced morphological protection and approximately 100% (mean 101.4% SD 8.0) survival of neurons against Aβ toxicity (55.6% ± 8.3) where TIMP-1 played a key role since its neutralization reduced the viability to 53.8% ± 6.9. Moreover, rat recombinant TIMP-1 (rrTIMP-1) recovered neuronal viability to 100.9% ± 7.2 against Aβ toxicity (50.8% ± 6.2). Akt, a central kinase in survival

signaling, was triggered profoundly upon rrTIMP-1 treatment to neurons denoting its role in cellular survival. To understand TIMP-1 function in vivo, we used stereotaxic rat model (bilaterally infusing Aβ into hippocampus of SD rat brain, 280-320 g) and 5XFAD mice model where TIMP-1 was injected intracerebroventricularly. We used coronal brain sections to follow Aβ deposition and apoptosis by Aβ-immunohistochemistry and TUNEL assay respectively and found that TIMP-1 reduced Aβ load and apoptosis in hippocampus. We also got evidence of cognitive recovery by TIMP-1 from Aβ-induced impairment in both models by behavioral studies. For example, in cue-dependent fear conditioning test, associative memory was assessed where animals previously exposed to a shock following light and sound cues were checked for freezing response following cues but without shock. Aβ-induced rat showed 55% ± 10 freezing as compared to 69% ± 9 of control which was significantly recovered by TIMP-1 to 74% ± 8 (1-way ANOVA, tukey's post hoc, n=6). Hence, it was evident that TIMP-1 infusion protected against Aβ induced cognitive impairments. Thus, TIMP-1 is an important cytokine secreted from reactivated astrocytes with neuroprotective function at early AD stage and can be developed into a potentially good therapeutic agent.

Disclosures: S. Sarkar: None. **P. Saha:** None. **P. Kumar:** None. **S.C. Biswas:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.10/C37

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The impact of high sucrose diet on the cortical pathogenesis and insulin sensitivity of APPswe/PS1dE9 mice

Authors: *H.-H. YAO, P.-C. KAO, L.-M. CHEN, L.-J. CHAO, H.-J. TSAY;
Neurosci., Natl. Yang-Ming Univ., Taipei, Taiwan

Abstract: The high fat and sugar-containing diet contributes to the prevalence of type II diabetes and Alzheimer's disease (AD). High fat diet (HFD) or high sugar-containing diet is known to increase the risk of AD. Our previous studies have suggested that the reciprocal augmentation between the HFD-induced metabolic stresses and AD central pathogenesis leads to accelerated cognitive impairments and fatty liver in HFD-fed APP/PS1d9E transgenic mice. Our previous studies demonstrate the deleterious effects of high fat diets on AD-related pathology; however, the impacts of a high sugar-containing diet on the AD pathogenesis remain unclear. Like HFD, the use of sugars and high fructose corn syrup in modern human diet also cause the epidemic of obesity and metabolic disorders. This study is focused at whether the high sucrose diet (HSD) accelerates APP/PS1 pathology and the impact of AD pathology on HSD-induced metabolic stresses. The peripheral metabolic index, daily capabilities, and neuroinflammation of HSD WT

and APP/PS1 mice were compared. These results will shed light on the deleterious effects of HSD on the pathology of APP/PS1 mice and the underlying mechanism. APPswe/PS1dE9 (APP/PS1) transgenic mice and wildtype mice were fed with HSD, and their biochemical index and cognitive behaviors were compared. The result showed that HSD increased the level of cortical and serum Aβ and cortical inflammation in APP/PS1 mice. HSD aggravated obesity, hyperinsulinemia, insulin resistance without inducing hyperphagia in APP/PS1 mice. The nesting capability was attenuated by HSD and APP/PS1 genetic background. Our study demonstrated that HSD exacerbated the cognitive dysfunction in APP/PS1 mice.

Disclosures: H. Yao: None. **P. Kao:** None. **L. Chen:** None. **L. Chao:** None. **H. Tsay:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.11/C38

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: RO1NS097722

Title: Elucidating the role of heat shock protein 27 in vascular cognitive impairment and dementia

Authors: A. E. WOOLUMS[1], B. R. PRICE[2], *T. L. SUDDUTH[1], C. A. DICKEY[4], D. M. WILCOCK[3];
[1]Sanders-Brown Ctr. on Aging, [2]Physiol., [3]Univ. of Kentucky, Lexington, KY; [4]Mol. Med./Byrd Inst., Univ. of South Florida, Tampa, FL

Abstract: Background: Hyperhomocysteinemia (HHcy) is a risk factor for vascular cognitive impairment and dementia (VCID), as well as Alzheimer’s disease. Using the HHcy mouse model of VCID, we found the earliest detectable event in the brain is a robust neuroinflammatory response. This is followed by neurovascular astrocyte disruptions, cerebral hypoperfusion, microhemorrhages, white matter degeneration, and cognitive impairment.To gain mechanistic insights into the signaling pathways by which HHcy induces these events, we focused on heat shock protein 27 (Hsp27). Hsp27 binds protein-folding intermediates and prevents their aggregation without directly refolding them itself. Aberrant phosphorylation of Hsp27 has been reported in a variety of neurodegenerative diseases. Given that Hsp27 is shown to be involved in cerebrovascular dysfunction, and is known to signal through the p38 MAPK signaling pathway, we hypothesized Hsp27 is an early mediator of HHcy-induced neuroinflammation. **Methods:** C8-DIA astrocytes, BV2 microglia, and primary endothelial cells were independently cultured, after which they were treated with homocysteine and levels of HSP27 were assessed. Additionally, C8-DIA astrocytes and primary endothelial cells were co-cultured, treated with

varying concentrations of rHsp27 and subject to TEER measurements.Wildtype and Hsp27$^{-/-}$ mice were subject to a HHcy-inducing diet for 14 weeks. Mice were assessed behaviorally during week 12 using radial arm water maze. Tissue from the left hemisphere was histologically examined for microglial activation, the astrocytic end-foot integrity, and microhemorrhages. Tissue from the right hemisphere was used to evaluate the neuroinflammatory state using qRT-PCR. **Results:** Our wildtype-HHcy model displayed significant pro-inflammatory responses and astrocytic end-foot disruptions. Importantly, we found that that Hsp27$^{-/-}$mice subjected to the HHcy-inducing diet exhibited a markedly different pro-inflammatory response. **Conclusions:** Hsp27 appears to be an early essential mediator of HHcy-induced pathology. Deletion of Hsp27 provides protection from neuroinflammation, astrocytic end-feet disruption, and cerebrovascular events. This suggests that Hsp27 may be an attractive therapeutic target for the treatment of VCID.

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Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.12/C39

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Fellowship F31NS092202 (EMW)
NIH grant 1RO1NS079637 (DMW)
NIH grant 1RO1NS097722 (DMW)
NIH training grant 5T32GM118292 (CES)

Title: Time course of neuropathological events in hyperhomocysteinemic amyloid depositing mice

Authors: N. W. FIELDER[1], *E. M. WEEKMAN[2], T. L. SUDDUTH[2], B. R. PRICE[2], A. E. WOOLUMS[2], D. HAWTHORNE[2], C. E. SEAKS, IV[2], D. M. WILCOCK[2];
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Abstract: Vascular contributions to cognitive impairment and dementia (VCID) are the second leading cause of dementia behind Alzheimer’s disease. In addition, VCID co-morbid with Alzheimer’s disease (AD) is estimated to occur in at least 60% of AD cases and is commonly found in the oldest old. This co-morbidity of vascular injury with AD pathologies is thought to act as an extra “hit” to the brain that increases the rate of cognitive decline. While the contribution of VCID to clinical dementia is increasingly recognized, the mechanistic underpinnings of VCID co-morbid with AD pathologies has been lacking.

We have previously shown that induction of hyperhomocysteinemia (HHcy) via a diet deficient in vitamins B6, B9, and B12 and enriched in methionine in APP/PS1 mice produces a co-morbidity model. While the pathological characteristics of HHcy have been identified, the time course for these changes is unclear. For this study, we examined neuropathological changes along a time course of 2, 6, 10, 14 and 18 weeks on diet in our co-morbidity model.
The first pathological changes that occur are an increase in microglial staining at 6 weeks along with a significant increase in the gene expression of several pro-inflammatory cytokines. Using the two-day radial arm water maze, we detected cognitive changes beginning at 10 weeks that persisted through the 18 weeks on diet. Prussian blue staining and T2* MRI revealed a significant increase in microhemorrhages starting at 14 weeks on the HHcy diet. Finally, induction of HHcy resulted in redistribution of amyloid from the parenchyma to the vasculature starting at 14 weeks on diet.
Overall, induction of HHcy in APP/PS1 mice initially leads to a pro-inflammatory response followed by cognitive decline. Interestingly, microhemorrhages and redistribution of amyloid to the vasculature occur after cognitive changes. However, taken together, this data suggests that neuroinflammation is an initiator in HHcy mediated VCID co-morbid with amyloid deposition and provides a possible target for therapeutics.

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Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.13/C40

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: DGAPA-PAPIIT Grant IN215716

Title: Central adiponectin prevents olfactory dysfunction induced by amyloid β_{1-42}

Authors: *M. A. GUZMÁN-RUIZ[1], E. ORTA- SALAZAR[2], A. HERRERA-GONZÁLEZ, Jr.[1], A. CANDELAS-JUÁREZ, Jr.[1], C. BERNAL-MONDRAGÓN, Jr.[1], S. DÍAZ-MIRANDA[3], R. GUEVARA-GUZMÁN[1];
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Abstract: Metabolic dysfunctions predispose subjects to the development of Alzheimer disease (AD) and specifically, insulin resistance, which plays a central role in the pathogenesis of this neurodegenerative disease.
AD characterizes for the development of memory impairment and, eventually, dementia. These

effects are related to neurodegenerative processes in brain areas such as the hippocampus and associated cortexes. Furthermore, Amyloid-β (Aβ) accumulation induces olfactory dysfunction or anosmia, a condition considered an early marker of AD, which is related with damages in the olfactory bulb, the hippocampus and other odor related cortexes.
Adiponectin (APN) is a hormone with protective functions including insulin sensitizing, anti-inflammatory and anti-oxidative effects. In addition, studies have demonstrated that APN administration is able to decrease Amyloid-β (Aβ) neurotoxicity and hyperphosphorylation in the hippocampus, hence, reducing cognitive impairment and neurotoxic damage.
There are no studies regarding the neuroprotective effects of APN in the olfactory dysfunction observed in a $A\beta_{1-42}$ model.
The aim of this study is to determine whether the central administration of APN can prevent the olfactory dysfunction observed in an icv $A\beta_{1-42}$ model.
To assess if APN improves the olfactory function of Wistar rats (220-250g) injected with 5µl of $A\beta_{1-42}$ (1µg/µl), we administered 5µl of intracerebroventricular APN (16 µg/µl) prior to (30 min before) to $A\beta_{1-42}$injection. We determined the olfactory function of these animals 24h after the infusion and evaluated olfactory memory using the social recognition test. We observed that the rats administered with APN prior to $A\beta_{1-42}$ increased the exploration time of an unfamiliar juvenile as compared to the amount of time of $A\beta_{1-42}$ infused rats.
In addition, we assessed olfactory discrimination making use of the buried chocolate test observing a significant decrease in the time that the rats injected with APN prior to $A\beta_{1-42}$ took to find 5g of dark chocolate compared to that of animals that were only infused with $A\beta_{1-42}$.
Lastly, we evaluated the olfactory bulb of these subjects observing a decrease in IBA1 immunoreactivity in both the olfactory bulb and the hippocampus as well as a conservation in the amount of NeuN marked cells in spite of $A\beta_{1-42}$. These results suggest that the elevated central levels of APN are able to prevent the damage caused by $A\beta_{1-42}$.
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Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.14/C41

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NSF Grant 1746511
NSF Grant 1513126
Florida High Tech Corridor Council

Title: Stereological analysis of neurodegeneration and neuroinflammation in Tg4510 mice using manual and automatic stereology

Authors: *R. H. PATEL[1], S. S. ALAHMARI[1], D. B. GOLDGOF[1], H. A. PHOULADY[2], P. DAVE[1], L. O. HALL[1], P. R. MOUTON[3,1];
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Abstract: A wide range of animal models are available for studying neurodegenerative and neurological diseases and evaluating novel strategies for the therapeutic management of patients. The Tg4510 mouse, a widely used model for studies of Alzheimer's disease (AD) and other tauopathies, has responder and activator transgenes that drive expression of a P301L tau mutation. The brains of Tg4510 mice express mutant tau that leads to neuron loss and activation of neuroglia cells in parallel with progressive cognitive decline. Here we use a series of six distinct manual, semi-automatic and fully-automatic applications of the unbiased optical fractionator method to quantify neurodegeneration and neuroinflammation in neocortex of Tg4510 mice. In contrast to conventional stereology based on user clicks without saving images, the present work involves automatic capturing and saving 3D stacks of images (disector stacks) labeled with the results of user counts, thereby allowing for comparison of the accuracy and identification of errors, i.e., false positives and negatives, in comparison to ground truth. Among the novel methods examined is a convolutional neural network (CNN) that has been previously trained from labeled images to allow self-counting (automatic) of immunostained cells using unbiased methods. This work uses n=12 Tg4510 mice aged 6-8 months and age- and sex-matched littermate controls. After brain removal and immersion fixation in 4% paraformaldehyde, 50-um frozen sections were cut through the entire neocortex and adjacent sets of sections were systematically sampled and immunostained for neurons (Neu-N) and microglia cells (Iba-1). Validation studies show the semi-automatic and fully automatic stereology approaches using unbiased methods are >5x and >10x faster, respectively, and the results show minimal variation (<3% error) compared to conventional manual stereology. We will also report on the effects of stain separation of immunostained sections processed with Nissl counterstain. The results from these ongoing blinded studies will establish baseline data for neurodegeneration and neuroinflammation in neocortex of Tg4510 mice, as well as identify the most accurate, precise and efficient methods for future studies in Tg4510 and other mouse models.

Disclosures: **R.H. Patel:** A. Employment/Salary (full or part-time):; Part-time, University of South Florida. **S.S. Alahmari:** A. Employment/Salary (full or part-time):; Part-time, University of South Florida. **D.B. Goldgof:** A. Employment/Salary (full or part-time):; Full-time, University of South Florida. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Science Foundation (NSF). **H.A. Phoulady:** A. Employment/Salary (full or part-time):; Full-time, University of Southern Maine. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National

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Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.15/C42

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01AG050518 (JRF)

Title: Age-related changes in basal forebrain microglial activation

Authors: *B. L. SOMERA, J. R. FADEL;
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Abstract: The basal forebrain is comprised of several nuclei including the substantia innominata, medial septum, nucleus basalis and diagonal band of broca. The basal forebrain is defined by the presence of cholinergic output neurons named the basal forebrain cholinergic system (BFCS) which provide the largest source of cholinergic neurons implicated in cognitive functions including attention, learning, and arousal. Moreover, evidence suggests basal forebrain neurons are particularly vulnerable to dysfunction and degeneration in aged humans and, more dramatically, in diseases such as Alzheimer's. Additionally, it is thought that age-related BFCS dysfunction may reflect alterations in afferent inputs and neuroinflammatory processes. In order to examine effects of aging on physiologically-relevant afferent stimulation of this area we deposited the retrograde neuronal tracer, cholera toxin B (CTb) in basal forebrain of aged (26-28 months) and young (2-3 months) F344/Brown Norway F1 hybrid rats and trained them for 7 days with repeated paired presentations of a conditioned stimulus consisting of palatable food and darkness. On the final test day, trained and control rats were either given the dark/food paired stimulus or a dark cue without food. Two hours later, animals were sacrificed, and their brains processed for immunohistochemical detection of the neuronal activity marker, c-Fos in

combination with several phenotypic markers of distinct neuronal populations. Additional tissue was process for microglial markers as a correlate of neuroinflammation. Aged rats showed altered activation of basal forebrain afferents located in the medial prelimbic cortex, infralimbic cortex, nucleus accumbens, and ventral tegmental area compared to young controls. Finally, in order to investigate the possible role of basal forebrain orexin signaling in these glial and neuronal alterations, we deposited an miRNA-expressing lentivirus designed to knock down orexin receptor 2 expression in the basal forebrain. Collectively, these studies suggest that early age-related alterations in afferent input to basal forebrain may contribute to BFCS dysfunction, and that orexin degeneration may contribute to these changes.

Disclosures: B.L. Somera: None. **J.R. Fadel:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

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Program #/Poster #: 558.16/C43

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA funded Wisconsin Alzheimer's Disease Research Center (ADRC) to Jeffrey A. Johnson (P50 AG033514)

Title: Nrf2 induced shift in APP/AB processing and autophagy dysfunction in APP_{swe}/PS1ΔE9mice

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Abstract: Alzheimer's disease (AD) is characterized by accumulation of extracellular amyloid beta (Aβ) peptides, intracellular hyperphosphorylated tau and dystrophic neurites. Failure in Aβ proteolytic clearance contributes to the neurodegenerative progression of AD. Additionally, axonal dystrophies interfere with the physiological intracellular proteolysis. These impairments could disrupt axonal transport, autophagic pathways and thus Aβ accumulation. Nrf2 (Nuclear Factor [erythroid derived 2] like 2) is a pivotal transcription factor regulating cellular homeostasis, particularly in response to oxidative stress and cellular injury. Previous studies in our laboratory using APP_{Swe}/PS1ΔE9 (APP-PS1) mice demonstrated that knockout of Nrf2 resulted in increased autophagic dysfunction leading to more Aß burden. Here, we analyze whether overexpression of astrocytic Nrf2 can modify and reverse autophagic dysfunction in APP-PS1 mice. Transgenic mice using the GFAP promoter to drive overexpression of Nrf2 in astroctyes have been generated (GFAP-Nrf2; Vargas et al. 2008) and were crossed with APP-PS1 mice. Hippocampus (HP) and cortex (CX) were fractionated into Triton-X-soluble, SDS-soluble and Urea-soluble fractions that were resolved on 10%Tris-tricine gels. Immuno-

histochemical and -fluorescence studies were also conducted. Our findings show decreased levels APP-FL, APP fragments, and Aβlevels in the SDS- and Urea-soluble fractions from CX and HP of APP-PS1/GFAP-Nrf2 double transgenic mice compared with APP-PS1 mice. The increase in phospho-APP(Thr668) observed in APP-PS1 mice was also reversed in the double transgenic. In accordance with the proteins results, 6E10 and phospho-APP histochemistry showed reduced staining intensity in plaques and neurons from CX and HP. Autophagy was evaluated by examining mTOR, AMPKα, p62, LC3B and numerous ATGs. The results indicate that autophagic dysfunction in the APP-PS1 mice is rescued by Nrf2 activation in astrocytes. Interestingly, the GFAP-Nrf2 mice alone had increased levels of phospho-AMPKαand ATG12, as well as reduced p62 in the Urea-soluble fraction suggesting an increased neuronal autophagic flux in these mice. In conclusion, the data strongly suggests that Nrf2 activation in astrocytes has significant modulatory effects on a neurons ability to produce and remove Aβin APP-PS1 mice.

Disclosures: R.X. Aviles-Reyes: None. **D. Johnson:** None. **J.A. Johnson:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.17/C44

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Ministry of Health & Welfare, Republic of Korea (grant number: HI17C1260)

Title: Expression of miRNA146 and regulation of neutrophil proinflammatory functions sheds new light on the pathogenesis of Alzheimer's disease

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Abstract: For more than two centuries now, Alzheimer disease (AD) is under research intending to develop various treatment and diagnosis. Despite decades of scientific advances, AD is still representing a challenge for contemporary medicine. Current drug therapies may provide a little relief about the quality of life of AD patients; however, they are still insufficient to reverse tissue injury and are often generating side-effects. The difficulty arises from the considerable fluctuation of the clinical course of AD among patients, making the predictive prognosis difficult. Resolution of inflammation needs effective and timely removal of dead cells and other toxic products of neutrophils, monocytes, and macrophages in AD mice model. In this study, we evaluated the role of monocytes in the clearance of neutrophil extracellular trap (NET) and apoptotic neutrophils in the inflammation site of early stage AD mice. For this study, immune cells were observed microscopically after exposing them with NETs and/or apoptotic bodies. A

subset of immune cells exposed to NETs ejected extracellular traps and this was shown to be mediated by proteins like elastase and citrullinated histones present in NET supernatant. More and more studies underline the profound influence of the neutrophil and immune cells multifaceted functions in the pathogenesis of AD. In this study, we aim to update the recent results on the multiple facets of neutrophils in AD, in particular their impact in promoting the inflammation-based AD through the release of the cytokine-like HMGB2 and S100A8/A9 protein complex, as well as the importance of NETosis in the disease progression and development. Furthermore, we delved into the complex question of neutrophil heterogeneity and plasticity and determine the emerging role of miRNA-146 and PTM (post-translational modification) markers influencing the inflammatory response of neutrophils in AD.
Acknowledgments This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI17C1260)

Disclosures: S. Kim: None. **S. Kim:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.18/C45

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: SHRF
CoMRAD
University of Saskatchewan Graduate Scholarship

Title: Acute systemic LPS injections attenuate high-sucrose diet-induced neurodegenerative processes in estrous female wild-type mice

Authors: *A. G. PACHOLKO[1], L. K. BEKAR[2];
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Abstract: Alzheimer’s disease (AD) incidence is expected to double by 2038. This coincides with similar trends in obesity, diabetes, and chronic inflammation. It is known that diabetic and chronic inflammatory conditions can increase the risk of AD-like neurodegeneration, likely through mechanisms involving brain insulin resistance. Insulin resistant brain states are associated with increased GSK3β activity, whose constitutive functions are inhibited, in part, by the insulin pathway. Aberrant GSK3β signalling contributes to increased β-amyloid production (senile plaques) and Tau protein hyperphosphorylation (neurofibrillary tangles), hallmarks of AD-like neurodegeneration. In addition, nearly two-thirds of AD patients are female, which

strongly suggests a role for the post-menopausal loss of the female sex hormone, estrogen, in the pathogenic events associated with AD. Estrogen is known to diminish neurodegenerative processes in a variety of animal models. A reduction in estrogen levels following menopause has also been associated with increased risk of diabetes and inflammation, thus necessitating exploration of the neurodegenerative potential of these conditions in a female animal model. Using a combination of a high-sucrose diet (20% of the drinking water) with systemic intraperitoneal LPS injections (0.1 mg/kg; 1x/month over 3 months) over seven months in estrous female wild-type mice (C57Bl/6; n=10/group), we demonstrated a protective rather than deleterious effect of LPS on hS-induced pathology. Results from our hS group confirmed that a high-sucrose diet is a suitable model of neurodegeneration, as evidenced by exaggerated fecal glucocorticoid expression, spatial learning deficits (Barnes maze), irregularities within the insulin pathway, and increased β-amyloid production and Tau phosphorylation. Interestingly, while LPS had little to no effect in isolation, it exerted a protective influence when added to animals sustained on a high-sucrose diet. Corticosterone homeostasis, Aβ and pTau levels, and insulin pathway second messenger expression were all rescued following addition of LPS. This effect may have been due to the chosen dose, as low-doses of LPS have been shown to attenuate the inflammatory response mounted to subsequent inflammatory insults. In summation, the work presented supports a protective role for low-dose inflammation against high-sucrose diet-induced neurodegeneration in estrous female mice. Future work comparing reproductively normal males and females to ovariectomized females would contribute to our understanding of the role of estrogen in the interaction between inflammation and dietary stress.

Disclosures: A.G. Pacholko: None. **L.K. Bekar:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.19/C46

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CONACYT 332999

Title: The role of IL-6 and glial response in neurotoxicity mediated by amyloid beta oligomers

Authors: *D. TORAL-RIOS[1], B. FLORAN-GARDUÑO[1], V. CAMPOS-PEÑA[2];
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[2]INSTITUTO NACIONAL DE NEUROLOGIA Y NEUROCIRUGIA, MEXICO CITY, Mexico

Abstract: For years, Amyloid beta (Ab) aggregates have been related to neurotoxicity and neuroinflammation in Alzheimer’s disease. A critical point for neuronal survival to withstand Ab insult is to preserve the balance between proinflammatory and anti-inflammatory responses in

the microenvironment. Several molecules secreted by glial cells are involved in this balance; some of them are the IL6 cytokine and the kynurenine pathway metabolites. In this sense, Ab could alter the KP metabolites production, such as Kynurenic Acid (KYNA) and Quinolinic Acid; both of them have important roles in neurotoxicity and neuroinflammation. The principal aim of this study was to elucidate if Ab could impair KP metabolites production and impact directly in the inflammatory response favoring neurodegeneration. For this purpose, we performed an intrahippocampal injection of Ab oligomers in rats and evaluated cellular and molecular responses in acute and chronic stages after the stereotaxic surgery. First, we found a strong correlation between glial activation and neurodegeneration. Furthermore, we realized that this effect could be related to the IL6 signaling pathway activation in glial cells probably mediated by an increased expression of Indoleamine-2,3-dioxygenase (IDO) and the posterior increase of KYNA synthesis.

Disclosures: D. Toral-rios: None. **B. Floran-garduño:** None. **V. Campos-peña:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.20/C47

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH RF1 AG058081
NIH RF1 AG056976
NIH R21 AG056025
College of Pharmacy, Academic Health Center of the University of Minnesota

Title: Role of triggering receptor expressed in myeloid cells 2 (TREM2) in aging

Authors: *W. QU[1], A. GRAM[2], L. LI[2,1];
[1]Neurosci., [2]Exptl. and Clin. Pharmacol., Univ. of Minnesota, Minneapolis, MN

Abstract: Human genetic studies have shown that triggering receptor expressed in myeloid cells 2 (TREM2) loss of function leads to elevated risks of developing late-onset Alzheimer’s disease (AD). TREM2 is expressed by microglia in the brain and modulates microglial phagocytosis and inflammatory responses. To recapitulate TREM2 loss of function in a mouse model, *Trem2*-/- (KO) mice were generated and tested for cognitive function. It has been shown that at six months of age, *Trem2* deficiency does not alter cognitive performances or learning and memory function. At twelve months of age, TREM2 KO mice show a trend towards but not statistically significant deficits in learning and memory. These findings suggest that the effects of TREM2 deficiency on learning and memory may be age-dependent. We hypothesized that TREM2 deficiency and aging act synergistically to impair cognitive function. To test this hypothesis,

TREM2 KO and wild-type (WT) mice at the age of six and eighteen months, respectively, are assessed for cognitive function by a battery of neurobehavioral tests, including the open field, elevated plus maze, and Morris water maze tests. In addition, electrophysiological experiments for hippocampal long-term potentiation (LTP) were conducted to evaluate synaptic plasticity in these TREM2 KO and WT mice. In the present study, both male and female mice were included and the experiments were conducted blind with respect to the knowledge of genotype. Consistent with previous studies, our preliminary results showed that the six-month-old TREM2 KO mice only showed a trend of impairment in cognitive function and displayed normal hippocampal LTP. Experiments are underway with the eighteen-month-old group of TREM2 KO and WT mice. Results from this study are expected to shed lights on the roles of TREM2 in aging and shaping neuronal functions and provide novel insights into the pathogenesis of AD.

Disclosures: W. Qu: None. **A. Gram:** None. **L. Li:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.21/C48

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant, 1R01AG057555
NIH Training Grant, 5T32HL135465-02

Title: Exploring adverse neuroinflammation for Alzheimer’s disease through prostaglandin D2 signaling

Authors: *C. H. WALLACE[1,4], G. OLIVEROS[1], R. SHRESTHA[1], P. ROCKWELL[1], L. XIE[2], P. SERRANO[3], M. FIGUEIREDO-PEREIRA[1];
[1]Biol. Sci., [2]Computer Sci., [3]Psychology, City Univ. of New York, Hunter Col., New York, NY; [4]Biochem. PhD Program, Grad. Ctr., New York, NY

Abstract: Non-resolving neuroinflammation plays a central role in Alzheimer’s disease (AD) and in accelerating AD pathology. Many studies link neuroinflammation to precede AD along with continuing during AD pathology. Our studies focus on a pathway of inflammation, the cyclooxygenase (COX) pathway, which has been explored for AD therapy, but requires further investigation. COX-2 is induced in AD and negatively impacts neuronal function. The COX pathway is required for the generation of prostaglandins (PGs), which are bioactive signaling lipids responsible for processes such as inflammation. Prostaglandin signaling is implicated in AD. Our goal is to elucidate the role of prostaglandin D2 (PGD2) signaling in AD. PGD2 is heavily studied in diseases with airway inflammation but is poorly understood in AD. Our hypothesis is that attenuating neuroinflammation in pre or early stages of AD by targeting PGD2

signaling, will slow down pathology. We focus on PGD2 signaling in conjunction with microgliosis known to occur in AD. PGD2 is the most abundant prostaglandin in the brain and is the one that increases most under pathological conditions. DP2 receptor activation by PGD2 leads to a decrease in cAMP and an increase in calcium mobilization, both of which can lead to neuronal damage. In fact, *in vitro* studies show adverse outcomes when treating cells with DP2 agonists. In our studies we analyzed the expression of PGD2 receptors and microgliosis in wild type rats, and TG-F344-AD (TG-AD) rats. TG-AD rats express human "Swedish" amyloid precursor protein (APPsw) and Δ exon 9 presenilin-1 (PS1ΔE9) driven by the prion promoter. TG-AD rats exhibit AD pathology including cerebral amyloidosis, tauopathy, gliosis, neuronal, and cognitive deficits are detected as early as 9 months of age. Our behavioral Active Place Avoidance data detected significant deficits in 9- and 11-month male TG-AD rats with outcome measures such as Maximum Avoidance Time and Latency, supporting hippocampal dysfunction. Changes in PGD2 receptor expression and gliosis were assessed by immunohistochemistry in the rat brains at pre-pathology (4 months of age) and when signs of neuroinflammation are significant (11 months of age). Our *in vivo* results demonstrate DP1 expression in microglia and DP2 expression in neurons. We also analyzed the levels of PGD2 in 4 month and 11 month WT and TG-AD rats. Our studies provide insights for the development of therapeutics that target PGD2 signaling to treat AD.

Disclosures: C.H. Wallace: None. **G. Oliveros:** None. **R. Shrestha:** None. **P. Rockwell:** None. **L. Xie:** None. **P. Serrano:** None. **M. Figueiredo-Pereira:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.22/C49

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: the Cure Alzheimer's Fund
BrightFocus Foundation Postdoctoral Fellowship Awards
the Edward H. Levi Fund
Open Philanthropy Project and Good Ventures Foundation

Title: Early life perturbation of the gut microbiome (short-term antibiotic) results in a sex-specific reduction of brain amyloidosis

Authors: H. B. DODIYA[1], ***J. XIA**[1], C. ZHANG[2], P. PATEL[3], X. ZHANG[1], M. J. SCHIPMA[3], R. E. TANZI[2], J. A. GILBERT[4], S. SISODIA[1];
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Abstract: Background: In continuation of our previous correlation studies (Minter M 2016, 2017), recently our group established a causal relation demonstrating long-term antibiotic (ABX)-mediated microbiome perturbations reducing cerebral Aβ amyloidosis and altered microglial phenotypes in the APPPS1-21 mouse model (Dodiya HB 2019). One limitation of this study is that (to prove causation) fecal microbiota transplantation (FMT) was performed simultaneously with diluted ABX in everyday drinking water. It is plausible that diluted ABX could impact the FMT efficiency that affects our measures of amyloidosis and microglia. To address this concern, we performed the present study evaluating short-term ABX microbiome perturbations and FMT transplantations in APPPS1-21 mice.
Method: Pups receiving ABX were gavaged with a cocktail of Kanamycin, Gentamicin, Colistin, Metronidazole, and Vancomycin in water from post-natal day (P)14 to P21. Control mice received water gavage. In addition, ABX+FMT (male mice only) group received fecal transplantation from control male mice. Mice were sacrificed at the age of 9 weeks and histopathology, microglia phenotype, brain transcriptome, peripheral cytokines and gut microbiota profiles were evaluated.
Results: Similar to our published results from $APP_{SWE}/PS1_{DE9}$ (Minter M 2017), histopathology and microscopic analysis showed significantly lower Aβ pathology in male APPPS1-21 mice with ABX treatment. Female APPPS1-21 mice showed no significant changes in amyloidosis. Importantly, ABX+FMT male mice showed complete restoration of brain amyloid pathology. These results were also confirmed using MSD analysis of insoluble Aβ40 and Aβ42 levels. RNA sequencing of total cortical RNA exhibited similar sex-specific effects. Specifically, DESeq analysis showed 942 altered genes in male mice while no changes in female mice with ABX treatment. As expected, FMT treatment in ABX-treated male mice restored this transcriptome profile similar to control mice showing only 76 altered genes. GO term enrichment analysis of biological process showed significantly different gliogenesis and microglia development pathways in ABX-treated male mice only. Further analysis is underway.
Conclusion: All together, early life microbiome perturbation using short-term ABX alters amyloidosis in a sex-specific manner. Data from the current study addresses concerns raised in our previous studies and strengthens the role of microbiota-microglia axis in AD pathogenesis.

Disclosures: H.B. Dodiya: None. **J. Xia:** None. **C. Zhang:** None. **P. Patel:** None. **X. Zhang:** None. **M.J. Schipma:** None. **R.E. Tanzi:** None. **J.A. Gilbert:** None. **S. Sisodia:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.23/C50

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH 5R01AG048993

NIH 5P20GM113123

Title: The effect of Alzheimer's disease associated mutations in APP on the progression of colorectal cancer induced by AOM/DSS in a mouse model

Authors: *M. SOHRABI, C. COMBS;
Biomed. Sci., Univ. of North Dakota, Grand Forks, ND

Abstract: Amyloid precursor protein (APP) is proteolyzed into specific fragments during its normal turnover in neurons. Although one product of APP metabolism is the Aβ peptide associated with Alzheimer's disease, there are several proteolytic products that are generated. In addition, APP is expressed by many cell types throughout the body. This suggests that the parent protein and/or its metabolites may regulate additional events beyond accumulation of extracellular Aβ peptide plaques in the brain. For example, we previously demonstrated in both mice and humans that APP is robustly expressed in intestinal epithelial cells which are capable of generating the Aβ peptide commonly associated with brain accumulation in Alzheimer's disease. Others have demonstrated that an additional fragment of APP, secreted APPα/β (sAPP α/β), is capable of regulating cell line proliferation *in vitro*. Based upon this data, we hypothesized that expression and proteolytic processing of APP may regulate colon cancer progression. To test this idea, we first verified robust expression of APP in human colorectal cancer (CRC) epithelial cells from various stage tumors. For further investigation, we utilized a common inflammation-associated colon cancer model in C57BL/6 wild type control, $APP^{-/-}$, and $App^{NL\text{-}G\text{-}F}$ mice to determine whether expression of APP or preferentially increased metabolism of APP into Aβ and sAPPβ fragments might influence the progression of disease. Both male and female mice at 5-8 months of age were treated with azoxymethane (AOM) and dextran sulfate sodium (DSS) to model human CRC. Mice were collected at the end of week 17 post-treatment and spleen weight, colon weight and length as well as tumor size and numbers were recorded. Interestingly, the male $App^{NL\text{-}G\text{-}F}$ mice demonstrated significantly larger spleen and colon weights compared to both wild type and $APP^{-/-}$ mice. This correlated with increased tumor number and size in these $App^{NL\text{-}G\text{-}F}$ mutant mice. On the other hand, female $App^{NL\text{-}G\text{-}F}$ mice had significantly smaller colon and spleen weights and developed fewer and smaller tumors than their wild type and $APP^{-/-}$ counterparts. These data demonstrated that mutations responsible for preferentially increasing metabolism of APP towards robust Aβ peptide production and accumulation in the brain during Alzheimer's disease also confer both protection against and increased risk of colon cancer progression in a sex dependent fashion. Further biochemical and histological analysis are needed to clarify the molecular mechanisms involved in these observations.

Disclosures: **M. Sohrabi:** None. **C. Combs:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.24/C51

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AG050597

Title: CSF1-R directed inhibition suppresses inflammation and plaque burden, but enhances neuritic dystrophy in a mouse model of Alzheimer's disease

Authors: *B. CASALI[1,2], E. G. REED-GEAGHAN[2], G. E. LANDRETH[3];
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Abstract: Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by extensive amyloid plaque deposits, inflammation, and cognitive decline. Microglia act primarily to provide important immune defense and perform tissue maintenance, but these functions are frequently perturbed in neurodegenerative diseases. Since microglial dysfunction has been implicated in the pathogenesis of AD, pharmacological interventions that restore microglia function and ameliorate pathology are of clinical interest. Microglia are reliant upon colony-stimulating factor receptor-1 (CSF1-R) activation for survival. Small-molecule therapeutics that inhibit CSF1-R signaling resulted in microglia death in the brain, reduced microglial activation, and enhanced neuronal survival in AD mouse models. However, depletion of microglia in a disease state may elicit deleterious side effects and potentially limit the clinical appeal for long-term CSF1-R inhibitor use. Accordingly, we tested whether administration of the highly selective CSF1-R inhibitor PLX5662 altered pathology in the 5xFAD mouse model of AD at 4 months of age. Consistent with prior studies, PLX5662 diminished, but did not fully deplete, microglia from various brain regions after approximately one month of administration. Surprisingly, we observed striking suppression of markers of inflammation and plaque burden in PLX5662-treated animals, even with greatly diminished numbers of microglia compared to control-treated animals. We also observed trends toward reductions in thioflavin-positive, dense-core plaque coverage and plaque number in these animals. While other markers of pathology were reduced with inhibitor treatment, neuritic dystrophy was paradoxically enhanced. CSF1-R targeted inhibition also suppressed expression of genes associated with homeostatic microglia—genes which may impart enhanced neuroprotection in other mouse models of AD and neurodegeneration. We also saw reduced ApoE levels in insoluble fractions of the brain, which are associated with amyloid-laden plaques. Future studies are aimed at elucidating if CSF1-R inhibition perturbs the ability of microglia to maintain plaques in an inert, thioflavin-positive form and subsequent expansion to more diffuse, neurotoxic plaques. These findings imply that

while CSF1-R inhibition ameliorates amyloid pathology, neuroprotection is compromised—most likely due to repressed microglial homeostatic genes, abrogated microglial activation and numbers, and possible changes in plaque composition. Our findings have the potential to limit clinical appeal for CSF1-R targeted therapeutics in AD.

Disclosures: B. Casali: None. **E.G. Reed-Geaghan:** None. **G.E. Landreth:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.25/C52

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG048205 to AZ
VA Merit Award I01BX002477 to AZ
NIH grant NS073670 to AZ

Title: Mast cells and neuroinflammation in Alzheimer’s disease pathogenesis

Authors: *K. DURAISAMY[1,2], G. SELVAKUMAR[1,2], M. E. AHMED[1,2], R. THANGAVEL[1,2], S. RAIKWAR[1,2], I. DUBOVA[1,2], K. PREMKUMAR[1], S. A. ZAHEER[1], S. IYER[1,2], A. ZAHEER[1,2];
[1]Neurol., Univ. of Missouri, Sch. of Med., Columbia, MO; [2]Harry S. Truman Mem. Veterans Hosp., Columbia, MO

Abstract: Neuroinflammation is one of the hallmarks of Alzheimer’s disease pathogenesis. Inflammatory cytokines and chemokines released from glial cells and immune cells are implicated in neuroinflammation, neuronal toxicity and neurodegeneration in neurodegenerative diseases such as Alzheimer’s disease (AD), Parkinson’s disease (PD) and Multiple sclerosis (MS). Mast cells are multifunctional immune and inflammatory cells that are implicated in neuroinflammation by releasing prestored and newly synthesized cytokines, chemokines and neurotoxic mediators. However, the exact mechanisms involved in this process is not clearly understood. Here, we examined mast cell-associated neuroinflammation using cultured mouse bone marrow-derived mast cells (BMMCs), mast cell-deficient (MC-KO) mice and 5XFAD mouse model of AD. We first examined mast cells in the brains of 5XFAD and wild type mice using toluidine blue staining. We found increased mast cell numbers and its activation in the brains of 5XFAD mice as compared to wild type control mice. Protease activated receptor-2 (PAR-2), a receptor for mast cell derived and other proteases, and proinflammatory CD36 expressions are increased in the brains of 5XFAD mice as compared to wild type mice and mast cell deficient mice (MC-KO). Moreover, BMMCs incubated with AD pathogenesis-associated beta amyloid 1-42 (Aβ1-42) showed increased expression of CD36 as well as the release of

chemokine (C-C motif) ligand 2 (CCL2) *in vitro.* We conclude that mast cells augment neuroinflammation and neurodegeneration in neurodegenerative diseases including AD.

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Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.26/C53

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH

Title: Down regulation of GMF inactivates NLRP3-inflammasome and improves neurobehavioural functions in 5XFAD mice

Authors: *M. AHMED[1,2], R. THANGAVEL[1,2], G. SELVAKUMAR[1,2], D. KEMPURAJ[1,2], I. DUBOVA[1,2], S. RAIKWAR[1,2], S. ZAHEER[1], S. IYER[1,2], A. ZAHEER[1,2];
[1]Neurol., Univ. of Missouri, Columbia, MO; [2]Harry S. Truman Mem. Veterans Hosp., Columbia, MO

Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by the presence of intracellular neurofibrillary tangles (NFTs) containing hyperphosphorylated tau, and the extracellular deposition of amyloid plaques (APs) with misfolded amyloid (Aβ) peptide. Glia maturation factor (GMF), a highly conserved pro-inflammatory protein was discovered in our laboratory, is a highly conserved protein predominantly localizes in glial cells and some neuronal cells has been shown to neuro inflammation and neurodegeneration in AD. Previously we have shown that inflammatory reaction promoted by the NLRP3-Caspase-1 inflammasome pathway triggers accumulation of Aβ which is amplified and regulated by GMF in human AD brain. We hypothesized that downregulation of GMF using GMF-specific shRNA could restrict the expression of NLRP3-inflammasome components. GMF-shRNA was injected bilaterally in 5XFAD mice brain to silence the GMF expression. Following 4 weeks of bilateral intracerebroventricular injection of GMF-shRNA, we observed improvement in cognition and reduction in the expression and co-localization of NLRP3 with Aβ, caspase-1 and product of inflammsosome activation IL-1β and IL-18 in the cortex of 9-month old 5XFAD mice brain. Furthermore, our data suggest that downregulation of GMF by using GMF-specific shRNA could be promising strategy to target neuro-inflammation and neurodegeneration in AD.

Disclosures: **M. Ahmed:** None. **R. Thangavel:** None. **G. Selvakumar:** None. **D. Kempuraj:** None. **I. Dubova:** None. **S. Raikwar:** None. **S. Zaheer:** None. **S. Iyer:** None. **A. Zaheer:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

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Program #/Poster #: 558.27/C54

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: The Swedish Research Council
The Swedish Alzheimer Foundation

Title: Alterations in free fatty acids and phospholipids in an APP knock-in mouse model for Alzheimer's disease

Authors: C. EMRE[1], B. JUN[2], P. NILSSON[1], N. G. BAZAN[2], *M. SCHULTZBERG[1]; [1]Karolinska Institutet, Stockholm, Sweden; [2]Neurosci. Ctr., Louisiana State Univ. Hlth. Sci. Ctr., New Orleans, LA

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder and its clinical symptoms are reflections of neuropathological changes in the brain, including aggregates of hyper-phosphorylated tau protein (p-Tau) in neurofibrillary tangles (NFTs) and extracellular deposits of amyloid β (Aβ) peptide in amyloid plaques. Inflammation is part of the neuropathology in AD involving microglial activation, astrocyte proliferation and increased levels of pro-inflammatory factors. Presence of Aβ induces an inflammatory response as outcome of a protective host response and, conversely, activation of glia and secretion of pro-inflammatory cytokines stimulate the production of Aβ resulting in a vicious circle. Normally, inflammation is terminated by an active process called resolution to decrease pro-inflammatory factors, increase phagocytosis of cell debris, restore the tissue and regain homeostasis. These mechanisms are orchestrated by specialized pro-resolving mediators (SPMs) derived from omega-3 and -6 fatty acids (FAs) including docosahexaenoic acid (DHA) and arachidonic acid (AA). Neuroprotective effects of SPMs in *in vitro* studies resulted in downregulation of pro-inflammatory markers, upregulation of neuroprotective factors and stimulation of $A\beta_{42}$ phagocytosis. In order to further understand the role of dysfunction of resolution for AD development and to identify novel treatment target(s) we investigate the correlation between resolution of inflammation and AD neuropathology using an *App* knock-in AD mouse model. This model is free of APP overexpression and harbours high $A\beta_{42}$ levels due to the Swedish, the Beyreuther and the arctic mutations, and exhibits robust neuroinflammation including microglial activation and astrocytosis. This exploratory study involves characterization of bioactive lipid mediators (LMs) and related molecules, investigating their structure and stereochemistry in extracts of the hippocampus, cortex, cerebellum and liver from the *App* knock-in mouse model and wild-type

(WT) mice. Using liquid chromatography-tandem mass spectrometry (LC-MS/MS), SPMs (maresin 1, NPD1, RvD1 and RvE1), monohydroxy-derivatives of DHA and AA (*e.g.* 14-HDHA, 17-HDHA, and PGD2, PGE2), and elongated DHAs (very long-chain polyunsaturated FAs, VLC-FAs), were analysed at different ages (2, 4, 8 and 18 months) of the mice. The data show differential distribution of LMs within the brain of the *App* knock-in mice, and that the levels change with age and differ between these mice and WT mice. The results support a dysfunctional resolution pathway in AD, and the potential for pro-resolving LMs as treatment strategy.

Disclosures: C. Emre: None. **P. Nilsson:** None. **N.G. Bazan:** None. **M. Schultzberg:** None. **B. Jun:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.28/C55

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: DGAPA IN 221417 to S.R-A

Title: Effect of repeated exposure at low ozone doses on the expression of inflammatory cytosines in hippocampi of rats

Authors: *A. E. RODRÍGUEZ-MARTÍNEZ[1], M. VALDÉS-FUENTES[2], A. MIRANDA-MARTÍNEZ[1], M. CRUZ-REYES[1], A. LÓPEZ-VALDEZ[2], E. HERNÁNDEZ-OROZCO[1], S. RIVAS-ARANCIBIA[1];
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Abstract: Repeated exposure to environmental pollution caused by ozone induces a state of chronic oxidative stress in the body. Which causes loss of regulation of the inflammatory response. Both factors, the state of oxidative stress and the dysregulation of the inflammatory response contributing to the maintenance of the neurodegenerative process. The objective of this work was to evaluate the changes in cytokines and their correlation with the inducible synthase of nitric oxide (iNOS), as well as with the manganese superoxide dismutase (MnSOD) in a model of environmental pollution by ozone. For this purpose, 72 rats housed individually and with free access to water and food were used. Animal care and handling were in accordance with the Norma Official Mexicana NOM-062-ZOO-1999 and approved by the Institutional Committee for the Care and the Use of Laboratory Animals (CICUAL), of the Medicine School at the Universidad Nacional Autónoma de México. Each group received one of the following

treatments: group 1) exposed to ozone-free air. Group 2, 3, 4. 5 and 6 exposed to ozone for 7, 15, 30, 60 and 90 days respectively. The ozone dose used was 0.25 ppm for 4 hours daily. Once the treatment was finished, the groups were processed for RT-PCR techniques, Western Blot, and spectrophotometry for the following markers: IL-17, IL-1β, FoxP3 transcription factor, MnSOD, iNOS. The results obtained show a significant increase of mRNA for IL-17 at 60 and 90 days ($P < 0.05$), IL-1β at 7 ($P < 0.05$) and FoxP3 at 30 days ($P < 0.05$). Both IL-17, IL-1β, iNOS increased at 60 and 90 days ($P < 0.05$), FoxP3 showed an increase at 30 days of ozone exposure ($P < 0.05$). With the results obtained we can conclude that repeated exposure to low doses of ozone, similar to days of high contamination, causes alterations in both the inflammatory response and the antioxidant response similar to what occurs in chronic degenerative diseases, as in the Alzheimer's disease.

Disclosures: **A.E. Rodríguez-Martínez:** None. **M. Valdés-Fuentes:** None. **A. Miranda-Martínez:** None. **M. Cruz-Reyes:** None. **A. López-Valdez:** None. **E. Hernández-Orozco:** None. **S. Rivas-Arancibia:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.29/C56

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIGMS P20 COBRE Award (5P20GM109025)

Title: Examining alterations of $GABA_B$ receptors in hyperglycemia and Alzheimer's disease related pathology

Authors: *A. A. ORTIZ, A. M. SALAZAR, A. M. LEISGANG, A. PLATT, M. PEREZ, C. GUESE, J. W. KINNEY;
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Abstract: Alzheimer’s disease (AD) is a neurodegenerative disorder that is characterized by progressive learning and memory deficits, neuronal loss, and cognitive impairments. The two core pathological hallmarks of AD are 1) senile plaques, composed of accumulated amyloid beta (Aβ) proteins and 2) neurofibrillary tangles, composed of accumulated hyperphosphorylated tau (ptau). A third characteristic that has emerged is a chronic inflammatory response within the brain. Several studies have demonstrated that chronic neuroinflammation exacerbates Aβ and ptau pathology. The exact cause of AD remains unknown; however, several risk factors exist that greatly increase the likelihood of developing AD. Genetic risk factors such as ApoE and a mis-sense mutation in TREM2 have been linked to increasing the likelihood of developing AD. Non-genetic risk factors include age, cardiovascular disease, obesity, and diabetes mellitus (DM).

Individuals with DM express high levels of glucose in the vasculature (hyperglycemia). DM confers up to a 4-fold increase in risk that arises based on hyperglycemia, insulin receptor resistance, and changes in the vasculature. Furthermore, 80% of individuals with AD have (DM) or are insulin resistance. We have previously demonstrated that intermittent administration of streptozotocin (STZ), induces sustained hyperglycemia in an otherwise healthy animal (Murtishaw et al. poster 44.25/N12 SFN 2017). STZ mice exhibit learning and memory deficits, increased ptau, and neuroinflammation. In AD, there is a general loss of γ-aminobutyric acid (GABA), thus, in the present study we investigated these same measures in a novel $GABA_B$ knockout mouse model of male and female mice over a year old since. Our data indicate altered fasting blood glucose, and differences between males and females in response to the STZ administration.

Disclosures: A.A. Ortiz: None. **A.M. Salazar:** None. **A.M. Leisgang:** None. **A. Platt:** None. **M. Perez:** None. **C. Guese:** None. **J.W. Kinney:** None.

Poster

558. Alzheimer's Disease: Neuroinflammation and Immune Actions

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 558.30/C57

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG048205
Veterans Affairs Merit Award I01BX002477

Title: Upregulation of GMF and TREM2 expression in the amyloid plaques of 5XFAD mouse model of Alzheimer’s disease

Authors: *R. THANGAVEL[1,2], M. E. AHMED[1,2], D. SAEED[1], K. WU[1], I. DUBOVA[1], S. A. SHAMIM[1], G. P. SELVAKUMAR[1], K. DURAISAMY[1,2], S. P. RAIKWAR[1,2], S. ZAHEER[1], S. S. IYER[1,2], A. ZAHEER[1,2];
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Abstract: Alzheimer’s disease (AD) is the most common type of dementia. AD is a chronic neurodegenerative disorder with cognitive impairment among elderly people. Neuroinflammation and neurodegeneration play a key role in the pathogenesis of AD. The two major neuropathological features of AD are amyloid plaques (APs) made up of β-amyloid peptide and neurofibrillary tangles of hyperphosphorylated tau protein. We previously demonstrated the increased expression of glia maturation factor (GMF) in different regions of human AD brain. Triggering receptor expressed in myeloid cells 2 (TREM2) strongly increases the risk of developing AD pathology and confirming the role of microglia in AD. Here, we

studied the expression of TREM2 and GMF and their association with APs in 5XFAD mice brains. We used immunohistochemical, single and double immunofluorescence labeling to confirm the co-localization of TREM2 and GMF with APs. We found that TREM2 was strongly expressed in activated microglia, and was seen to be closely associated with APs. Results revealed an increased expression and co-association of GMF and TREM2 in 5XFAD mice brain compared to non-transgenic mice brain. TREM2 is upregulated and associated with GMF in the vicinity of APs. Additionally, an increased TREM2 immunoreactivity was found to correlate with strong immunolabeling of ionized calcium-binding adaptor molecule-1 (Iba-1), an activated microglial marker, along with anti-Aβ(6E10) labeled APs. Different brain regions with increased APs were associated with TREM2-immunoreactive microglia as well as GMF in 5XFAD mice brain. Furthermore, immunoblot analysis also revealed an upregulation of GMF and TREM2 proteins in 5XFAD transgenic compared with nontransgenic mice. These findings suggest that the increased expression and co-localization of GMF, TREM2 and Iba-1 within APs exacerbates neuroinflammation and neurodegeneration and together may be contributing to the pathogenesis of AD. In this study, we outlined our understanding of the involvement of GMF and TREM2 in AD development that may open new therapeutic strategies specifically targeting the microglia to control AD pathogenesis.

Disclosures: R. Thangavel: None. **M.E. Ahmed:** None. **D. Saeed:** None. **K. Wu:** None. **I. Dubova:** None. **S.A. Shamim:** None. **G.P. Selvakumar:** None. **K. Duraisamy:** None. **S.P. Raikwar:** None. **S. Zaheer:** None. **S.S. Iyer:** None. **A. Zaheer:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.01/C58

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R44ES026268-02
NIH Grant R44ES026268-02S1

Title: Hyperactivity of hiPSC-glutamatergic neurons in response to $PM_{2.5}$ particles: A potential mechanism linking air pollution to increased incidence of Alzheimer's disease

Authors: *K. L. GORDON[1], C. HANDLEY[1], R. C. B. BASA[1], S. ANKAM[1], Y. HUANG[2], J. ZHENG[2], W. DING[3], J. H. PRICE[1,4], P. MCDONOUGH[1];
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Abstract: Recent epidemiology studies link air pollution, notably particulate matter of 2.5 μm or less in diameter ($PM_{2.5}$), to increased Alzheimer’s disease (AD) but the mechanisms responsible

for this have not yet been fully elucidated. Air pollution particles have been found within the brain and it is possible that they enter the brain along tracts of olfactory neurons from nasal cavities to the olfactory bulb. Consistent with this hypothesis, loss of olfactory function is a common prodromal symptom of AD, and AD-related pathology is commonly observed in the olfactory bulb, post-mortem. To investigate potential dysregulation of CNS neuron function by $PM_{2.5}$, we seeded excitatory glutamatergic neurons derived from human induced pluripotent stem cells (hiPSC-Gluts) into 384-well plates, and exposed the neurons to $PM_{2.5}$ (at doses of 0.625, 12.5, 25, 50, and 100 µg/ml) for 4 or 24 hrs. We then loaded the cells with Rhod-4 (an indicator of intracellular calcium) and monitored neuronal activity via kinetic image cytometry, a method featuring an automated digital microscope workstation, collection of video movies (20 seconds at 4 frames per second) from each well, and analysis of the videos on a cell-by-cell basis to quantify Rhod-4 fluorescence. Exposure to $PM_{2.5}$ increased calcium activity in a dose- and time-responsive manner (with a 2.4-fold increase in integrated activity above baseline at 100 µg/ml, at 24 hr). This suggests that $PM_{2.5}$ may increase calcium transients in the neurons, a stress that may correspond to hyperactivity and excitotoxicity, and ultimately, increased mortality of the neurons. Development of a high throughput assay system to test air pollution components for neurotoxic effects will enable research into the mechanisms that link air pollution to AD, and spur the search for agents that may protect against this neurodegenerative stimulus.

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Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.02/C59

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Ablation of $p75^{NTR}$ signaling strengthens interaction of gamma and theta rhythms and counteracts amyloid beta induced degradation of neuronal dynamics in mouse hippocampus *in vitro*

Authors: *Y. ANDRADE-TALAVERA, H. BALLEZA-TAPIA, P. DOLZ-GAITÓN, A. FISAHN;
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Abstract: Gamma and theta oscillations have been associated with hippocampus-dependent cognitive tasks. These two brain rhythms are known to coexist and their interaction results in a cross-frequency coupling than can affect the features of gamma oscillations. The hippocampal theta rhythm depends, at least partially, on the cholinergic and GABAergic inputs from the

medial septum-diagonal band of Broca (MS/DB). MS/DB cholinergic neurons undergo a moderate degeneration during aging, likely due to an attenuation of the neurotrophic signalling. Among the receptors involved in the neurotrophic response, $p75^{NTR}$ is of special importance for the viability of these neurons. Also, they are among the few cell types in the brain that maintain high levels of expression of $p75^{NTR}$ throughout adulthood.
The role of the $p75^{NTR}$ receptor is still puzzling mediating both pro-apototic and survival signaling pathways. To test whether $p75^{NTR}$ plays a role for the MS/DB cholinergic projection onto hippocampus, particularly for the neuronal rhythms that are associated with its function, we performed local field recordings on $p75^{NTR}$ knockout ($p75^{-/-}$) mouse brain slices in presence of the muscarinic agonist carbachol. We found that gamma power and rhythmicity are increased in $p75^{-/-}$ mice. Furthermore, gamma activity is more phase-locked to the underlying theta phase compared to WT mice. We also found an increase in the amplitude-modulation of the gamma rhythm within the theta-frequency band. On the cellular level we found that fast-spiking interneurons (FSNs) fire more synchronized to a preferred gamma phase in the absence of $p75^{NTR}$ signalling. In addition, we found that the excitatory input onto FSN displayed an oscillatory pattern in the gamma range in accordance with the ongoing gamma oscillations in both mouse strains. However, the rhythmicity of the EPSCs input in the $p75^{-/-}$ strain was higher. Moreover, by analyzing the relationship between the field oscillations and the EPSCs we found a higher similarity in the $p75^{-/-}$ oscillatory patterns compared to $p75^{+/+}$. Notably, the ablation of $p75^{NTR}$ counteracted the Aβ-induced degradation of gamma oscillations and its relation with the underlying theta rhythm.
Our results show that the lack of $p75^{NTR}$signalling strengthens cholinergic modulation of hippocampal gamma rhythms pointing towards the involvement of this receptor in the downregulation of neuronal network dynamics during cognitive-relevant rhythmic activity in hippocampus. Functional data provided here suggest $p75^{NTR}$ as a suitable target in the search of efficacious treatments to counteract the loss of function observed in amyloid-driven pathologies such as Alzheimer´s Disease.

Disclosures: **Y. Andrade-Talavera:** None. **H. Balleza-Tapia:** None. **P. Dolz-Gaitón:** None. **A. Fisahn:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.03/C60

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01 NS108808
NC TraCS ECBR004
UNC Department of Neurology

Title: Early network dysfunction in P301S tau transgenic neurons cultured on microelectrode arrays

Authors: *R. B. MEEKER, **A. DOMBROSKI**, T. DEMARSE, B. HARRIS;
Neurol., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Inflammation occurs early in the pathogenesis of Alzheimer's Disease (AD) in mouse models and is believed to contribute to disease progression. When in the presence of pathological entities such as oligomeric amyloid beta ($A\beta_o$), microglia and macrophages release factors that disrupt neuronal calcium homeostasis and induce cytoskeletal changes including modifications of the microtubule associated protein Tau. These changes are thought to increase the sensitivity of neurons to excitatory stimuli, leading to hyperactivity and further disease progression. However, the impact of this hyperactivity on neural communication within networks and the role of pathological modifications of Tau are not well understood. To better understand the functional impact of inflammation and early Tau modifications, we challenged primary wild type (WT) and P301S/PS19 Tau-transgenic mouse neurons with medium from microglia treated with Aβ oligomers (Aβ-MgCM) to mimic *in vivo* inflammation. The resulting electrophysiological and calcium changes under basal and inflammatory conditions were collected from microelectrode arrays (MEAs) to assess the effects of inflammation and aberrant Tau on neural network function. Under basal conditions, the PS19 neurons showed increased synchronous calcium signaling relative to WT neurons. Electrophysiologically, the PS19 neurons typically had a higher rate of action potentials within bursts, but exhibited shorter burst durations. We also found that PS19 networks exhibited lower node degrees and higher path lengths, indicating poor functional connectivity. Under inflammatory conditions, both the WT and PS19 cultures displayed network disruption in response to the conditioned medium. The PS19 neurons responded with a smaller increase in mean firing rate but an increased frequency within bursts suggesting a hyperactive phenotype within more limited networks. The aberrant development of neural network activity in the PS19 neurons and the altered responses to inflammation suggest that pre-tangle forms of Tau mediate neural dysfunction that may contribute to cognitive decline. This early dysfunction may provide opportunities for the development of new therapeutic strategies that slow the progression of AD and other neurodegenerative diseases.

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Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.04/C61

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: FNRS-FRS Fria Grant

Title: Exploring the impact of hyperphosphorylated tau on neuronal network connectivity

Authors: *L. RIS[1], P. VERSTRAELEN[2], G. GARCIA-DIAZ BARRIGA[2], A. VILLERS[1], B. LEROY[1], R. WATTIEZ[1], W. DE VOS[2], M. WAUTERS[1];
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Abstract: In recent years, it has become clear that small species of Tau protein have the propensity to induce synaptic toxicity in neurons before larger aggregates appear. Moreover, it has been shown that Tau protein can be released in the extracellular space while its role and potential toxicity in this compartment is unknown. This may have important implications for the pathophysiology of tauopathies including Alzheimer's disease. To address the need for pathophysiologically relevant tau preparations, we have optimised a Multiple Reaction Monitoring (MRM)-based purification of tau proteins in mammalian cells. This approach was used to extract normal (Tau) and hyperphosphorylated (P-Tau) isoforms with sufficiently high concentration. While we are currently analysing the phosphorylation and O-glycosylation sites by mass spectrometry, we have already confirmed increased Serine 396 phosphorylation in P-Tau extracts compared to Tau using SDS PAGE with phospho-specific antibodies. Furthermore, native gel electrophoresis confirmed that the proteins remain in a soluble state. To study the toxicity of extracellular Tau and P-Tau, we incubated cortical cultures with the extracted tau proteins and immunolabelled the exogenously administered proteins by targeting their TEV-site. Next, we asked whether (one of) the proteins exerted a synaptotoxic effect. To this end, we quantified the synapse density after an acute exposure to one of two concentrations of tau protein (Tau or P-Tau) in immunostained cultures and we quantified functional connectivity in the neuronal networks using electrophysiology and a previously optimised live cell imaging approach based on a genetically encoded calcium reporter (GCAMP6, Verstraelen et al, Front Neurosci. 2018). We found that the application of physiologically relevant amount of P-Tau (60 ng) induced modifications in synaptic connections from 1h to 6h after the addition of the protein. This effect, absent when the protein is not hyperphosphorylated (Tau), disappeared after 24h when the protein is internalized and seems to be degraded in lysosomes. This result suggests that the release of P-Tau by neurons could impact synaptic function and neuronal processing.
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Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.05/C62

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: University Grants Commission of India
Tata Program Grant
Indian Institute of Science
Department of Biotechnology, INDIA

Title: Molecular determinants regulating the instantaneous localization of amyloid precursor protein on plasma membrane

Authors: *V. BELAPURKAR[1], A. BABU[3], S. KEDIA[1], D. KUMARAN NAIR[2];
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Abstract: Phosphatidylinositol binding clathrin assembly protein (PICALM) is a cytosolic protein involved in clathrin-mediated endocytosis and a well-known risk gene for Alzheimer's Disease. PICALM gene has been identified with SNPs through multiple genome-wide association studies across various populations. PICALM has a central role in the regulation of clathrin-mediated endocytosis and has been well characterized along with LRP-1 in transcytosis of Aβ peptides across the blood-brain barrier. However, little is known about its function at synapses and how it regulates endocytosis of Amyloid Precursor Protein (APP). Differential subcellular localization of APP has the potential to affect the production of Aβ peptides. Through endocytosis, PICALM has the potential to compartmentalize APP from the plasma membrane to intracellular endocytic organelles. Dissecting out the molecular interaction between the two proteins is important to understand the localization of APP at presynapse, postsynapse, and perisynapse. We show data for APP-PICALM interaction which is consistent with the literature. Dynamics of wild-type APP and Swedish APP on cell membrane were studied in abundance of PICALM. Which elucidated a potential role of PICALM in regulating the mobility of APP and affecting subcellular localization by internalization. To study dynamics of internalization and interaction of APP with PICALM, we designed a strategy to alter the “YENPTY” sequence present at Carboxy-terminal tail of APP. To further characterize the role of APP-PICALM interaction and its implication on synapses, we performed a detailed analysis of compartmentalization of APP and PICALM in presynapse, postsynapse and perisynapse of rat hippocampal neurons using conventional and super-resolution microscopy.

Disclosures: V. Belapurkar: None. **A. Babu:** None. **S. Kedia:** None. **D. Kumaran Nair:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.06/C63

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: FONDECYT 1161078
FONDECYT 1170252

Title: Neuroprotective effects of elephant black garlic extract against beta amyloid peptide toxicity on hippocampal slices

Authors: *J. A. GAVILAN[1], J. D. PANES[1], P. A. GODOY[1], T. B. SILVA-GRECCHI[1], G. B. SALGADO[1], N. MUÑOZ[1], O. RAMIREZ[1], P. VARAS[2], C. PEREZ[3], G. YEVENES[1], J. FUENTEALBA[1];
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Abstract: It is widely known that the toxic effects of the beta-amyloid soluble oligomers (SO-Aβ) are central elements on the pathogenesis of the Alzheimer Disease (AD). In our group, it has been demonstrated that SO-Aβ have the capacity to induce the pore formation in the plasma membrane, this produce an influx of calcium and leakage of big molecules, like ATP. Mainly, the cytosolic Ca^{2+} overload, induce mitochondrial dysfunction and synaptic failure, leading to cellular death. Several evidence suggests that common black garlic (*Allium sativum*) have a beneficial effects on the Aβ toxicity, and these effects are proposed could be mediated by S-allyl-cysteine (SAC), the main organosulfur metabolite present in the garlic. *Allium ampeloprasum* is an endemic species from the Chiloé Island, located in the Northwestern Patagonia of Chile, the study of the Elephant Black Garlic Extract (BG) has recently started in our lab, and the chemical composition and the neuromodulatory properties are the main objective of this research. BG (10 µg/mL) induce a neuroprotective effect evaluated by viability assays (MTT), recovery the cell viability about 52±5% on PC12 cell treated with Aβ during 24h. Additionally, the synaptic activity measured by Ca^{2+} oscillation on hippocampal neurons, show that BG recovered the frequency of Ca^{2+} oscillations of the neurons previously treated with Aβ during 24 h, about in a 54±6%. To corroborate these effects on more physiological model, we used hippocampal slices to tests the effects of BG on slices treated acutely (3h) with Aβ (2.5 µM). We observed that the slice viability was maintained near to control conditions when the BG was co-incubated with Aβ (Aβ: 53±5%; Aβ+BG: 113±6%). In parallel, the mitochondrial functionality was measured on hippocampal slices using JC-1 dye and fluorescence techniques. The presence of Aβ induced a strong fall in the mitochondrial potential near to 36±7%, while the co-incubation with BG maintain a potential with values near to control conditions. These last observations where correlated with changes on the key proteins related with mitochondrial dynamics in hippocampal slices [(Mfn1, Aβ: 48±7%; Aβ+BG: 79±9%) (DRP1, Aβ: 118±15%; Aβ+BG: 103±14%)]. Our result suggest that BG can induce a strong protection of the neuronal network against Aβ toxicity and could represent an interesting source of new compounds that can be useful to interfere with the physiopathology of amyloid beta peptide oligomers.

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Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

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Program #/Poster #: 559.07/C64

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH-funded Layton Aging and Alzheimer's Disease Center Pilot Project Program
Carlson College of Veterinary Medicine Pilot Project Program

Title: Early sex differences in AMPA and NMDA receptor responses in 5xFAD

Authors: E. P. SACKINGER, T. VU, A. RADKE, F. NIGUSSIE, *K. R. MAGNUSSON; Oregon State Univ., Corvallis, OR

Abstract: Alzheimer's disease (AD), the most common form of dementia, affects 10% of the population over age 65. Mutations in presenillin or amyloid precursor protein (APP) in familial AD lead to overproduction of amyloid. Changes in amyloid occur early in AD, before the onset of behavioral signs. Based on this, and early changes seen in N-methyl-D-aspartate receptors (NMDARs) in presenillin models with single mutations, we aimed to study the difference in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and NMDAR between young mice that do not yet show behavioral signs of amyloid-related degeneration and older mice that do. In 5xFAD (two presenillin and 3 APP mutations) mice that were 15-days or 4 months old, the field excitatory post synaptic potentials (fEPSPs) of the CA3 Schaffer collateral to CA1 synapses in hippocampal slices were analyzed using a MED64 multielectrode array system. Antagonists of AMPAR, GluN2A and Glun2B NMDAR subunits, and full NMDAR were applied. The mice were euthanized via transcardial perfusion of ice-cold artificial cerebrospinal fluid (aCSF) and brain slices were prepared. Slices began in regular aCSF, followed by 30μM DNQX (AMPAR antagonist). Slices were changed into 0.5mM $MgSO_4$ aCSF, 30μM DNQX & 10μM picrotoxin (γ-aminobutyric acid (GABA) receptor antagonist) solution, followed by adding 4μM Ro-25-6981 (GluN2B antagonist), 500nM PEAQX (GluN2A antagonist), then 50μM AP5 (NMDAR antagonist). After drugs equilibrated, a stimulus response study was performed and the input (fiber volley amplitude) / output (fEPSP amplitude) was analyzed. The 15-day old hemizygous 5xFAD male mice showed increased fEPSP amplitudes for the AMPARs, NMDARs, GluN2A subunits and remaining NMDARs. By 4 months old, amplitudes were reduced in comparison to the wild type (WT) mice. Female hemizygous mice, however, showed no genotypic differences at 15-days old for AMPAR fEPSPs, but the hemizygotes had lower fEPSPs per given fiber volley amplitude than the WT mice by 4 months of age. Female hemizygotes were slightly hyporesponsive at 15- days old, but there was no genotype difference at 4 months for NMDARs. GluN2A fEPSPs for the female hemizygotes were reduced from WT at both 15-days and 4 months of age and for the remaining NMDARs

there were no differences between hemizygotes and WT at 15-days or 4 months of age. This data suggests that either the disease progresses differently in females then males, e.g., glutamate receptor changes may begin earlier than 15-days of age in female mice or the early enhancements in male glutamate receptors are not related to the later reductions seen in both sexes.

Disclosures: E.P. Sackinger: None. **T. Vu:** None. **A. Radke:** None. **F. Nigussie:** None. **K.R. Magnusson:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.08/C65

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: RF1 AG006173
I01BX003527
I21 BX003807

Title: Exosomes from induced pluripotent stem cell-derived neurons of Alzheimer’s patients modulate synaptic plasticity

Authors: *S. LI[1], A. GELB[2], M. CHEN[2], D. J. SELKOE[3], W. XIA[4];
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Abstract: Alzheimer’s disease (AD) is a chronically progressive disorder that causes synaptic and metabolic dysfunction before neuronal death, and AD begins in a ‘preclinical' stage before progressing to mild cognitive impairment and memory loss. Research on molecular events occurring during preclinical and clinical stages of AD has yielded insights into early pathogenic events, including the linked roles of amyloid β-protein (Aβ) and tau proteins. The Aβ peptide is produced in the early endosomal compartment and is released via exosomes. Exosomes from the central nervous system are under investigation, with a specific focus on their components or biochemical features. Their effect on the synaptic functions remains elusive. Field excitatory postsynaptic potentials (fEPSP) were recorded in stratum radiatum of CA1 in mouse hippocampal slices, with the stimulating electrode in the Schaffer collaterals. We found that exosomes from the media of induced pluripotent stem cell (iPSC)-differentiated neurons of AD patients impaired Hebbian synaptic plasticity (such as long-term potentiation, LTP). Similar studies also revealed that neurons exposed to low concentrations of Aβ (as in preclinical phases

of AD) lead to increased neuronal excitability, whereas higher doses of Aβ as in later phases of AD lead to decreased synaptic activity. These results suggest the homeostatic synaptic plasticity dysfunction closely links to Aβ and Aβ/tau-rich exosomes that promote AD pathogenesis.

Disclosures: **S. Li:** None. **A. Gelb:** None. **M. Chen:** None. **D.J. Selkoe:** None. **W. Xia:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.09/C66

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NSERC

Title: Effects of amyloid beta on excitatory synaptic transmission in layer II of the entorhinal cortex

Authors: ***M. E. SUVANTO**[1], J. SARAGOSA[1], O. J. OLAJIDE[2], C. A. CHAPMAN[1];
[1]Ctr. for Studies in Behavioural Neurobio., Concordia Univ., Montreal, QC, Canada; [2]Dept. of Anat. (Neuroscience Unit), Univ. of Ilorin, Ilorin, Nigeria

Abstract: Neuronal degeneration of the hippocampus and entorhinal cortex resulting from accumulation of amyloid-β protein (Aβ) are key factors in Alzheimer's disease (AD). Although the entorhinal cortex has a central role in the integration of sensory information and memory formation, and degenerates early in AD, synaptic effects of Aβ within the entorhinal cortex have not been studied extensively. Accumulation of Aβ in the hippocampus disrupts excitatory glutamatergic synaptic transmission. Previous studies in the hippocampus have shown that Aβ enhances activation of extrasynaptic NMDA glutamate receptors, which can result in calcium-dependent excitotoxicity that contributes to neuronal degeneration. We used electrophysiological measures to assess the effects of short-term application of Aβ on excitatory synaptic transmission in the rat entorhinal cortex in vitro. Evoked field EPSPs were recorded from layer II of the medial entorhinal cortex. Following stable baseline recordings in normal ACSF, the application of 10 nM Aβ for 20 min resulted in an increase in fEPSPs that persisted during the 30 min washout period (n=6). Effects of longer-term exposure to Aβ were also assessed in groups of slices incubated for 45 min to 3 h in either 10 nM Aβ or control ACSF (n=11). Field EPSPs were evoked in tests in which either the duration or intensity of stimulation pulses was varied. Results showed that fEPSP amplitude was increased in slices incubated in Aβ, and that longer-term incubation in Aβ resulted in a greater enhancement of fEPSPs in comparison to shorter-term acute exposure. The facilitation of synaptic responses induced by Aβ may result from activation of presynaptic NMDA receptors that enhance transmitter release, or may depend upon postsynaptic NMDA receptors that can enhance calcium influx. These effects of short-term

exposure to Aβ may contribute to mechanisms of excitotoxicity and neuronal degeneration that contribute to cognitive declines observed early during the progression of AD.

Disclosures: M.E. Suvanto: None. **C.A. Chapman:** None. **J. Saragosa:** None. **O.J. Olajide:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.10/C67

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG039668 (Z.L.M.)
Connecticut Science Fund Grant (V.M.)

Title: Accumulation of oligomeric Aβ within neurons, and Tau phosphorylation, are part of a homeostatic mechanism aimed at restoring temporarily impeded axonal transport

Authors: *V. MURESAN, Z. LADESCU MURESAN;
Pharmacology, Physiol. and Neurosci., New Jersey Med. School, Rutgers Univ., Newark, NJ

Abstract: A primary challenge in Alzheimer's disease (AD) research is to identify the mechanisms that lead to the main pathological lesions (i.e., Aβ plaques, neurofibrillary tangles, granulovacuolar degeneration - GVD), and to provide a logical reason for why they develop. Here, we propose that these lesions are the result of persistent activation of a homeostatic mechanism that generates oligomeric Aβ (oAβ) and phosphorylated Tau (pTau) in an attempt to restore a temporarily halted axonal transport. We previously showed that, normally, a fraction of the Aβ precursor protein (APP) is transported into neurites by recruiting the microtubule motor, kinesin-1, via the adaptor protein, Fe65. Using CAD neuronal cells, we now show that, when axonal transport is experimentally impeded, an APP:Fe65:JNK complex accumulates in the soma, leading to phosphorylation of APP at Thr^{668}, while it resides at the endoplasmic reticulum (ER). This phosphorylation facilitates the amyloidogenic cleavage of APP, and leads to the accumulation of oAβ inside the ER. As a result of diminished affinity for phosphorylated APP, Fe65 is released, translocates into the nucleus, and upregulates GSK3β expression. Phosphorylation of Tau by GSK3β leads to its release from microtubules. We show that, in CAD cells cultured for extended time in conditions that block transport, pTau becomes localized to large spherical particles that accumulate in the soma, and show similarity to GVD bodies. The above-described events could be part of a "stress response" triggered by cargo accumulation in the soma, aimed at "decongesting" the impeded transport routes, and restoring the normal transport. We propose that the ER-accumulated oAβ binds to the nascent secretory proteins, preventing their exit from the ER and the clogging of the transport route, while the release of

pTau from microtubules allows for unhindered cargo translocation along microtubules. We also propose that the GVD bodies - likely autophagic in nature - appear as secondary response aimed at relieving the toxicity of overproduced pTau, when axonal transport is chronically impeded, and the homeostatic mechanism is persistently activated. Our results argue for physiological, beneficial, and independent roles of oAβ and pTau.

Disclosures: V. Muresan: None. **Z. Ladescu Muresan:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.11/C68

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Asymptotic long-term depression in aged Dp16 mice, a genetic model of 'Alzheimer's disease in Down syndrome'

Authors: A. V. BONDAR[1,2], M. Y. KHOTIMCHENKO[1], ***A. M. KLESCHEVNIKOV**[2];
[1]Sch. of Biomedicine, Far Eastern Federal Univ., Vladivostok, Russian Federation;
[2]Neurosciences, Univ. of California San Diego, La Jolla, CA

Abstract: Down syndrome (DS) can be considered as a model of Alzheimer disease (AD), since all people with DS have an AD-type pathology by the age of 40. Loss of memory in AD is best correlated with synaptic loss, and long-term depression (LTD) - like mechanisms can contribute to these changes. In this study, we assessed the asymptotic (extreme) LTD in hippocampal slices of aged (12-15 mo old) Dp16 mice, a genetic model of 'Alzheimer disease in Down syndrome' (AD/DS). The experiments were performed in ACSF containing 3 mM Ca^{+2} and 1 mM Mg^{+2}. LTD was induced in the CA1 slices by 2 series of low-frequency stimulation (LFS = 20 min x 2 Hz) with an interval of 2 h between the LFS series. In each series, 5 LFS were applied with an interval of 10 min. Presumably, such intense low-frequency stimulation would accelerate and exaggerate the synaptic changes, such as those that occur in AD/DS. We observed that LTD did not differ after the first series of LFS in Dp16 compared with the control littermate normosomic 2N mice (2N: 82.1 ± 7.5%, n = 6; Dp16: 73.5 ± 5.7%, n = 5; $p = 0.12$). In contrast, LTD was considerably greater in Dp16 than in 2N slices after the second LFS series (2N: 76.3 ± 15.4%, n = 6; Dp16: 45.5 ± 7.0%, n = 5; $p = 0.049$). Thus, total LTD evoked by both LFS series was significantly greater in Dp16 than in 2N slices (2N: 67.0 ± 17.9%, n = 6; Dp16: 31.4 ± 6.0%, n = 5; $p = 0.037$). Interestingly, the 'within genotype' comparison of LTD induced by the first and the second LFS series showed no difference in 2N slices (1^{st} LFS series: 82.1 ± 7.5%; 2^{nd} LFS series: 76.3 ± 15.4%; $p = 0.71$), but a significant increase of LTD induced by the second *vs.* first LFS series in Dp16 slices (1^{st} LFS series: 73.5 ± 5.7%; 2^{nd} LFS series: 45.5 ± 7.0%; $p = 0.01$). The results demonstrate that the hippocampus of aged Dp16 mice is prone to LTD, especially

during prolonged synaptic activity. *App* gene triplication in the DS model likely contributes to these changes.

Disclosures: A.V. Bondar: None. **M.Y. Khotimchenko:** None. **A.M. Kleschevnikov:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.12/C69

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG053740 to AL and JCL
NIH Grant HD079823 to JCL
NIMH Grant MH113177 to AL

Title: Increased functional excitatory/inhibitory synaptic ratio in the parietal cortex of Alzheimer's disease but not Down syndrome

Authors: J. C. LAUTERBORN[1], P. SCADUTO[2], C. M. GALL[3], C. D. KEENE[4], ***A. LIMON**[2]; [1]Julie Lauterborn, Irvine, CA; [2]UTMB, Galveston, TX; [3]Anat. and Neurobio., Univ. of California, Irvine, CA; [4]Univ. of Washington, Seattle, WA

Abstract: Disturbances in excitatory to inhibitory (E/I) balance in forebrain circuits may be a contributing factor to the progression of Alzheimer’s disease (AD) and dementia, although direct evidence for synaptic E/I imbalance in the human condition has not been shown. In the present study, fluorescent deconvolution tomography was used to assess the global synaptic E/I ratio in post-mortem parietal cortex samples from middle-aged individuals with AD, Down syndrome (DS), and controls. Although levels of both excitatory (PSD-95; DLG4) and inhibitory (gephyrin; GPHN) postsynaptic density proteins were reduced in AD and DS, the *anatomical E/I ratio* of PSD-95/gephyrin levels was markedly increased in AD only. Microtransplantation of synaptic membranes from each subject was then used to assess the *electrophysiological E/I ratio* for postsynaptic receptor responses. Peak responses to kainate (via AMPA receptors) and GABA revealed significantly elevated E/I ratios for the AD, but not DS, group vs controls. Surprisingly, phosphorylated Tau levels did not correlate with anatomical or electrophysical measures in the AD group but were negatively correlated with kainate current amplitudes and numbers of high intensity PSD-95-positive synapses in DS. Analyses using publicly available RNA-Seq transcriptional datasets for AD parietal cortex also demonstrated an increased transcriptional DLG4/GPHN ratio in AD vs controls. The collective findings provide the first evidence that despite a loss of both excitatory and inhibitory synaptic proteins, AD individuals exhibit a marked pro-excitatory perturbation of postsynaptic densities and electrophysiological synaptic E/I balance. As the parietal cortex is part of the default mode network that has been shown in AD

to be overly active and fails to deactivate during cognitive tasks, the present findings support the broader hypothesis that E/I imbalance in AD plays a role in the disruption of forebrain circuits that, in turn, contributes to the cognitive decline seen in this disorder.

Disclosures: **J.C. Lauterborn:** None. **P. Scaduto:** None. **C.M. Gall:** None. **C.D. Keene:** None. **A. Limon:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.13/C70

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant RO1

Title: Impaired degradation dynamics of synaptic vesicle machinery in APP KI mice

Authors: T. HARK[1], ***N. R. RAO**[1], E. BOMBA[2], J. N. SAVAS[2];
[1]Neurol., [2]Northwestern Univ., Chicago, IL

Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that is characterized as the onset of dementia with the presence of tangles and amyloid-beta plaques. Synapses are an example of areas where AD pathology could spread via synaptic vesicle exocytosis and endocytosis. Along with the progressive spread of pathology, another hallmark of AD is impaired protein degradation dynamics. The inability for proper degradation to occur effectively leads to the build-up of proteins, such as APP fragments and toxic Aβ42 which forms into plaques. Aβ oligomers have also previously been shown to bind to synaptic vesicle machinery, specifically in the SNARE complex. (Yang et al., 2015) We hypothesize that in an APP KI AD mouse model, the increase of Aβ42 leads to selectively impaired degradation of synaptic vesicle (SV) machinery. To investigate this question, we used APP KI mice at 6 and 12 months and compared the abundance of synaptic vesicle machinery proteins in NL, NLF, and NLGF animals. Immunoprecipitation of APP was performed to identify interactions between APP and SV proteins. Cell culture treatments of primary rat hippocampal neurons with retrograde inhibitors or Aβ42 and SILAC labeling were utilized with LC-MS/MS. SILAC treatment allows for LC-MS/MS identification of which proteins are newly synthesized. An increased abundance in SV machinery could be attributed to impaired degradation. One explanation for this could be that degradation needs to occur in the soma and Aβ42 or APP fragments prevent retrograde transport to the soma for degradation. In order to investigate this hypothesis, we used CiliobrevinD to inhibit retrograde transport with SILAC media with treatment. Another explanation could be that Aβ42 binds to SNARE complexes preventing their ability to properly be degraded when necessary. Preliminary results indicate that blocking

retrograde transport does not affect the degradation of SV machinery. We used TMT labeling and SILAC LC-MS/MS analysis to investigate the protein degradation and turnover dynamics in response to these treatments. These preliminary results indicate that in APP KI mice, there is selective impairment of SV machinery degradation and that this degradation impairment does not seem to be attributed to the inability for proteins to travel to the soma for degradation. Preliminary results also indicate that addition of synthetic Aβ42 increases the abundance of synaptic proteins that were not degraded during the treatment. Developing an understanding of selectively impaired protein degradation dynamics in AD could prove important to uncovering the mechanism of pathogenic protein aggregation and impairment.

Disclosures: **T. Hark:** None. **N.R. Rao:** None. **E. Bomba:** None. **J.N. Savas:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.14/C71

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Korea Health Industry Development Institute (KHIDI) (HI19C0646)
Human Frontier Science Program (RGY0073/2015)
National Research Foundation (NRF) (NRF-2015M3C7A1028790)

Title: Optogenetic activation of somatostatin interneurons selectively restores hippocampal spike timing-dependent long-term potentiation impaired by Aβ oligomers

Authors: *J. LEE[1], K. PARK[1], H. JANG[1], B. A. RICHARDS[2], M. M. KOHL[3], J. KWAG[1]; [1]Dept. of Brain and Cognitive Engin., Korea Univ., Seoul, Korea, Republic of; [2]Biol. Sci., Univ. of Toronto Scarborough, Scarborough, ON, Canada; [3]Dept. of Physiology, Anat. and Genet., Univ. of Oxford, Oxford, United Kingdom

Abstract: Abnormal accumulation of amyloid beta oligomer (AβO) in the hippocampus impairs long-term potentiation (LTP), which may underlie learning and memory deficits observed in Alzheimer’s disease (AD). Recent reports suggest that AβO causes structural dysfunctions in somatostatin-positive (SST^+) interneurons that are known to gate hippocampal LTP induction of CA1 pyramidal cells (PC) by providing disinhibition to CA1 PC proximal dendrites. However, the contribution of SST^+ interneurons to hippocampal LTP impairment in AD remains unclear. In order to address this question, we first induced spike timing-dependent long-term potentiation (tLTP) at CA3-CA1 synapse in DMSO and AβO (200 nM)-treated hippocampal slices by performing whole-cell current-clamp recordings in CA1 PC and pairing presynaptic excitatory postsynaptic potential evoked by Schaffer Collaterals (SC) stimulation with postsynaptic CA1 PC spike bursts (4 spikes at 100 Hz) with 10 ms time window, repeated 200 times at 5 Hz. Our

tLTP induction protocol induced robust NMDA receptor (NMDAR)-dependent tLTP at CA3-CA1 synapses in DMSO-treated slices, which was completely blocked in AβO-treated slices. Next, to test the role of SST^+ interneurons on AβO-impaired tLTP induction, we selectively expressed channelrhodopsin-2 (ChR2) to CA1 SST^+ interneurons using AAV virus (AAV-CaMKII-ChR2-mCherry) in SST-Cre mice and optogenetically activated them using blue light (470 nm) during tLTP induction. Surprisingly, optogenetic activation of SST^+ interneurons could fully restore NMDAR-dependent tLTP in AβO-treated slices. Since SST^+ interneuron-mediated disinhibition of proximal dendrites of CA1 PC has been shown to gate LTP induction, we next investigated whether AβO impaired SST^+ interneuron-mediated disinhibition, and thereby tLTP at the CA3-CA1 synapse. To analyze SST^+ interneurons-mediated disinhibition, we recorded SC stimulation-evoked inhibitory postsynaptic current (SC-IPSC) from CA1 PC through whole-cell voltage-clamp recordings and calculated the difference between SC-IPSCs before and during tLTP induction. We found that SST^+ interneuron-mediated disinhibition during tLTP induction significantly decreased in AβO-treated slices compared to that in DMSO-treated slices, which could be fully restored by optical stimulation of ChR2-expressing SST^+ interneurons to a level similar to that in DMSO-treated slices. These results show for the first time that reinstating SST^+ interneuron-mediated disinhibition during tLTP induction could restore tLTP impaired by AβO, indicating that SST^+ interneurons could be a potential therapeutic target for Alzheimer's disease.

Disclosures: **J. Lee:** None. **K. Park:** None. **H. Jang:** None. **B.A. Richards:** None. **M.M. Kohl:** None. **J. Kwag:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.15/C72

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Human Frontier Science Program (RGY0073/2015)
Korea Health Industry Development Institute (KHIDI) (HI19C0646)
Brain Research Program (NRF-2015M3C7A1028790)
Fostering Core Leaders of the Future Basic Science Program/Global Ph.D. Fellowship Program (NRF-2016H1A2A1907615)

Title: Optogenetic activation of parvalbumin-positive interneurons restores hippocampal theta-nested gamma oscillation impairment by Aβ oligomers

Authors: *K. PARK[1], J. LEE[1], M. M. KOHL[2], B. A. RICHARDS[3], J. KWAG[1];
[1]Dept. of Brain and Cognitive Engin., Korea Univ., Seoul, Korea, Republic of; [2]Dept. of Physiology, Anat. and Genet., Univ. of Oxford, Oxford, United Kingdom; [3]Biol. Sci., Univ. of Toronto Scarborough, Scarborough, ON, Canada

Abstract: Abnormal accumulation of amyloid beta oligomers (AβO) in the hippocampus is a hallmark of Alzheimer's disease (AD), which leads to learning and memory deficits. Hippocampal gamma (20 - 120 Hz) oscillations, generated by synchronized activation of reciprocally connected CA1 pyramidal cells (PCs) and parvalbumin-positive interneurons (PV^+ INs), contribute to memory function. This gamma oscillations have been shown to be impaired by AβO. However, the underlying synaptic mechanisms remain unclear due to experimental challenges in electrophysiological recordings of synaptic activity during gamma oscillations *in vivo*. Recent study showed that optical stimulation of channelrhodopsin-2 (ChR2)-expressing CA1 PCs at theta-frequency (5 Hz) could induce *in vivo*-like hippocampal theta-nested gamma oscillations *in vitro*. Using this experimental paradigm, we made targeted whole-cell current/voltage-clamp recordings from CA1 PC and PV^+ IN during theta-nested gamma oscillations in DMSO- and AβO-treated hippocampal slices. In DMSO-treated hippocampal slices, theta-nested gamma oscillations could be reliably induced with CA1 PC spike, CA1 PC-evoked excitatory postsynaptic currents (EPSCs) in PV^+ IN, PV^+ IN spike and PV^+ IN-evoked inhibitory postsynaptic currents (IPSCs) in CA1 PC each sequentially synchronized to a specific phase relative to the gamma oscillations. However, 20 min treatment with 200 nM AβO significantly reduced the peak power of gamma oscillations and also desynchronized spikes/synaptic currents of CA1 PC and PV^+ IN. In particular, AβO decreased the amplitudes of PV^+ IN-evoked IPSCs in CA1 PC and CA1 PC-evoked EPSCs in PV^+ IN during theta-nested gamma oscillations. Analysis of paired-pulse ratio and short-term plasticity of EPSCs in PV^+ IN and IPSCs in CA1 PC revealed that a presynaptic locus of dysfunction at reciprocal synapses between CA1 PC and PV^+ IN. Finally, to investigate whether optical activation of PV^+ IN could restore AβO-induced impairment of theta-nested gamma oscillations, we expressed C1V1 to PV^+ IN and ChR2 to CA1 PC in AβO-treated slices and optically stimulated them at 5 Hz with yellow and blue light, respectively, to find that activation of PV^+ IN restored the peak power of gamma oscillations to the level as observed in DMSO-treated slice by resynchronizing PV^+ IN and CA1 PC's spikes/synaptic currents relative to gamma oscillations. Our results show that presynaptic dysfunction of reciprocal CA1 PC and PV^+ IN synapses underlie AβO-induced impairment of theta-nested gamma oscillation, pointing towards PV^+ IN as a potential therapeutic target for AD.

Disclosures: K. Park: None. **J. Lee:** None. **M.M. Kohl:** None. **B.A. Richards:** None. **J. Kwag:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.16/C73

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant P50AG05138
NIH Grant AG-008200
NIH Grant 2R01-NS047229

Title: Interaction of Presenilin 1 with NMDA receptor: Effects of FAD mutants

Authors: *C. DIMOVASILI, M. A. RAHIM, A. GEORGAKOPOULOS, N. K. ROBAKIS; Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Mutations in presenilin 1 (PS1), account for the majority of familial Alzheimer's disease (FAD) cases. It has been reported that, besides its role as the catalytic component of γ-secretase complex, PS1 has also γ-secretase-independent functions such as neuroprotection and neurotransmitter trafficking. Importantly, PS1 has been reported to interact with transmembrane proteins including the NR1 subunit of the NMDA receptor. In addition to playing important roles in glutamate neurotransmission, NMDAR also modulates neurotrophin receptors and is critical to neuronal survival. Here we asked whether PS1 interacts with NR1 in brain, neurons and in an *in vitro* HEK293T cell system. To this end we coexpressed NR1 and WT PS1 holoprotein or its endo-proteolytic fragments NTF or CTF carried on PMX-IRES-GFP vectors, and tested the interaction by co-immunoprecipitation (co-IP) with anti-NR1 and anti-PS1 fragment-specific antibodies. Also, we coexpressed NR1 and WT PS1, M146V or I213T FAD mutants, constructed in our lab in the effective FCBAIGW vector and used co-IP experiments to test the interactions, as before. We found that both in neurons and in HEK293 cells overexpressing NR1 and PS1, the two proteins form complexes. Also, we obtained evidence that both full length PS1 as well as the PS1/NTF and PS1/CTF PS1 fragments associate with NR1. We also obtained preliminary evidence that the PS1-NR1 interaction is altered in cells expressing PS1 FAD mutants. Specifically, M146V and I213T tend to associate more potently with NR1 than WT PS1. The data that PS1 associates and possibly regulates the function of NMDAR reveals a possible connection of two major players of AD-related pathways. These data also provide a hopeful basis for attempts of therapeutic approaches, since targeting NMDAR function and/or its association with PS1 is a realistic goal for therapeutic interventions. Future studies will test this association on a functional level, focused on NMDAR regulation by PS1.

Disclosures: C. Dimovasili: None. **M.A. Rahim:** None. **A. Georgakopoulos:** None. **N.K. Robakis:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.17/C74

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CONACyT student scholarship (DB)
UCL DEMENTIA RESEARCH INSTITUTE (DMC)

Title: Assessment of microglia influence in synaptic transmission and early amyloid-beta plaque deposition in knock-in mouse models of Alzheimer's disease

Authors: *D. P. BENITEZ[1], C. N. E. PEERBOOM[2], D. M. CUMMINGS[1], F. A. EDWARDS[1]; [1]Neurosci. Physiol. and Pharmacol., Univ. Col. London, London, United Kingdom; [2]Cell Biol., Utrecht Univ., Utrecht, Netherlands

Abstract: Genome-wide association studies have indicated that immune processes play an important role in Alzheimer's disease (AD). In transgenic mouse models, the expression of similar immune genes is altered in a tight correlation to amyloid-β (Aβ) pathology and are therefore potential targets for altering the progression of AD. Here we examine the role of microglia by blocking the microglial survival factor colony-stimulating factor 1 receptor (CSF1R) in APP knock-in mice (Saito et al, Nat Neurosci 2014;17:661) that harbour the Swedish and Beyreuther/Iberian mutations, with (NL-G-F) or without (NL-F) the Artic mutation. We then assess changes in CA1 hippocampal synaptic transmission and plasticity at an early stage of amyloidopathy.

NL-G-F mice were fed the selective CSF1R inhibitor PLX5622 (0, 300 and 1200 ppm of food) from 1.5-months-old for 7 weeks (i.e. prior to plaque deposition through to when the first plaques are detected). The low and high doses reduced IBA1+ microglial densities by ~50% and >95%, respectively but in control and 300 ppm PLX5622-fed animals, microglial counts were slightly higher in NL-G-F than wild type counterparts. The proportion of CD68+ microglia remained unchanged despite the changes in total microglial densities. The percentage coverage of the hippocampus by Aβ plaque was unaffected by treatment with PLX5622.

Assessment of CA3-CA1 hippocampal field excitatory postsynaptic potentials (fEPSPs) showed a larger input-output relationship in NL-G-F than in wild type animals. Paired-pulse ratios (PPRs) were identical between the genotypes (both fEPSPs and whole-cell excitatory postsynaptic currents -EPSCs). Treatment with PLX5622 had no further effect on either fEPSP slope or PPRs. Finally, the magnitude of long-term potentiation was similar, irrespective of genotype or drug treatment.

Long-term ablation of microglia was also studied in NL-F mice, which were fed PLX5622 from 7 to 10 months of age. Unlike the NL-G-F mice, when plaques were first detected at 9 months of age in the NL-F mice, PPRs were lower than in their wild type counterparts, indicating a higher probability of glutamate release. However, again, preliminary results show that the absence of microglia has no effect on PPRs.

These data indicate that, while NL-F and NL-G-F mice display different phenotypes regarding the probability of glutamate release at the stage when plaques are first detected, microglia have little effect on this. Similarly, ablation of microglia prior to the detection of plaques has no effect on plaque deposition, supporting the idea that the role of microglia in early AD is not removal of amyloid-β.

Disclosures: D.P. Benitez: None. **C.N.E. Peerboom:** None. **D.M. Cummings:** None. **F.A. Edwards:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.18/C75

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01AA025718-0251

Title: Alterations in membrane excitability and synaptic properties of nucleus accumbens neurons in Alzheimer's disease mouse models

Authors: *S. S. GALLEGOS[1], E. J. FERNANDEZ[1], A. ARAYA[1], N. RIFFO[1], P. CISTERNAS[2], N. INESTROSA[2], B. MUÑOZ[3], B. K. ATWOOD[3], L. G. AGUAYO[1]; [1]Physiol., Univ. of Concepcion, Concepcion, Chile; [2]Dept. de Biología Celular y Molecular, Facultad de Ciencias Biológicas, Pontificia Univ. Católica de Chile, Santiago, Chile; [3]Dept. of Psychiatry, Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Introduction
It is now recognized that clinical signs of Alzheimer´s disease (AD) involve impairment in brain functions including, but not limited to, language and memory. It is becoming clear that cognitive and executive functions predominantly mediated by limbic areas are also significantly affected in the disease. Recent studies investigating brain morphology and dementia showed alterations in the nucleus Accumbens (nAc). The nAc is a key component of the limbic reward system and is involved in cognition and emotional behaviors such as pleasure, fear, aggression and motivations; all affected in neurodegenerative diseases such as AD. Therefore, this study was initiated to examine if nAc was affected in AD animal models.

Results
Using Thioflavin-T (ThT), we detected the presence of amyloid plaques in the nAc of 2xTg (APP/PS1) mice, but not in the control WT aged mice (8-11 months). The presence of AD pathology was associated with alterations in membrane excitability and synaptic properties measured by recording dissociated medium spiny neurons (MSNs) from 2xTg (11 months) and J20 (14 months) mouse AD models. We found similar results in recordings of nAc MSNs in brain slices made from 5xFAD mice (6 months), another Alzheimer's disease mouse model strain. The whole cell recordings showed that several properties of action potentials, such as amplitude and firing, were affected in J20 and 5xFAD mice. On the other hand, most passive properties examined were unchanged, with the exception of input resistance. The J20 mice showed reduced amplitude of the AMPA-elicited current in dissociated neurons. In addition, inhibitory receptors appeared to be significantly affected in the three AD models. For example, the $GABA_A$-induced current desensitized to a larger extent with the second agonist application in J20 mice. The 2xTg mice exhibited a similar pattern to that observed in J20, but the magnitude

of the effects was less marked. In addition, the amplitude of inhibitory postsynaptic currents ($GABA_A$-mediated, IPSCs) elicited in the 5xFAD mice was also reduced.

Conclusions

Overall, these findings support the idea that increased Aβ production in the nAc can reduce inhibitory mechanisms affecting neuronal physiology, which might explain the higher excitability reported in AD models.

Disclosures: S.S. Gallegos: None. **E.J. Fernandez:** None. **A. Araya:** None. **N. Riffo:** None. **P. Cisternas:** None. **N. Inestrosa:** None. **B. Muñoz:** None. **B.K. Atwood:** None. **L.G. Aguayo:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.19/C76

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Fondo Nacional de Desarrollo Cientifico y Tecnologico FONDECYT inicio 11161056
Programa de Apoyo a Centros con Financiamiento Basal AFB17004 to Fundación Ciencia y Vida
Fondo Nacional de Desarrollo Cientifico y Tecnologico FONDECYT 1161284

Title: Local synaptic PKR activation is involved in amiloyd-beta oligomer induced synapse degeneration

Authors: *N. W. MARTINEZ, S. MATUS, I. ALFARO;
Res. and Develop., Fundación Ciencia y Vida, Santiago de Chile, Chile

Abstract: Cognitive dysfunction during AD is strongly correlated with synaptic loss. Interestingly, local amyloid peptide beta (Aβ) accumulation has been related with nearby spine density reduction, changes in synaptic protein expression, synaptic morphology and neurotransmission. This suggests that synapse degeneration is mediated by a local synaptic response induced by Aβ. However, the molecular mechanism that mediates the Aβ induced synapse degeneration remains unknown. Recently, PKR activity has been related to Aβ induced significant LTP impairment at hippocampus and memory deficit. Furthermore, activation of PKR at CNS is a predictor of Alzheimer disease cognitive decline. Additionally, PKR co- localizes with histological features of Alzheimer pathology. However, the role of PKR in Aβ related synaptic morpho-functional changes remain unexplored. Considering this, we explore local synaptic PKR activation as a potential regulator of synapse degeneration induced by Aβ. To this goal, we explored the local activation of PKR at synapses by immunofluorescence analysis and

the role of PKR activation on synapse integrity in response to Aβ toxicity by 3D reconstruction of synaptic terminals. **Methods:** Local PKR activation was assayed by fluorescence intensity of phosphorylated PKR (Thr446) after colocalization with pre and post synaptic markers on 14DIV hippocampal neurons *in vitro*. Synapse integrity was analyzed by microscopy deconvolution and 3D reconstruction of EGFP transfected 14 DIV hippocampal neurons dendrites. Activation of PKR was induced by replacing neuronal culture media with Aβ oligomers containing conditioned media from CHO7PA2 cells. PKR activation was pharmacologically inhibited by addition of C16 (1 μM) to culture media. **Results:** PKR was found in discrete protein clusters in axonal and dendritic projections, partially colocalizing with pre- and post-synaptic compartments. We found that conditioned media containing Aβ oligomers induced a significant local activation of PKR at pre and post synaptic compartments on hippocampal neurons. Concomitantly, conditioned media containing Aβ oligomers induced morphological changes of post synaptic spines. Interestingly, synaptic integrity was preserved under pharmacological inhibition of PKR activation by C16 1μM. Discusions: These results suggest that PKR is a novel mediator of Aβ induced synaptic degeneration. However, whether induction of PKR activation by local Aβ oligomers leads to synapse degeneration as a local response remains unanswered. To address this, we are currently setting up live cell analysis of compartmentalized synapses in response to local treatment with Aβ oligomers.

Disclosures: N.W. Martinez: None. **S. Matus:** None. **I. Alfaro:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.20/C77

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: ERDF grant CENTRO-01-0145-FEDER-000012-HealthyAging2020
FCT grant POCI-01-0145-FEDER-007440
FCT grant UID/NEU/04539/2019
FCT grant CPF0005B01-POCI-01-0145-FEDER-032316

Title: Modified mitochondrial function by histone deacetylase inhibitors in neuronal models of Alzheimer's disease

Authors: *I. L. FERREIRA[1], D. MARINHO[1], A. C. REGO[2];
[1]Univ. of Coimbra, Ctr. for Neurosci. and Cell Biol., Coimbra, Portugal; [2]Univ. of Coimbra, Ctr. for Neurosci. and Cell Biol. and Fac. of Med., Coimbra, Portugal

Abstract: Alzheimer’s disease (AD) is the most prevalent age-related neurodegenerative disorder associated with loss of neurons in the hippocampus, progressing to the cortex.

Extracellular senile plaques containing amyloid-beta peptide (Abeta) and intracellular neurofibrillary tangles constitute AD pathological hallmarks. Several molecular pathways have been described in AD, including repressed gene transcription, excitotoxicity and mitochondrial dysfunction; however, no effective therapeutics exist. In the present study we analysed the role of class I histone deacetylase inhibitors (HDACi), sodium butyrate (SB), suberoylanilide hydroxamic acid (SAHA) and tacedinaline (Tac), on mitochondrial function in AD hippocampal cells. Selective activation of *N*-methyl-D-aspartate (NMDA) receptor (NMDAR) containing GluN2B subunit leads to increased mitochondrial Ca^{2+} (mitoCa) retention along with mitochondrial hyperpolarization in 3xTg-AD, compared with WT hippocampal neurons. Both mouse hippocampal neurons and HT22 cells treated with nontoxic HDACi increased H3 histone acetylation. SB and Tac also prevented HT22 cytotoxic effects exerted by $Abeta_{1-42}$ oligomers (AbetaO). $Ca^{2+}{}_i$ levels evoked by NMDA/glycine decreased after SB, SAHA and Tac in 3xTg-AD, but not after immediate exposure to AbetaO in hippocampal neurons. However, enhanced mitoCa retention observed in NMDA/gly-stimulated 3xTg-AD neurons remained unchanged following HDACi treatment. Incubation with SB, SAHA and Tac significantly increased mmp after NMDAR activation in WT neurons, but only Tac showed this effect following immediate AbetaO exposure or in 3xTg-AD neurons. Data reveal the importance of defining the role of HDACs and their inhibitors in AD pathogenesis involving hippocampal glutamatergic synapses.

Disclosures: I.L. Ferreira: None. **D. Marinho:** None. **A.C. Rego:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.21/C78

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 5R01AG050631-03

Title: Investigating the role of CD2AP, an Alzheimer's disease susceptibility gene, in mammalian synaptic structure and function

Authors: *M. PAVESKOVIC[1], S. A. OJELADE[2], B. T. PEKAREK[3], B. R. ARENKIEL[3], J. M. SHULMAN[2];
[1]Neurosci., [2]Neurol., [3]Mol. and Human Genet., Baylor Col. of Med., Houston, TX

Abstract: *CD2-Associated protein* (*CD2AP*) is an Alzheimer's disease (AD)-susceptibility gene that has a largely unknown role in the mammalian nervous system. In *Drosophila,* the *CD2AP* homolog, *cindr*, genetically interacts with tau neurotoxicity and modulates protein turnover and synaptic function. Based on studies using either an *in vivo* reporter (*Elav>GFP-CL1*) or direct biochemical assays, proteasome activity is compromised in *cindr* mutants. We also discovered

reduced expression of multiple regulatory subunits of the ubiquitin proteasome system (UPS) in *cindr* mutants, and genetic manipulation of the UPS phenocopies loss of *cindr*. Further supporting a defect in protein turnover, mutant flies have increased expression of the synaptic protein Synapsin as well as the Plasma Membrane Cytoplasmic ATPase (PMCA). Consistent with this, neurophysiologic studies at the *Drosophila* larval neuromuscular junction reveal impaired synaptic transmission and plasticity. Brain homogenates from *CD2AP*$^{-/-}$ mice show consistent changes in UPS activity and aberrantly increased levels of Synapsins1-3 and PMCA. Moreover, in mouse primary neuronal cultures *CD2AP* loss causes altered synapse structure, including decreased dendritic branching and increased PSD95 expression. In ongoing studies, we are also investigating potential electrophysiological changes in primary cultures. We are also generating a *CD2AP* conditional knockout strain (*CD2AP* cKO) to examine the *in vivo* consequences of neuron-specific loss for proteostasis and synaptic structure/function. Our results will inform both an understanding of requirements of *CD2AP* in the adult mammalian brain, as well as provide clues to its impact on AD pathogenesis.

Disclosures: M. Paveskovic: None. **S.A. Ojelade:** None. **B.T. Pekarek:** None. **B.R. Arenkiel:** None. **J.M. Shulman:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.22/C79

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Alzheimer’s disease pathogenesis: The denied access model

Authors: *S. XU[1], W. DAUBERMAN[2];
[1]Florida Inst. of Technol., Melbourne, FL; [2]Biomed. Chem. Engin. and Sci., Florida institute of Technol., Melbourne, FL

Abstract: Amyloid plaques are hydrogels and their physical properties in Alzheimer’s disease pathogenesis are examined. In nature, hydrogels can be formed by fibers of aggregated proteins and polysaccharides. Examples of protein fibers like fibrin, gelatin and amyloid plaques, and polysaccharide gels like agarose gels, starch gels, and fruit jello. From a physics perspective, hydrogels are known to be capable of blocking fluid flow (Woodard et al. 2014). However, fluid movement is critical in circulating ions and molecules to and from cells including neurons to maintain cell homeostasis. When fibrin hydrogels are formed around nerve fibers, the propagation of action potential was reduced by 40% (Dauberman et al., 2017). Images of atomic force microscopy and transmission electron microscopy indicate that amyloid plaques have pore sizes much smaller than those in the fibrin gels, and the fiber bundles in the amyloid plaques would further reduce the pore size and then the transport of ions and molecules. Viscosity

analysis using a molecular rotor, 9-(2-carboxy-2-cyanovinyl)julolidine, for the change of the fluorescence intensity, shows a 42% increase in the viscosity of the media during hydrogel formation. Since Brownian motion and then diffusivity is dependent on viscosity, hydrogel formation, as occurred in amyloid plaque deposition, would also reduce the diffusion of molecules and ions in addition to the effect on fluid bulk flow. Indeed, diffusivity of amyloid plaques in AD brain is 47% lower than the surrounding normal tissue when analyzed using the method of fluorescence recovery after photobleaching. Buried inside each of the amyloid plaques in AD brain are thousands neurites. In theory, each plaque can then compromise the function of a large number of neurons. Such evidence led us to propose the denied access model in Alzheimer's disease pathogenesis, that amyloid fibers can further aggregate and form hydrogels, and the hydrogels are capable of eliminating bulk flow and reducing diffusion, which then attenuates the circulation of ions and molecules that are essential for neuronal function.
Woodard, D. et al. (2014). PLoS One **9**(4): e94789.
Dauberman, W. et al. (2017). Journal of Alzheimer's Disease & Parkingsonism **7**(4): 1000349.

Disclosures: S. Xu: None. **W. Dauberman:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.23/C80

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01NS075487
T32NS095775
Alzheimer's Association

Title: The Alzheimer's disease risk gene BIN1 regulates neuronal hyperexcitability

Authors: *Y. VOSKOBIYNYK, J. ROTH, J. COCHRAN, T. RUSH, K. M. GREATHOUSE, N. CARULLO, L. L. MCMAHON, J. H. HERSKOWITZ, J. J. DAY, E. D. ROBERSON; Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Alzheimer's disease (AD) affects about five million Americans, who receive only a very modest benefit from current treatment options. Multiple clinical trials have failed in the past, raising interest in identifying new targets to treat AD. Genome wide association studies (GWAS) have identified bridging integrator 1 (*BIN1*) as one of the leading genetic risk factors in AD. Neurons express a unique BIN1 isoform, though the function of this isoform remains unclear and its contribution to AD is critical to investigate. A key question for the role of neuronal BIN1 in AD pathophysiology is whether it has a direct effect on the neuron's primary function - neuronal firing. To address this question, we developed a human neuronal isoform

BIN1 vector and evaluated the effects of BIN1 overexpression in primary hippocampal cultures. First, we determined that robust AAV-driven BIN1 overexpression increases spike and burst frequency on multielectrode arrays. Next, we determined that sparse transient transfection-driven BIN1 overexpression increases calcium influx of transfected neurons on calcium imaging of GCaMP6f calcium indicator. In addition, we determined that higher BIN1 levels induced changes in both excitatory and inhibitory synaptic transmission. To investigate the mechanism by which higher BIN1 induces network hyperexcitability, we evaluated the effect of higher BIN1 levels on intrinsic neuronal excitability using whole-cell patch clamp electrophysiology. In addition, we evaluated the effect of higher BIN1 level on both neuronal morphology by determining the complexity of dendritic arbors and spine morphometry. These data show BIN1's important role in regulating neuronal firing and network hyperexcitability and generate fundamental insights about the mechanistic role BIN1 plays in AD.

Disclosures: **Y. Voskobiynyk:** None. **J. Roth:** None. **J. Cochran:** None. **T. Rush:** None. **K.M. Greathouse:** None. **N. Carullo:** None. **L.L. McMahon:** None. **J.H. Herskowitz:** None. **J.J. Day:** None. **E.D. Roberson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EDR is an owner of intellectual property relating to Tau..

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.24/C81

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: NIH grants R01NS075487, R01AG059405, UL1TR001417, and T32NS061455
BrightFocus Foundation grant A2015693S
Alabama Drug Discovery Alliance
UAB Center for Clinical and Translational Sciences
Weston Brain Institute

Title: Tau-SH3 interactions are critical mediators of amyloid-β toxicity in primary neurons

Authors: *J. R. ROTH, T. J. RUSH, S. J. THOMPSON, A. R. ALDAHER, J. S. MESINA, J. COCHRAN, E. D. ROBERSON;
Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: The microtubule-associated protein Tau is strongly implicated in Alzheimer's disease (AD) and aggregates into neurofibrillary tangles in AD. Genetic reduction of Tau is protective in several animal models of AD and cell culture models of amyloid-β (Aβ) toxicity, making it an exciting therapeutic target for treating AD. A variety of evidence indicates that Tau's interactions

with Fyn kinase and other SH3 domain-containing proteins, which bind to PxxP motifs in Tau's proline-rich domain, may contribute to AD deficits and Aβ toxicity. Thus, we sought to determine if inhibiting Tau-SH3 interactions ameliorates Aβ toxicity. We developed a peptide inhibitor of Tau-SH3 interactions and a proximity ligation assay (PLA)-based target engagement assay. Then, we used membrane trafficking and neurite degeneration assays to determine if inhibiting Tau-SH3 interactions ameliorated Aβ oligomer (Aβo)-induced toxicity in primary hippocampal neurons from rats. We verified that Tau reduction ameliorated Aβo toxicity in neurons. Using PLA, we identified a peptide inhibitor that reduced Tau-SH3 interactions in HEK-293 cells and primary neurons. In primary neurons, endogenous Tau-Fyn interaction was present primarily in neurites and was reduced by the peptide inhibitor, demonstrating target engagement. Reducing Tau-SH3 interactions in neurons ameliorated Aβo toxicity by multiple outcome measures, namely Aβo-induced membrane trafficking dysfunction and neurite degeneration. Our results indicate that Tau-SH3 interactions are critical for Aβo toxicity and that inhibiting them is a promising therapeutic target for AD.

Disclosures: **J.R. Roth:** None. **T.J. Rush:** None. **S.J. Thompson:** None. **A.R. Aldaher:** None. **J.S. Mesina:** None. **J. Cochran:** None. **E.D. Roberson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EDR is an owner of intellectual property relating to Tau..

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.25/C82

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01 AG056259
R01 AG057409
DP1 DA041722

Title: Hyperexcitability in Alzheimer's disease hiPSC derived neurons and cerebral organoids is a result of both increased excitation and decreased inhibition

Authors: ***S. GHATAK**[1], N. DOLATABADI[1], R. GAO[3], D. TRUDLER[1], Y. WU[1], X. ZHANG[1], A. SULTAN[4], M. V. TALANTOVA[1], R. AMBASUDHAN[4], B. VOYTEK[3], S. A. LIPTON[2];
[1]Dept. of Mol. Med., [2]Departments of Mol. Med. and Neuroscience, Ctr. for Translational Neurosci., The Scripps Res. Inst., La Jolla, CA; [3]Cognitive Sci., Univ. of California San Diego Dept. of Cognitive Sci., La Jolla, CA; [4]Neurodegenerative Dis. Ctr., Scintillon Inst., San Diego, CA

Abstract: Human Alzheimer's disease (AD) brains manifest hyperexcitability. This aberrant electrical activity is caused, at least in part, by neurite degeneration and ion channel dysfunction contributing to synaptic dysfunction (Siskova et al., Neuron 84, 1023-1033 (2014)) which represents the major pathophysiological correlate of cognitive decline. However, the underlying mechanism for this excessive excitability remains incompletely understood. To investigate the basis for the hyperactivity, we performed patch-clamp recordings, Ca2+-imaging, and immunofluorescence studies on hiPSC-derived cerebrocortical neuronal cultures and 3D cerebral organoids bearing AD-related mutations in presenilin 1 or amyloid precursor protein vs. controls. We found increased hypersynchronous electrical activity in AD hiPSC-derived neurons and in organoids compared to gene-corrected isogenic controls. Sodium currents in AD hiPSC-derived neurons showed increased amplitude and faster kinetics. AD hiPSC-derived neurons also displayed shorter neuritic processes. Additionally, AD hiPSC-derived neurons exhibited increased frequency and amplitude of miniature excitatory postsynaptic currents (mEPSCs) but decreased frequency of miniature inhibitory postsynaptic synaptic currents (mIPSCs). Along similar lines, we found that AD hiPSC-derived neurons manifested a smaller number of inhibitory neurons, lower VGAT levels/synapses, and diminished GABA-evoked whole-cell currents, while glutamate-evoked currents were larger in amplitude. Taken together, these results indicate that both active and passive mechanisms underlie the hypersynchronous excitatory burst activity of these neurons. Both pre- and postsynaptic changes are also involved that affect ion channel, vesicular release, and receptor properties. Importantly, the new dual allosteric-acting NMDAR antagonist NitroSynapsin, but not the FDA-approved drug memantine, robustly abrogated this hyperactivity in both hiPSC-derived cerebrocortical neuronal cultures and 3D cerebral organoids, while virtually sparing physiological synaptic activity. Our findings establish hiPSC-derived AD neurons as a relevant model of the aberrant hyperexcitability that is known to occur in human AD brain. Moreover, we suggest that hiPSC models of AD are suitable for initial drug screening aimed at decreasing excessive excitation and improving synaptic function.

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Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.26/C83

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant NS094738
NIH Grant AG056147
Alzheimer's Association Research Grant

Title: Membrane cholesterol homeostasis is regulated by amyloid precursor protein at axon terminals

Authors: *Q. Z. ZHANG[1], O. PELLETIER[2], S. ALAMGIR[2], H. HUANG[3], C. R. SANDERS[3]; [1]Biomed. Sci., Florida Atlantic Univ., Jupiter, FL; [2]The Brain Inst. at FAU, Jupiter, FL; [3]Vanderbilt Univ., Nashville, TN

Abstract: Cholesterol (Chol) is crucial for lipid membrane fusion and fission and thus greatly influences synaptic vesicle (SV) release and retrieval. SV membrane has the highest Chol content than any other neuronal membrane compartments, including the plasma membrane at the presynaptic active zone. Presynaptic terminals often undergo much more lipid exchange than any other parts of neurons. Moreover, long and thin axons lack Golgi and endoplasmic reticulum, in which cellular Chol sensor and regulator reside. Therefore, a local membrane Chol (mChol) sensor/regulator at presynaptic terminals is needed. Our previous studies have revealed that amyloid precursor protein (APP) at presynaptic surface membrane exhibits an inverse correlation to presynaptic mChol, which requires its Chol-binding motif (CBM). In the current study, we test if APP directly regulates mChol homeostasis at presynaptic terminals. First, we devise two ratiometric methods to monitor mChol fluctuation accompanied with SV exo-/endocytosis in live neurons. Second, we bidirectionally manipulate whole-cell Chol or plasma mChol and elucidate their impact on presynaptic mChol homeostasis during neuronal firing. Third, we implement a collection of APP point mutations associated with familial Alzheimer's disease (fAD), which are either outside or within its CBM and alters APP's trafficking or affinity to mChol. Our data illustrate how these APP mutants alters presynaptic mChol homeostasis, SV turnover and synaptic transmission. Fourth, we survey presynaptic Ca^{2+}-homeostasis, membrane integrity, SV organization and Tau hyperphosphorylation in mutant-expressing neurons. Our results not only reinforce the idea that APP is a presynaptic mChol sensor/regulator, but also indicate that the pathological contribution of those fAD mutations is likely through the disruption of presynaptic mChol homeostasis instead of the promotion of beta-amyloid aggregation.

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Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.27/C84

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The damage of astrocytes induced by fatty acids may contribute to diabetic encephalopathy

Authors: *D. LI[1], F. MA[2], S. SHI[2], X. WANG[2];
[1]Pharmacol., Chinese Acad. of Med. Sci., Beijing, China; [2]Inst. Materia Med., Beijing, China

Abstract: Disturbance of glucose and lipid metabolism related with Diabetes could lead to diabetic encephalopathy (DE). The incidence of dementia was about twice as high as in the non-diabetic group of the same age. In our study with KK-A^y diabetic mice, it was found that in the early stage of diabetes, about 3-5-month-old mice, neuron damage was relatively mild, while glial cells showed obvious lesions. Further study found that increased levels of blood glucose and lipids could not significantly cause changes to neurons, but could cause damage to astrocytes, especially the fatty acids represented by palmitic acid (PA), which aggravate the apoptosis of astrocytes. The expression of fatty acid transporter, CD36 on astrocytes was about 3 times higher than that of neurons. Sulfo-N-succinimidyloleate (SSO), an inhibitor of CD36, could significantly reduce the uptake of PA and subsequently decrease the damage of PA to astrocytes. After entering astrocytes, PA significantly increased the release of Ca2+, the content of ceramide and oxidative stress injury, while SSO could reduce the above substances and cell apoptosis. In the co-culture experiments of neurons and astrocytes, it was further found that astrocytes could significantly protect neurons and reduce the damage to neurons induced by glutamate. When PA was added, the protective effect of astrocytes on neurons decreased. SSO could restore the protective effect of astrocytes. It is demonstrated that astrocytes could clear fatty acids in the brain. Therefore, at the early stage of DE, neurons do not damage seriously. However, neurons injury increased as the state of astrocytes become worse due to continuously damage of fatty acids. DE is different from AD because it is reversible by low-fat diet or medicine treatment.
Conclusion: the injury of astrocytes caused by fatty acids is an important cause of diabetic encephalopathy. CD36, an important fatty acid transporter in astrocytes, may be a potential therapeutic target for diabetic encephalopathy.
Keywords:diabetic encephalopathy, fatty acid, CD36, astrocyte, dementia

Disclosures: D. Li: None. **F. Ma:** None. **S. Shi:** None. **X. Wang:** None.

Poster

559. Synaptic Dysfunction in Alzheimer's Disease: In Vitro Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 559.28/C85

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: *In vitro* modelling of progressive tauopathy in neuronal circuits using a novel high throughput assay platform

Authors: *S. ILLES, A. KARLSSON, P. KARILA, J. PIHL, M. KARLSSON;
Cellectricon AB, Mölndal, Sweden

Abstract: The appearance and spreading of misfolded tau protein within patient brain cells are common neuropathological hallmarks in several types of dementia (e.g. Alzheimer's disease, Pick´s disease and frontotemporal dementia). Deciphering the mechanisms behind uptake, spreading, aggregation, and propagation of tau is of high relevance for preclinical medical research programs.
Here, we combined our previously established optical electrophysiology system with a newly developed microfluidics platform to create a unique, high throughput *in vitro* assay platform. This platform allows for the assessment of spreading of neuropathological processes within spatially separated neuronal circuits. Furthermore, the screening plate design allows for local induction and intervention of neuropathology.
In detail, E18 mouse cortical neurons plated in wells of custom-developed microplates develop extensive processes and form functional synaptic connections within 14 days. Fluorescently labelled heparin-induced tau filaments were applied to cortical cultures to evaluate dose- and time-dependency of tau seed uptake and well-to-well spreading in cortical axons. By using sarkosyl-insoluble tau extracted from AD brain tissue, we describe concentration- and time-dependent AD tau-caused cell death and tau aggregation. Furthermore, we demonstrate that AD tau causes axonal retrograde spreading of tau aggregation.
The assay platform described here shows sufficient capacity and robustness to allow for screening and profiling of larger compound sets, in the search for molecules preventing progressive tauopathy processes spreading across synaptically coupled neurons.

Disclosures: S. Illes: A. Employment/Salary (full or part-time):; Cellectricon AB, Mölndal, Sweden. **A. Karlsson:** A. Employment/Salary (full or part-time):; Cellectricon AB, Mölndal, Sweden. **P. Karila:** A. Employment/Salary (full or part-time):; Cellectricon AB, Mölndal, Sweden. **J. Pihl:** A. Employment/Salary (full or part-time):; Cellectricon AB, Mölndal, Sweden. **M. Karlsson:** A. Employment/Salary (full or part-time):; Cellectricon AB, Mölndal, Sweden.

Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.01/C86

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The neuroprotective actions of an active core sequence of amyloid beta on amyloid beta-induced neurotoxicity involves cellular prion protein

Authors: *R. M. TAKETA[1], R. A. NICHOLS[2];
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Abstract: Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by cognitive decline and memory loss. Currently, there is no cure and the exact cellular mechanism underlying the disease is still unknown. Pathological aggregation of soluble beta-amyloid (Aβ) into insoluble Aβ-plaques is one of two hallmarks of the disease, the other being hyperphosphorylated tau. The production of Aβ is through sequential enzymatic cleavage of the amyloid precursor protein (APP) resulting in a series of Aβ peptides. The most well-known, $A\beta_{1-42}$ ($A\beta_{42}$) is a primary component of Aβ-plaques and underlies synaptic dysfunction and neurotoxicity. Our laboratory has shown that in the presence of high affinity nicotinic acetylcholine receptors (nAChRs), low "physiological" levels of $A\beta_{42}$ (pM-nM) sensitize neurons to $A\beta_{42}$-induced toxicity, while high levels of $A\beta_{42}$ (μM) induce apoptosis independently of nAChRs, verifying the neuromodulator functions of $A\beta_{42}$. In contrast, we've shown an endogenously cleaved N-terminal Aβ Fragment (N- $A\beta_{1-15,16}$) and an essential core sequence, YEVHHQ (N- Aβcore) within it, is neuroprotective against $A\beta_{42}$-induced oxidative stress and apoptosis in *vitro* and ex *vivo* studies.
Here, we investigated the mechanism of the N- Aβcore in our neuroblastoma cell line and primary hippocampal cultures through high affinity targets for Aβ, such as nAChRs and cellular prion (PrP^c). We utilized a neuronal cell line null of functional nAChRs and methods such as monoclonal antibodies, to preferentially block, knockdown, and/or delete target receptors to assess the impact on neuroprotection. In primary hippocampal cultures, attenuation of elevated reactive oxygen species (ROS) via an anti-PrP^c antibody were similar to those mediated by the N-Aβcore at pathological concentrations of $A\beta_{42}$. In order to further understand the cellular mechanisms of the N- Aβcore, we examined markers for cellular stress, apoptosis, and synaptotoxicity. Differential receptor-linked protein levels downstream of nAChRs and PrP^c were compared via immunoblotting and immunohistochemistry.
Delineating the neuroprotective molecular mechanisms of the N- Aβcore will provide essential guidance for future use as a potential therapeutic. In addition, it will dissect the multiple and perhaps converging pathways involving nAChRs and PrP^c in $A\beta_{42}$-induced toxicity.
Funding: NIH and the UH Foundation

Disclosures: R.M. Taketa: None. **R.A. Nichols:** None.

Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.02/C87

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association AARG-16-440031

Title: Modulation of voltage-gated calcium channels via protofibrillar amyloid-β

Authors: *E. KAISIS, L. THEI, G. STEPHENS, M. DALLAS;
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Abstract: The amyloid-cascade hypothesis proposes that one of the main protagonists in Alzheimer's disease is oligomeric amyloid-β (Aβ). Protofibrillar $A\beta_{1-42}$ induces cytotoxicity through various signalling cascades, including calcium dysregulation through neuronal voltage-gated calcium channels (VGCCs). SH-SY5Y cells express a host of VGCCs. Within undifferentiated cells, $Ca_v1.2$, $Ca_v1.3$, $Ca_v2.2$ and $Ca_v3.1$ were detected at gene level (PCR). Upon retinoic acid (RTA; 10μM; 3 days) differentiation, a reduction in $Ca_v3.1$ was observed. No expression of $Ca_v1.1$, $Ca_v1.4$, $Ca_v2.1$, $Ca_v2.3$, $Ca_v3.2$ and $Ca_v3.3$ at gene level was detected in SH-SY5Y of both differentiation states. Here, we examine the role of protofibrillar $A\beta_{1-42}$ on modulating VGCCs. Transmission electron microscopy, demonstrated time-dependent formation of $A\beta_{1-42}$ protofibrils (>100nm in length), prepared via pre-treatment in NH_4OH and further dilution in 2% SDS/PBS over a 48hr incubation period. XTT viability experiments revealed that exposure to protofibrillar $A\beta_{1-42}$ (24hr) induced neurotoxicity in undifferentiated SH-SY5Y, at a concentration-dependent manner, with 3μM (78.9±6.1%; n=11; $P<0.05$) and 10μM (76.1±6.8%; n=8; $P<0.01$) significantly reducing viability. In contrast, 100nM $A\beta_{1-42}$ (3.7±5.5%; n=16; NS) and 1μM (2.7±5.4%; n=17; NS) did not induce cytotoxicity. In parallel, PCR gene expression analysis revealed a reduction in $Ca_v1.3$ expression (19.0±4.3%; n=5; $P<0.05$) with 100nM $A\beta_{1-42}$ treatment (24hr) and an increase in $Ca_v1.2$ expression (78.7±14.9%; n=3; $P<0.05$) with 1μM $A\beta_{1-42}$ treatment (24hr), demonstrating differential $A\beta_{1-42}$ concentration-dependent modulation of VGCCs. Collectively, our work demonstrates that protofibrillar $A\beta_{1-42}$ can induce neurotoxicity, and can modulate VGCCs through changes in gene expression. Our work will aid the understanding of amyloid pathology, and highlight the potential to target VGCCs to suppress Aβ neurotoxicity. Ongoing work will investigate the effect of protofibrillar $A\beta_{1-42}$ on VGCCs at functional level (whole-cell patch clamp), and address novel VGCC modulators, which may go on to provide a novel therapeutic strategy to tackle dementia.

Disclosures: E. Kaisis: None. **L. Thei:** None. **G. Stephens:** None. **M. Dallas:** None.

Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.03/C88

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Modulation of protein synthesis' regulators by amyloid beta oligomers

Authors: *F. CAMPOS RIBEIRO, D. COZACHENCO FERREIRA, F. GUARINO DE FELICE, S. TEIXEIRA FERREIRA;
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Abstract: Synapse loss is a key feature of Alzheimer's disease (AD) and the best correlate of cognitive decline in AD patients. Nevertheless, the specific mechanisms that mediate reduction of synaptic proteins and, ultimately, synapse elimination in AD remain to be fully understood. Reduced brain protein synthesis (translation) is an additional feature of AD that could explain the reduction in synaptic proteins. However, the interplay between the many regulators of translation during the course of the disease is not well established, with controversial literature reports on the levels of regulators of translation in AD and their roles in disease. Here, we have investigated levels of major regulators of protein synthesis using Western blotting in hippocampal extracts from mice that received an intracerebroventricular (i.c.v.) infusion of Aβ oligomers (AβOs),which are implicated as proximal synaptotoxins in AD. We found that AβOs trigger decreases in levels of p-eIF4E, p-4EBP1, p-S6K, p-S6, p-ERK, p-mTOR, and an increase in the levels of ATF4 in the hippocampi of mice 7 days, but not 24 h, after i.c.v. infusion of AβOs. Results thus, indicate that positive regulators of translation are reduced, while a translational repressor (ATF4) is enhanced in the hippocampi of AβO-infused mice. Future studies will attempt to correlate these findings with inhibition of translation in AD models and further investigate the specific role of each of these proteins in aberrant regulation of brain protein synthesis in AD.

Disclosures: F. Campos Ribeiro: None. **D. Cozachenco Ferreira:** None. **F. Guarino De Felice:** None. **S. Teixeira Ferreira:** None.

Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.04/C89

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: FONDECYT 1161078
CONICYT 21181247

Title: Synaptic failure and mitochondrial dysfunction are induced by direct interaction of soluble oligomers of beta amyloid with mitochondrial membranes

Authors: *J. PANES-FERNÁNDEZ, J. GAVILÁN, P. A. GODOY RIVERA, T. B. SILVA-GRECCHI, O. RAMÍREZ-MOLINA, N. MUNOZ-MOLINA, C. MUNOZ-MONTECINO, J. FUENTEALBA;
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by impaired learning and memory loss. Amyloid beta peptide (Aβ) plays a key role in the pathogenesis of AD, especially soluble oligomers (SO-Aβ) because can reproduce the major aspects of the

disease.In vitro studies have associated mitochondrial dysfunction with an early role in the AD; however, the molecular events that underlie this effect are not understood with precision. In this work, we have studied the intracellular effects of acute and chronic SO-Aβ treatments, on key parameter of mitochondria functionality; morphology and mitochondrial potential. To develop this research, we use hippocampal primary cultures and hippocampal slices. First, using immunofluorescence techniques we performed colocalization analysis of fluorescent Aβ (Aβ-FAM) with an outer mitochondrial membrane marker (TOM20 antibody). We found that the degree of colocalization between Aβ and TOM20 was increasing, presenting a maximum of colocalization at 24 h of SO-Aβ treatments, with a Manders coefficient (0.640 ± 0.1). In parallel, we evaluated the mitochondrial membrane potential (ΔΨm) using the JC-1 probe, we observed that at chronic treatments (24h), SO-Aβ shown a decrease on ΔΨm near to 50% of the control conditions. Additionally, at the same times (SO-Aβ, 24h) strong changes were observed in the size of the mitochondrial network in primary cultures, displacing the equilibrium towards a more granular pattern in mitochondria that present a positive colocalization with Aβ. Secondly, the intracellular distribution of SO-Aβ (2.5uM) in a mouse hippocampal slices model was evaluated by immunohistochemistry (IHC) and electron transmission microscopy (TEM), Using the immunogold technique, we observed the presence Aβ targeted with gold nanoparticles in an intramitochondrial zone. On the other hand, it was observed that ΔΨm showed a progressive decrease in time manner on hippocampal slices under SO-Aβ treatments (JC-1590/520 C: 1.01 ± 0.01; SO-Aβ 40min: 0.94 ± 0.03; SO-Aβ 3h: 0.78 ± 0.04). This study suggest a new pathogenic mechanism in AD, where cytotoxic effects of SO-Aβ are related with their direct interaction with the mitochondria, and reveals a novel therapeutic strategies for neuroprotection.

Disclosures: **J. Panes-Fernández:** None. **J. Gavilán:** None. **P.A. Godoy Rivera:** None. **T.B. Silva-Grecchi:** None. **O. Ramírez-Molina:** None. **N. Munoz-Molina:** None. **C. Munoz-Montecino:** None. **J. Fuentealba:** None.

Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.05/C90

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: GAL-101 prevents beta-amyloid induced membrane depolarization in two different types of retinal cells

Authors: *C. G. PARSONS[1], M. MAZZANTI[2], S. V. GORNATI[3], E. PIZZI[4], G. RAMMES[5]; [1]Galimedix, Kensington, MD; [2]Univ. di Milano, Milano, Italy; [3]Erasmus MC, Rotterdam, Netherlands; [4]Univ. of Milan, Milano, Italy; [5]Clin. Rechts der Isar, Munich, Germany

Abstract: Glaucoma and age-related macular degeneration (AMD) are two of the major causes of progressive loss of vision and ultimate blindness worldwide. Retinopathies share several pathological features with Alzheimer´s disease (AD). Among other neurodegenerative events, in AD abnormalities in the retina such as visual function impairment, optic neuropathy, retinal ganglion cell (RGC) loss, decreased number of optic nerve fibres, astrocytosis and activation of immune competent microglia and Muller cells are evident. AD as well as glaucoma and AMD are characterized by the presence of elevated concentrations of amyloid beta (Aβ) peptide. Under such conditions $A\beta_{1-42}$has the tendency to aggregate forming toxic soluble oligomers that are now considered to be the most harmful amyloid species. One strategy adopted to prevent cell damage caused by these soluble toxic oligomers is to impair their aggregation. In the present work, using electrophysiological patch clamp measurements, we show that exposure of acutely isolated retinal cells to $A\beta_{1-42}$ caused a strong depolarization of the resting potential of the plasma membrane. The average resting membrane potential of cultured RGCs and retinal pigment epithelium (RPE) cells was -68.3 ± 1.9 mV and -40.2 ± 2.4 mV respectively. Acute application of $A\beta_{1-42}$ depolarized the membrane potential of RGCs with an $EC_{50}$of 44.1 ± 6.3 nM and a maximal effect at 100 nM to around -10 mV. Higher concentrations of $A\beta_{1-42}$ were required to cause depolarization of RPE cells (EC_{50}= 790 ± 80 nM). GAL-101 is a small D-amino acid dipeptide that modulates $A\beta_{1-42}$ aggregation by triggering a non-amyloidogenic aggregation pathway and thereby reduces the amount of intermediate toxic soluble oligomeric $A\beta_{1-42}$ species. Pre-incubation of RGCs for one hour with a 20:1 ratio was able to stabilize the cell resting potential to around -50 mV. Similar effects were seen with a 20:1 ratio of GAL-101 to $A\beta_{1-42}$ for RPE cells. Under therapeutic conditions, e.g. in the treatment of dry AMD or glaucoma, the pathological changes are more subtle in that there are much lower elevated concentrations of Aß but these persist chronically. Stoichiometric requirements for GAL-101 in relation to Aß would therefore no longer be an issue, but rather be superseded by the true affinity of GAL-101 for Aß of around 30 nM.

Disclosures: **C.G. Parsons:** A. Employment/Salary (full or part-time):; Galimedix. **M. Mazzanti:** None. **S.V. Gornati:** None. **E. Pizzi:** None. **G. Rammes:** F. Consulting Fees (e.g., advisory boards); Galimedix.

Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.06/C91

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: VIEP BUAP 2018-2019

Title: The injection of the beta amyloid peptide 25-35 in the fornix impairs learning, decreases the activity of acetylcholinesterase and changes the expression of Nrf2

Authors: *L. G. SÁNCHEZ-ABDÓN[1], G. MORALES-FLORES[1], I. MARTÍNEZ-GARCÍA[2], A. RAMÍREZ-MATA[3], A. PATRICIO-MARTINEZ[1,4], I. D. LIMÓN[1];
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Abstract: Previous studies have shown that the administration of the $A\beta_{25-35}$ peptide in the hippocampus and the *medial septum* produces learning and spatial memory impairment and changes in cholinergic markers. I*n vitro* and *in vivo* studies show that $A\beta_{25-35}$ decreases the expresión of the nuclear factor erythroid 2-related factor 2 (Nrf2) in the hippocampuss. However there is no evidence about the efect of the administration of $A\beta_{25-35}$ into white matter like fornix. The aim of the study was to evaluate the effect of the administration of $A\beta_{25-35}$ into the precomisural fórnix on spatial memory, activity of acetylcholinesterase (AChE) and expression of Nrf2. Male Wistar rats were used and four experimental group were formed: control, SSI, $A\beta_{25-35}$ and KA. The rat were injected with 2 μL of SSI, KA (as positive control) or $A\beta_{25-35}$ [1mM] into the fornix.The learning assesment was made in eight-arm radial maze (Med Associates) at 21 days post injection and after 17 days of the test, the spatial memory was evaluated. The brain were obteined to asses the activity of a cholinergic marker like AChE in *medial septum* and hippocamppus by the Ellman assay and also a transcription factor like Nr2 in *medial septum* by immunofluorescence. Our findings shows that the injection of $A\beta_{25-35}$ into the fornix causes learning but not memory impairtment. Also, it causes a decrease of AChE´s activity in hippocamppus but not in *medial septum* and modifies the expresión of Nrf2 in *medial septum* fourty days after injection. These results suggest that $A\beta_{25-35}$ peptide can damage the axons which impairs the neural communication and causes learning impairment, decrease of the activity of the AChE in the hippocampus and the cytoplasmic localization of Nrf2 in the medial septum neurons that indicates a reduction in the antioxidant response.
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Disclosures: L.G. Sánchez-Abdón: None. **G. Morales-Flores:** None. **I. Martínez-García:** None. **A. Ramírez-Mata:** None. **A. Patricio-Martinez:** None. **I.D. Limón:** None.

Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.07/C92

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG034389

Title: Association of aβ with astrocyte-derived and ceramide-enriched exosomes mediates aβ mitotoxicity in neurons which is prevented by novel ceramide analogs

Authors: *A. ELSHERBINI, H. QIN, Z. ZHU, S. KARKI, S. CRIVELLI, P. TRIPATHI, G. WANG, E. BIEBERICH;
Univ. of Kentucky, Lexington, KY

Abstract: The cause for neurotoxicity of Aβ in Alzheimer's disease (AD) is still not clear. Here, we show that serum from 5xFAD mice and AD patients, but not serum from wild type mice or healthy human controls contains a proportion of ceramide-enriched and astrocyte-derived (GFAP positive) exosomes termed astrosomes that are associated with Aβ. The novel ceramide analog N-oleoyl serinol (S18) prevented Aβ association with astrosomes suggesting that ceramide-mediated binding of Aβ to astrosomes. In contrast to Aβ alone, Aβ-associated astrosomes increased neurite fragmentation and neuronal cell death by 3-fold, suggesting that association with astrosomes enhanced Aβ neurotoxicity. Aβ-associated astrosomes from familial AD (5xFAD) mice and AD patient serum were taken up by mouse Neuro 2a cells and human iPS cell-derived neurons. They were transported to mitochondria and increased the concentration of Aβ and ceramide, induced mitochondrial clustering, and upregulated the fission protein Drp-1. We tested if Aβ-associated astrosomes mediated binding of Aβ to VDAC1, an ADP/ATP transporter known to form pro-apoptotic pores in mitochondria when bound to Aβ. Aβ-associated astrosomes induced complex formation between Aβ and VDAC1 concurrent with caspase activation. Complex formation and caspase activation were not observed with exosomes from wild type and human control serum or Aβ alone. Our data suggest that the association of Aβ with ceramide in astrosomes enhances Aβ interaction with VDAC1 and mediates Aβ neurotoxicity in AD, which can be prevented novel ceramide analogs.

Disclosures: **A. Elsherbini:** None. **H. Qin:** None. **Z. zhu:** None. **S. Karki:** None. **S. Crivelli:** None. **P. Tripathi:** None. **G. wang:** None. **E. Bieberich:** None.

Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.08/D1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH RO1AG048993
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NIH P20GM103442

Title: Comparison of salivary Aβ levels and oral microbiome in two different mouse models of AD

Authors: *A. M. FLODEN, M. SOHRABI, S. NOOKALA, G. D. MANOCHA, C. K. COMBS; Biomed. Sci., Univ. of North Dakota, Grand Forks, ND

Abstract: The amyloid precursor protein (APP) is robustly expressed by neurons. APP is proteolyzed into the peptide fragment, amyloid β (Aβ), which can aggregate to form extracellular plaques associated with Alzheimer's disease brains. However, APP is expressed by numerous cell types where its proteolysis and function remain less clear. For example, our prior work demonstrated robust expression of APP in intestinal epithelial cells which are also capable of producing and secreting Aβ. Based upon this finding, we hypothesized that salivary gland epithelium would also express APP and secrete Aβ peptide. To test this idea, we first verified immunoreactivity of APP and Aβ in ductal epithelium of control and AD salivary glands. We next assessed the consequences of APP expression and metabolism using male and female C57BL/6 wild type and $APP^{-/-}$ mice compared to two transgenic mouse models of AD, APP/PS1 and $App^{NL\text{-}G\text{-}F}$ mice. As observed in human samples, APP was robustly expressed in ductal epithelium of wild type, APP/PS1, and $App^{NL\text{-}G\text{-}F}$ mice. To quantify proteolysis of APP, we measured salivary Aβ levels. Only $App^{NL\text{-}G\text{-}F}$ saliva contained Aβ 1-42 with no detectable Aβ 1-40 in either APP/PS1 or $App^{NL\text{-}G\text{-}F}$ mice. No significant differences in total volume or flow rate were observed across genotypes. In order to examine consequences of attenuated or mutant APP expression on oral health, cavities and oral microbiome were assessed. There were no increases in cavity numbers in male or female APP/PS1 and $App^{NL\text{-}G\text{-}F}$ compared to wild type mice. However, male but not female $APP^{-/-}$ mice had increased cavities compared to wild type mice. Sequencing of oral microbiome from each line demonstrated that $App^{NL\text{-}G\text{-}F}$ mice had significantly higher abundance of the phyla Firmicutes and lower abundance of Proteobacteria compared to wild type mice. Consistent with the lack of detectable saliva Aβ 1-42 from APP/PS1 mice, this line demonstrated no differences in Firmicutes or Proteobacteria compared to wild type mice. These data indicate that APP expression outside of neurons may have specific effects on other organ systems that may or may not be relevant to AD. In addition, we have found that APP expression or its metabolites influences the oral microbiome in at least one transgenic mouse model of AD.

Disclosures: A.M. Floden: None. **M. Sohrabi:** None. **S. Nookala:** None. **G.D. Manocha:** None. **C.K. Combs:** None.

Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.09/D2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Fondecyt 1161078
Beca Conicyt 21160392

Title: Expression of P2X2 purinergic receptor in N2a differentiated cells, as a model to study amyloid beta related pathways

Authors: *P. A. GODOY[1], I. CUCHILLO-IBAÑEZ[2,3], D. MENNICKENT[1], O. RAMÍREZ-MOLINA[1], T. B. SILVA-GRECCHI[1], J. PANES-FERNÁNDEZ[1], J. GAVILÁN[1], J. SÁEZ-VALERO[2,3], J. FUENTEALBA[1];
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Abstract: Purinergic receptors P2X (P2XR) are a family of trimeric receptors activated by ATP. Seven subunits have been described in mammals, from P2X1 to P2X7, with different affinities for the ligand, expression pattern and ion permeability. There are two main isoforms of P2X2 receptor, P2X2a and P2X2b. The longest isoform, P2X2a, is capable to interact with Fe65, an adaptor protein able to interact with the amyloid precursor protein (APP) and regulate its endocytosis and amyloidogenic processing. P2XR expression pattern is regulated in target tissues and cells during differentiation. N2a cells are a fast-growing neuroblastoma cell line that can be differentiated to a neuron-like phenotype in specific culture conditions, and therefore they can be used as a model to study neuronal signaling pathways. Undifferentiated N2a cells express mainly P2X1, P2X3, P2X4, P2X5 and P2X7, while it has been reported that P2X2 is barely expressed at mRNA and protein levels. After neuronal-like differentiation, it has been described that P2X7 levels are lower respect to those in undifferentiated cells, but to our knowledge possible changes in P2X2 expression have not been studied yet. In our hands, chronic exposure of soluble amyloid beta oligomers (SOAβ) in hippocampal neurons resulted in 30% increment of endogenous P2X2a isoform subunit protein levels, respect to that in non-treated neurons, which could be the predominant isoform in these primary cultures. Here, our aim is to study the expression and distribution of P2X2 subunit in neuronal-like differentiated N2a cells, and to analyze the effect of overexpressing both P2X2a and P2X2b isoforms on APP endocytosis, processing and amyloid beta production. Our preliminary results suggest that N2a cells cultured with 10% fetal bovine serum (FBS) express mainly the P2X2a isoform, while cells cultured with 5% FBS during 7 days express lower levels of P2X2a isoform (50% decrease respect to cells cultured in 5% FBS during 2 days) and P2X2b isoform become predominant (150% increase respect to cells cultured in 5% FBS during 2 days), in a time curse dependent manner (we examined 2 days, 5 days and 7 days cultures). These results show that N2a cells express P2X2 subunits and furthermore, along neuron-like differentiation, the isoforms expression is modulated. The possibility that Aβ, in turn, alters P2X2 expression pattern in N2a cells, and that P2X2 has a role modulating endogenous APP endocytosis and processing is assessed.

Disclosures: **P.A. Godoy:** None. **I. Cuchillo-Ibañez:** None. **D. Mennickent:** None. **O. Ramírez-Molina:** None. **T.B. Silva-Grecchi:** None. **J. Panes-Fernández:** None. **J. Gavilán:** None. **J. Sáez-Valero:** None. **J. Fuentealba:** None.

Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

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Program #/Poster #: 560.10/D3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: DFG KO 1679/10-1

Title: Amyloid-beta dimers interfere with amyloid-beta plaque formation

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Abstract: Background. Alzheimer’s disease (AD) is one of the most prevalent neurodegenerative disease in humans, with a growing burden on the human society. In AD, the presence of amyloid beta (Aβ) plaques in the brain is one of the pathological hallmarks. Soluble oligomers of the Aβ peptide are thought to be the primary neurotoxic species. Previously, our lab developed a mouse line producing exclusively covalently linked Aβ S8C dimers (tgDimer) to study the exclusive effect of Aβ dimers on the brain. The sole presence of Aβ S8C dimers in the brain of the tgDimer mouse did not result in Aβ plaques after 24 months, even though the animals showed cognitive deficits. After crossing the tgDimer mouse with the tgCRND8 mouse, which displays a robust plaque pathology, we observed incorporated Aβ S8C dimers in the plaques. Our objective here was to study the effect of Aβ S8C dimers on plaque formation in the brains. **Methods.** For this purpose, we performed immunohistological staining and microscopic imaging on brain sections derived from 3 and 5 months old tgCRND8/tgDimer animals. We measured the levels of Aβ40 and Aβ42 in the brain by performing a four-step ultracentrifugation biochemical fractionation followed by an Enzyme-Linked Immunosorbent Assay (ELISA). **Results and Conclusion.** We observed a significant lower number of Aβ plaques in the brain of tgCRND8/tgDimer animals compared to tgCRND8 animals, whereas the size of the plaques remained the same. The insoluble Aβ42/total Aβ ratio in the brain was significant lower in the tgCRND8/tgDimer animals compared to the tgCRND8 animals for both ages. These results confirm that Aβ S8C dimers can be incorporated into fibrils and indicate that they interfere with the initial seeding phase of plaque generation.

Disclosures: **E. van Gerresheim:** None. **A. Herring:** None. **A. Müller-Schiffmann:** None. **K. Keyvani:** None. **C. Korth:** None.

Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.11/D4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Donald W. Reynolds Predoctoral Fellowship
Oklahoma Nathan Shock Center
AG37847
NS56218
T32 AG052363

Title: Sensitivity of the aging brain to amyloid beta oligomers increases with age

Authors: *A. YEGANEH[1], S. LOGAN[2], H. PORTER[2], D. OWEN[2], J. FARLEY[2], W. M. FREEMAN[3], W. E. SONNTAG[4];
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Abstract: Introduction: Age is, by far, the single most important risk factor for cognitive decline, neurodegeneration and Alzheimer's disease (AD). The etiology for the age-related increase in cognitive impairment and risk for neurodegenerative disease is unknown. The vast majority of animal models used in Alzheimer's research utilize a transgenic approach that has provided compelling information on the role of amyloid and tau in AD. Nevertheless, these models do not address the primary risk factor for AD, age. This series of studies were designed to assess the cellular changes associated with age that confer sensitivity to insults such as Aβ, thereby compromising cognitive function.
Methods: Male 4 and 24 month old C57Bl/6J mice were implanted with intracerebroventricular (ICV) osmotic mini-pumps into the lateral ventricle and 150µg of $A\beta^{1-42}$ oligomers or scrambled $A\beta^{1-42}$ (control) infused for 28 days. On day 21, mice were assessed for spatial learning and working memory using a discrimination task based on a food reward. The first two days (initial discrimination) mice learned to enter the feeding area through the left entrance and the correct entrance was reversed on days 3 and 4 (reversal). Data were recorded using Ethovision video tracking software and performance was assessed as a Cumulative Learning Index (Correct-Incorrect/Total entries). At the conclusion of behavior, were processed and utilized for RNAseq analysis to relate changes in gene expression to behavior.
Results: Preliminary studies indicated that oligomerized Aβ injected ICV rapidly crosses the

tanycyte barrier and enters the brain. Young and Aged mice with or without amyloid oligomers were equally able to learn the behavioral task during initial discrimination. However, cognitive plasticity (the ability of the animal to extinguish a memory and learn the reversal task) was impaired with age and the effect was exacerbated by Aβ in old but not young animals. RNAseq analysis revealed 68 transcripts that were differentially expressed in response to Aβ between groups. Additionally, there was a robust increase in TNF and other proinflammatory TNF associated transcripts as well as microglial transcripts in response to $A\beta^{1-42}$.
Conclusion: Our studies indicate that aged mice exhibit increased sensitive to oligomeric Aβ-induced cognitive deficits compared to young animals. Understanding the mechanisms contributing to the age-related component of the disease process and developing interventions may be a promising, novel and prudent approach to delay the onset and progression of Aβ related dementia.

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Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.12/D5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: KIHA 2019- 294811

Title: Inhibition of polyamine synthesis decreases beta amyloid mediated apoptosis

Authors: *A. SANDBERG[1], A. JOHNSON[1], D. FUDGE[1], S. MELGAR[2], C. HICKS[1], D. PATTERSON[3], G. VACANO[3], M. MARGITTAI[4], H. WEISMILLER[4], S. HARVEY[5], L. HERNANDEZ[7], P. A. CAVIEDES[8,9], A. LEDREUX[2], Y. QIN[6], A.-C. GRANHOLM[2], D. A. LINSEMAN[1], D. PAREDES[2];
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Abstract: The dysfunctional accumulation of amyloid beta (Aβ) plaques in neuronal cells is widely regarded as a hallmark sign of Alzheimer’s disease (AD). However, despite extensive knowledge pertaining to the genesis of such plaques, the mechanisms by which Aβ causes the rampant apoptosis that leads to the characteristic memory loss and dementia observed in AD patients are much less understood. In this study, the regulatory relationship between $A\beta_{1-42}$, a

particularly toxic member of the Aβ peptide family, and polyamines (PA), a ubiquitous class of molecules associated with cell growth and proliferation, was investigated. Specifically, HT22 hippocampal cells were transfected with either empty IRES control or $A\beta_{1-42}$ expressing vectors to establish whether intracellular PA were upregulated by Aβ overexpression as well as determine if the inhibition of such upregulation had any effect on amyloidogenic aggregation and, by extension, neuronal cell death. Ultimately, it was found that $A\beta_{1-42}$ increases PA levels in a dose dependent fashion through enhanced expression of ornithine decarboxylase (ODC), the rate limiting enzyme of PA biosynthesis. Furthermore, treatment with the irreversible ODC inhibitor L--difluoromethylornithine (DFMO) was shown to decrease both $A\beta_{1-42}$ aggregation and cell death in transfected cells. Together, these data suggest that increased intracellular concentrations of PA are not only the result of aberrant amyloidogenic accumulation, but also that these molecules in turn contribute to $A\beta_{1-42}$ toxicity. Moreover, the protective benefits imparted on HT22 cells by DFMO offer a potentially novel therapeutic avenue to mitigating amyloid plaque aggregation in the treatment of AD.

Disclosures: **A. Sandberg:** None. **A. Johnson:** None. **D. Fudge:** None. **S. Melgar:** None. **C. Hicks:** None. **D. Patterson:** None. **G. Vacano:** None. **M. Margittai:** None. **H. Weismiller:** None. **S. Harvey:** None. **L. Hernandez:** None. **P.A. Caviedes:** None. **Y. Qin:** None. **A. Granholm:** None. **D.A. Linseman:** None. **D. Paredes:** None. **A. Ledreux:** None.

Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.13/D6

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Role and regulation of E3 ubiquitin ligase itch in neuronal apoptosis

Authors: *M. CHAUHAN, P. K. MODI, P. SHARMA;
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Abstract: Subsequent to differentiation, neurons exit the cell cycle and remain in terminally differentiated state. However, neurotoxic insults like Alzheimer's disease (AD) related amyloid beta peptide $A\beta_{42}$ compel neurons to re-enter the cell cycle, which results in their apoptosis. The mechanisms underlying cell cycle re-entry and apoptosis of neurons are poorly understood. We recently reported that p73 family member TAp73 is degraded in response to $A\beta_{42}$, which results in Cell Cycle Related Neuronal Apoptosis (CRNA). In this study, we report that E3 ubiquitin ligase Itch mediates proteasomal degradation of TAp73 and promotes CRNA. We observed enhanced interaction of Itch with TAp73 in cortical neurons treated with $A\beta_{42}$ or derived from AD transgenic mouse model (TgAD). Itch knockdown significantly reversed the process of CRNA indicating it to be a regulator of CRNA. Our studies indicate that post-translational

modifications like phosphorylation and self-ubiquitination of Itch, which is aberrantly regulated in response to $A\beta_{42,}$ facilitates TAp73 degradation. Furthermore, phosphorylation and auto-ubiquitnation site null mutants reverted TAp73 degradation and CRNA. Collectively, our study reveals a novel role for Itch in cell cycle related neuronal apoptosis in the process of neurodegeneration and shed light on its regulation during this process.

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Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.14/D7

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Increased cell cycle reporter activity is not associated with amyloid β-induced death of neurons

Authors: *L. M. ITTNER[1], S. IPPATI[1,2], Y. DENG[1], J. VAN DER HOVEN[1], Y. LIN[1], A. ITTNER[1], N. HAASS[3], Y. D. KE[1];
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Abstract: Neurons are post-mitotic cells that do not undergo division after terminal differentiation. Re-activation of the cell cycle by neurons with multiplication of chromosomes, but pre-mitotic arrest has been reported in Alzheimer’s disease (AD) brains and models. This gave rise to the hypothesis that neurons that have re-entered the cell cycle become more vulnerable. However, the previous studies relied on staining of cell cycle proteins or DNA content allowing only snap-shot assessment. With the introduction of novel live reporter systems, such as the fluorescence ubiquitination cell cycle indicator (FUCCI) technology, it has become possible to visualize stages of the cell cycle in living cells; The two colour FUCCI system includes expression of FUCCI-red during the G1(G0) phase of the cell cycle, which is replaced by FUCCI-green expression during S/G2/M in dividing cells. Using the FUCCI reporter in primary neurons for live cell microscopy together with oligomeric amyloid-β (oAβ) challenging, we addressed the temporal connection between Aβ-induced re-activation of the cell cycle and death of neurons. Consistent with their post-mitotic state, all neurons expressed the FUCCI-red reporter. Interestingly, we found transient expression of FUCCI-green in the absence of cell division in a small subpopulation of naïve neurons in culture, possible suggesting physiological transient, self-terminating entry in early S/G2. Consistent with previous studies, challenging neurons with oAβ caused cell death, here visualized with the Draq7 dye. Furthermore, we

observed increased, persistent FUCCI-green expression upon oAβ treatment, indicative of cell cycle re-entry. Importantly, oAβ-induced death ($Draq7^+$) and persistent high FUCCI-green expression did virtually never occur in the same neurons. Consistent with our cell culture data, we found frequent and high expression of FUCCI-green in APP transgenic but not non-transgenic mice. Taken together, our data suggest that neurons with oAβ-induced cell cycle reporter activation have adopted a state that protected them from death, while cells that did not induce cell cycle reporter expression were vulnerable. This challenges the concept that molecular events associated with cell cycle re-entry renders neurons more vulnerable in AD.

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Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

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Program #/Poster #: 560.15/D8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant P01AG014449
NIH Grant PO1AG025204

Title: Concentration of pyroglutamate Abeta42 in the frontal cortex of high-pathology elderly controls, mild cognitive impairment, and Alzheimer’s disease

Authors: V. N. PIVTORAIKO[1], E. E. ABRAHAMSON[1], E. J. MUFSON[2], *M. D. IKONOMOVIC[1];
[1]Neurol., Univ. of Pittsburgh, Pittsburgh, PA; [2]Neurobio., Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Background: Pyroglutamate amyloid-β (AβNpE) peptides are highly aggregation-prone truncated and modified Aβ forms present in amyloid deposits in Alzheimer’s disease (AD). Regional differences in concentrations of AβNpE relative to full-length Aβ as well as neuropathology burden and cognitive dysfunction in AD are unknown. We reported previously that AβNpE3-42 and Aβ1-42 concentrations are markedly higher in the posterior cingulate cortex of AD compared to both mild cognitive impairment (MCI) and controls (no cognitive impairment, NCI). The present study quantified AβNpE3-42 and Aβ1-42 concentrations in the frontal cortex (FC, BA10) and examined their relationship with [H-3]PiB binding, global cognition, and neuropathology ratings across the clinical-pathological spectrum of NCI, MCI, and AD. **Methods:** Samples of frozen FC were obtained postmortem from 52 participants in the Rush Religious Order Study with clinical diagnosis of NCI, MCI, or AD. The NCI subjects were divided into low pathology (LP-NCI) and high pathology (HP-NCI) groups. ELISA concentrations of formic acid-extracted AβNpE3-42 and Aβ1-42 as well as [H-3]PiB binding

were compared among the clinical groups and correlated with the last Mini Mental State Examination (MMSE) and neuropathology scores by CERAD and Braak staging. **Results:** FC concentration of AβNpE3-42 in AD was higher than in LP-NCI and MCI, but it did not differ from the HP-NCI group. FC Aβ1-42 concentration and [H-3]PiB binding were only higher in AD compared to the LP-NCI. Spearman rank correlation showed strong associations of FC AβNpE3-42 and Aβ1-42 concentrations with [H-3]PiB ($r=0.80$ and $r=0.76$, both $p<0.0001$), MMSE (r, -0.44, $p=0.001$ and r, -0.42, $p=0.003$), CERAD (r, -0.66, $p<0.0001$ and r, -0.57, $p<0.0001$), and Braak ($r=0.57$, $p<0.0001$ and $r=0.45$, $p=0.002$). **Conclusions:** This study demonstrates a relationship of AβNpE3-42 and full-length Aβ1-42 concentrations in FC with neuropathological and clinical progression of AD. While the observed associations are compelling, they do not prove a causality, thus changes in these molecules need to be investigated further in relation to other pathologies (e.g., tau, synaptic changes, inflammation) in key cortical associational areas across clinical stages of AD.

Disclosures: V.N. Pivtoraiko: None. **E.E. Abrahamson:** None. **E.J. Mufson:** None. **M.D. Ikonomovic:** None.

Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.16/D9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant P01AG01449

Title: Dendritic spine density in the frontal cortex of high-pathology elderly controls, mild cognitive impairment, and Alzheimer’s disease

Authors: *E. E. ABRAHAMSON[1], Z. MI[1], M. A. KNAPP[2], K. N. FISH[3], R. A. SWEET[3], E. J. MUFSON[4], M. D. IKONOMOVIC[1];
[1]Neurol., [2]Neurosci., [3]Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA; [4]Neurobio., Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Background: Frontal cortex (FC), a key component of the default mode network (DMN), undergoes marked amyloid deposition early in Alzheimer’s disease (AD). Previous studies report FC plasticity in prodromal AD, but the exact type of synaptic changes involved and their relation to regional increases in amyloid burden are not known. We studied changes in dendritic spines, dynamic postsynaptic structures associated with excitatory neurotransmission, and correlated their density with amyloid pathology in FC during the clinical-pathological course of AD. **Methods:** Dendritic spine densities were quantified using confocal microscopy and spinophilin/phalloidin fluorescence in postmortem tissue sections of FC (BA10) from 44 Rush

Religious Order Study (RROS) subjects with last antemortem clinical diagnosis of no cognitive impairment (NCI, n=19), mild cognitive impairment (MCI, n=10), and AD (n=15). NCI subjects were divided into low pathology (LP-NCI, n=9) and high pathology (HP-NCI, n=10) subgroups, and AD subjects were divided into mild-moderate AD (mAD, MMSE 11-19, n=8) and severe AD (MMSE less than 10, n=7). Dendritic spine density was compared among the clinical-pathological groups and correlated with amyloid burden marked with CN-PiB or X-34, CERAD and Braak neuropathology scores, and tests of global cognition and episodic, semantic, and working memory. **Results:** Densities of FC dendritic spines were higher in LP-NCI and MCI compared to severe AD (p=0.018 and p=0.003, respectively) but not the HP-NCI or mAD groups. Across all cases, lower densities of dendritic spines correlated with greater amyloid burden by CN-PiB (R, -0.41, p=0.007) and X-34 (R, -0.37, p=0.016), and CERAD (R=0.36, p=0.016), but not with Braak neuropathology scores or tests of cognition. **Conclusions:** Density of FC dendritic spines reaches significant loss only in frank AD dementia, which could explain lack of correlation with cognitive measures across the entire clinical AD continuum. While the process of synaptic loss appears to parallel advancement of amyloid pathology, overall stability of dendritic spines in HP-NCI, MCI, and mAD further indicates resilience of the FC to AD progression. How this compares to synaptic and amyloid changes in other regions of the DMN is currently under investigation.

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Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.17/DP03/D10

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Dynamic Poster
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JSPS grant number 16K14704
JSPS grant number 16H03288

Title: Real time imaging using quantum dot nanoprobes revealed cell membrane protrusion-dependent amyloid β_{42} aggregation at peripheral region of PC12 cells

Authors: Y. CHIKAI[1], R. YAMASHITA[1], ***M. KURAGANO**[1], M. TAKAHASHI[2], K. TOKURAKU[1];
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Abstract: Alzheimer's disease (AD) is a progressive disorder of brain that gradually decreases thinking and memory skills. The amyloid cascade hypothesis is that the neurodegeneration in AD causes abnormal accumulation of amyloid β (Aβ) in the aged brain. Aβ consists of 39-43 amino acid residues and is derived from amyloid precursor protein that is cleaved by β- and γ-secretase. It is thought that the aggregation process of Aβ is a key step in the development of AD because aggregates of $A\beta_{42}$ showed neurocytotoxicity. However, the molecular mechanism of the cytotoxicity by $A\beta_{42}$ has not been clearly elucidated. Previously, we reported that a real time imaging method of $A\beta_{42}$ aggregation using quantum dot (QD) nanoprobes. To investigate the mechanism of $A\beta_{42}$ neurocytotoxicity, in this study, we tried to visualize the process of $A\beta_{42}$ aggregation around PC12 cells by applying QD imaging method. First, we examined whether $A\beta_{42}$ aggregation was observed in culture medium. PC12 cells were differentiated by 4.5 ng/ml neuronal growth factor, and then were incubated with 20 μM $A\beta_{42}$ and 30 nM QD$A\beta_{40}$ for 24 h. After incubation, we observed $A\beta_{42}$ aggregates by conventional fluorescence microscopy and confocal laser microscopy. The observation showed that $A\beta_{42}$ aggregates were particularly formed around cells. The 3D observation using confocal laser microscopy revealed that $A\beta_{42}$ aggregates did not localize at the top of cells. Next, we performed live cell imaging using QD to reveal $A\beta_{42}$ aggregation process at the cell peripheral region. Neuronal growth factor treated cells formed many protrusions. $A\beta_{42}$ preferentially started to aggregate at the region where membrane protrusions were frequently formed. Then, protrusions were suppressed at the cell membrane where excessive $A\beta_{42}$ aggregates had been accumulated. Finally, to investigate whether cell membrane motility promotes aggregation of $A\beta_{42}$, we inhibited actin polymerization using 20 μg/ml Cytochalasin D. The 3D observation revealed that Cytochalasin D treatment suppressed $A\beta_{42}$ aggregation around cells. These results indicate that actin-dependent cell motility is responsible for the promotion of $A\beta_{42}$ aggregation at peripheral region of PC12 cells. We hypothesize that the diffusion of $A\beta_{42}$ is transited from 3-dimensional in culture medium to 2-dimensional on the cell surface, and that the active cell membrane protrusions dramatically increase the frequency of collisions among $A\beta_{42}$ at the cell surface, which promotes additional $A\beta_{42}$ aggregation. Moreover, we have found the possibility that the reduction of cell membrane plasticity by $A\beta_{42}$ accumulation is involved in the expression of its neurocytotoxicity.

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Poster

560. Alzheimer's Disease: Amyloid-Beta Toxicity

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 560.18/D11

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Single walled carbon nanotube optical reporter for amyloid beta detection

Authors: *M. ANTMAN- PASSIG[1], A. S. AGUSTINUS[2], Z. CHEN[3], D. A. HELLER[1]; [1]Mem. Sloan Kettering Cancer CTR, New York, NY; [2]Pharmacol., [3]Weill Cornell Grad. Sch. of Med. Sci., New York, NY

Abstract: Amyloid beta (Aß) extracellular deposits are one of the pathohistological hallmarks of Alzheimer's disease (AD). In recent years intracellular accumulation of Aß has been linked with early pathogenic mechanisms and may serve as a marker for AD onset and progression. Aβ can be produced or uptaken into the early/late endosome system, where the acidic pH creates a favorable environment for generation and aggregation of Aβ. Numerous reports now associate intracellular Aβ accumulation, and lysosomal disfunction as an early event in the disease, preceding extracellular amyloid-deposits. Today methods to visualize intracellular Aβ accumulation rely on antibody staining or pre-labeled Aβ. Thus, a reporter that can probe intracellular Aß accumulation in live cells can greatly enhance the tool-kit for investigative research as well as potentially for drug screening applications. We have developed a carbon nanotube optical sensor that can monitor Aß in live cells dynamically and longitudinally. We based our design on previous reports indicating high affinity central hydrophobic core of Aß and single wall carbon nanotubes (SWCNTs). Notably, SWCNTs present advantages as optical sensors owing to their near-infrared emission, as well as photostability and high-sensitivity. SWCNT emission spectra (wavelength ranges of 1100-1150nm) is within the biological transparency window (1000-1700nm) allowing for optimal imaging in live samples. We bio-functionalized SWCNTs in aqueous solutions based on methods developed by ours and other reports. Our results indicate bio-functionalized nanotube sensors (BF-NS) produce a significant wavelength shift in response to biologically relevant concentrations of Aβ, as well as a dose-dependent response to increasing Aβ concentration. Additionally, in cell models, BF-NS accumulate intracellularly and specifically probe Aß (1-42) introduced to cells.

Disclosures: M. Antman- Passig: None. **A.S. Agustinus:** None. **Z. Chen:** None. **D.A. Heller:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); LipidSense, Inc, Goldilocks Therapeutics, Inc. F. Consulting Fees (e.g., advisory boards); Oncorus, Inc.

Poster

561. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 561.01/D12

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Air Force Material Command, USAF, under grant number FA8655-05-1-3065
Air Force Office of Scientific Research (EOARD, London, UK),
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Society for Study on Neuroprotection & Neuroplasticity (SSNN), Cluj-Napoca, Romania
Astra Zeneca, Mölndal, Sweden (HSS/AS),
Alzheimer's Association (IIRG-09- 132087), the National Institutes of Health (R01 AG028679)

Title: Stress induced exacerbation of Alzheimer's disease brain pathology is thwarted by co-administration of nanowired cerebrolysin and amyloid beta peptide antibodies

Authors: *H. S. SHARMA[1], D. F. MURESANU[2], A. NOZARI[3], R. J. CASTELLANI[4], A. OZKIZILCIK[5], H. MOESSLER[6], J. V. LAFUENTE[7], R. TIAN[8], I. MANZHULO[9,10], A. SHARMA[1];
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Abstract: Several lines of evidences suggest that apart from genetic factors, lifetime stressful events contribute to the pathophysiology of Alzheimer's disease (AD). Stressors induce breakdown of the blood-brain barrier (BBB) permeability leading to transport of amyloid beta peptide (ABP) and other toxicological elements from plasma to brain. This could cause biochemical, pathological and immunological challenges and phosphorylation of tau (p-tau). Generation of other free radicals ad oxidants such as nitric oxide (NO), carbon monoxide (CO) and other oxygen radical lead to further brain pathology. In this study we examined role of immobilization stress representing isolation and depressive state on the pathophysiology of ABP infused AD cases was examined in a rat model.
AD like brain pathology was induced by intracerebroventricular (i.c.v.) administration of soluble form of ABP 200 ng/30 µl per day into the left lateral ventricle for 4 weeks in a rat model. Identical ABP was also infused in chronic immobilized rats in a partial restraint tube 2 h daily for 4 weeks. Our observations showed that ABP infusion in immobilized rats resulted in 120 to 210 % increase in the BBB breakdown to serum proteins and Evans blue and 35 to 56 % greater accumulation of ABP in the brain and in CSF as compared to normal rats after identical ABP infusion. Immunoreactivity of heat shock protein (HSP 72) and neuronal nitric oxide synthase (nNOS) showed 43 to 68 & higher upregulation in stressed rats after ABP infusion in several brain regions associated with neuronal, glial and axonal injuries. CSF levels of ABP and p-tau were 95 to 134 % higher in stressed rats after ABP infusion that in normal rats. Immobilization

alone however did not show any brain pathology or accumulation of ABP, p-tau, HSP or nNOS in the brain. TiO2 nanowired delivery of cerebrolysin-a multimodal drug comprising several neurotrophic factors and active peptide fragments together with antibodies to ABP (1:20, 50 µl, i.c.v. daily for 2 weeks after ABP infusion) significantly attenuated brain pathology and BBB breakdown in both control and in stressed group. Deposition of of ABP, p-tau, HSP 72 and nNOS were much less evident in treated group in AD rats with or without stress. These observations are the first to show that stress could exacerbate AD brain pathology probably via generation of oxidative stress, free radicals and BBB breakdown. Neutralization of ABP by antibodies together with exogenous supplement of neurotrophic factors using nanowired delivery enhance neuroprotection in AD brain pathology, not reported earlier.

Disclosures: H.S. Sharma: None. **D.F. Muresanu:** None. **A. Nozari:** None. **R.J. Castellani:** None. **A. Ozkizilcik:** None. **H. Moessler:** None. **J.V. Lafuente:** None. **R. Tian:** None. **I. Manzhulo:** None. **A. Sharma:** None.

Poster

561. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 561.02/D13

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Air Force Material Command, USAF, under grant number FA8655-05-1-3065
Air Force Office of Scientific Research (EOARD, London, UK),
Swedish Medical Research Council (Nr 2710-HSS)
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
Swedish Strategic Foundation, Stockholm, Sweden (HSS/AS)
Society for study on Neuroprotection and Neuroplasticity, Romania
Alzheimer's Association (IIRG-09- 132087), the National Institutes of Health (R01 AG028679)

Title: Nanodelivery of antioxidant H-290/51 with select neurotrophic factors cerebrolysin thwarted chronic nicotine exposure induced exacerbation of Alzheimer's disease brain pathology

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Abstract: Smoking induced nicotine exposure is a serious health hazard to human populations worldwide. Interestingly there are reports that smoking tendency is about 25 to 30 % higher in military personnel. Whether chronic nicotine exposure could accelerates brain pathology of neurodegenerative diseases is not well known. Thus, effect of nicotine on the development of neurodegenerative diseases requires further investigations.

Previous experiments from our laboratory have shown that nicotine (9 mg/kg, s.c.) for 1 week results in blood-brain barrier (BBB) breakdown and cell injuries. Since military personnel are also very probe to development of Alzheimer’s disease (AD), it would be possible that nicotine exposure could play some role in AD pathology. Few reports on nicotine induce amyloid beta peptide (ABP) is controversial. Thus, some suggests that nicotine exposure improves catabolism of ABP where several repots indicate worse deposition of ABP in nicotine exposed human cases or in preclinical studies.

In this investigation, we examine ABP infusion induced AD brain pathology and its modification with prior nicotine exposure. AD like symptoms was produced in normal rats or chronically nicotine exposed group by intraventricular (i.c.v.) administration of AβP (1-40) in the left lateral ventricle (250 ng/10 µl, once daily) for 4 weeks. After 30 days, the rats were examined for a degrading enzyme for ABP neprilysin (NPL) and AβP concentrations in the brain and related pathology. Our observations show that BBB to Evans blue is 124 to 153 % increased together with brain pathology in nicotine exposed AD rats as compared to naïve animals after ABP infusion. Interestingly, in nicotine-exposed rats ABP infusion resulted in 54 to 62 % decrease in NPL concentrations from the ABP alone group (NPL 65±8 pg/g nicotine+ABP, saline control 424±12 pg/g, ABP alone 122±5 pg/g). Whereas, ABP deposition significantly increased in nicotine exposed AD group (Nicotine+AD 98±6 pg/g; ABP alone 78±4 pg/g, control 38±9 pg/g). Treatment with cerebrolysin-a select combination of neurotrophic factors together with a chain breaking antioxidant H-290/51 significantly thwarted nicotine induced AD brain pathology. TiO2 nanodelivery of cerebrolysin (2 ml/kg, i.v.) with H-290/51 (50 mg/kg, i.p.) daily for 3 days after nicotine exposure resulted in significant reduction in ABP accumulation and marked enhancement of NPL activity together with decrease in BBB breakdown and cell injuries. These observations are the first to show that nicotine stimulates ABP deposition and decrease NPL activity thereby enhancing brain pathology in AD, not reported earlier.

Disclosures: S. Sharma: None. **A. Sharma:** None. **A. Ozkizilcik:** None. **P.K. Menon:** None. **R. Patnaik:** None. **A. Nozari:** None. **H. Moessler:** None. **R.J. Castellani:** None. **D.F. Muresanu:** None. **J.V. Lafuente:** None. **R. Tian:** None. **H.S. Sharma:** None.

Poster

561. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 561.03/D14

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Ministry of Science & Technology, People Republic of China
US air Force Material Command grant number FA8655-05-1-3065
Swedish Medical Research Council (Nr 2710-HSS)
Swedish Strategic Research Foundation, Stockholm, Sweden
Society for Study on Neuroprotection & Neuroplasticity (SSNN), Cluj-Napoca, Romania
India-EU Grant Support, Ministry Of Biotechnology, Govt. of India
India-EU Co-operation Program (RP/AS/HSS)

Title: Co-administration of DL-3-n-butylphthalide and neprilysin is neuroprotective in Alzheimer disease

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Abstract: DL-3-n-butylphthalide (DL-NBP) is one of the constituents of Chinese celery extract that is used to treat stroke, dementia and ischemic diseases. However, its role in Alzheimer's disease (AD) is not yet well known. In this investigation, neuroprotective effects of DL-NBP in AD induced brain pathology were explored in a rat model. Since neprilysin (NPL) is an enzyme that degrades amyloid beta peptide (AbP) is downregulated, we explored the combination of NBP and NPL in AD model to achieve neuroprotection. We used TiO2 nanowired delivery of NBP and NPL on reduction in brain pathology in AD. AD like symptoms was produced by intraventricular (i.c.v.) administration of AβP (1-40) in the left lateral ventricle (250 ng/10 µl, once daily) for 4 weeks. After 30 days, the rats were examined for NPL and AβP concentrations in the brain and related pathology. Co-administration of TiO2 nanowired NPL (50 ng in 20 µl) once daily for 1 week after 2 weeks of AβP infusion together with nanowired NBP (40 mg/kg,

i.p.) for 1 week. Control group received saline instead of NPL and NBP in identical manner in AD model. Untreated AD group showed profound blood-brain barrier (BBB) disruption and brain edema together with neuronal injuries 4 weeks after AbP infusion as compared to intact control group. Nanowired treatment with NBP and NPL significantly attenuated AD induced BBB breakdown, brain edema and neuronal damages. Biochemical measurement of NPL showed a significant increase in hippocampus (360 pg/g) from untreated AD group (120 pg/g; Control 420±8 pg/g brain) along with significant decrease in the AβP deposition (55 pg/g from untreated AD control 75 pg/g; saline control 40±4 pg/g). Interestingly, these changes were also evident with moderate neuroprotection when normal NBP (60 mg/kg) or NPL (100 ng in 20 µl) were given in identical manner in AD group. Neuronal damages, gliosis and myelin vesiculation were also markedly reduced by the combined treatment of TiO2 NBP and NPL in AD. These observations are the first to show that co-administration of TiO2-nanowired NBP and NPL has superior neuroprotective effects in AD probably due to increasing the brain NPL level and decreasing AbP deposition effectively. Taken together our observations are the first to suggest that (i) DL-NBP is quite effective in reducing brain pathology and, (ii) nanodelivery of DL-NBP with NPL has far more superior effects in AD, not reported earlier.

Disclosures: **F. Niu:** None. **A. Sharma:** None. **L. Feng:** None. **D.F. Muresanu:** None. **J.V. Lafuente:** None. **A. Nozari:** None. **A. Ozkizilcik:** None. **R. Tian:** None. **H.S. Sharma:** None.

Poster

561. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 561.04/D15

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: US Air Force Research Laboratory, USA
Air Force Material Command, USAF Grant nr FA8655-05-1-3065
Swedish Medical Research Council (Nr 2710-HSS)
Swedish Strategic Research Foundation, Stockholm, Sweden
Society for Study on Neuroprotection & Neuroplasticity (SSNN), Cluj-Napoca, Romania
University Grants Commission, Govt. of India
India-EU Grant Support, Ministry Of Biotechnology, Govt. of India

Title: Pathophysiology of sleep deprivation enhances amyloid beta peptide and p-tau in the CSF and brain. Neuroprotective effects of nanowired delivery of multomodal drug cerebrolysin

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Abstract: Sleep deprivation (SD) is a serious problem in military, emergency workers, intensive care unit professionals leading to judgmental error, intellectual disturbances and precipitation of neurological disorders. Military personnel often develop Alzheimer's disease (AD) that could be linked to post-traumatic stress disorder (PTSD) or traumatic brain injury (TBI). Thus, it would be interesting to explore contribution of SD in process.

Previous experiments from our laboratory show that SD for 12 to 72 h progressively induces blood-brain barrier (BBB) breakdown to proteins leading to edema formation and brain pathology. In this investigation we explored a link between SD and AD by examining brain and CSF levels of amyloid beta peptide (AbP) and phosphorylated tau (p-tau), the hallmarks of AD after SD in a rat model.

SD was induced in rats using the inverted flowerpot surrounded by water level 1 cm below the platform (6.5 cm in diameter). This set up allows free movement of rats but deep sleep is disturbed in animals when they fell down in water. AbP and p-tau was measured using commercial ELISA kit in the CSF obtained from cisterna magna and in the frontal, parietal, cingulate and temporal cortices as well as in hippocampus, thalamus and hypothalamus.

Our observations show that 12 to 72 h SD enhanced AbP deposition in the brain and in CSF in a progressive manner as compared to normal controls. p-tau levels followed closely with AbP in SD groups. SD increased brain AbP by 86 to 134 % (24 h) 150 to 185 % (48 h) and 205 to 265 % (72 h) from controls. In the CSF SD increased AbP levels by 35 % (24 h), 66 % (24 h) and 84 % (72 h) as compared to control group. The p-tau showed marked increase in SD by 92 to 134 % (24 h), 156 to 194 % (48 h) and 189 to 234 % (72 h) compared to controls. The CSF p-tau in SD enhanced by 67 % (24 h), 89 % (48 h) and 138 % (72 h) from respective controls. A close correspondence with neuronal damages with AbP and p-tau levels was seen in SD.

TiO2 nanowired delivery of cerebrolysin-a balanced composition of several neurotrophic factors and active peptide fragments (5 ml/kg, i.v.) significantly attenuates these enhancement of AbP and p-tau levels at 24 to 72 h following 6 and 12 h SD in 24 h; 6, 12, and 18 h in 48 h SD; and 6,12,18 and 24 h in 72 h SD groups. TiO2-naowired cerebrolysin also reduced cellular injuries in SD groups. These observations are the first to show that SD has the capability to induce AbP and p-tau accumulation in the brain and CSF that could be one of the key factors responsible for precipitating AD. Furthermore timely intervention with nanodelivery of cerebrolysin significantly induces neuroprotection and thwarted AbP and p-tau accumulation in SD, not reported earlier.

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Poster

561. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 561.05/D16

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Air Force Material Command, USAF, under grant number FA8655-05-1-3065
Air Force Office of Scientific Research (EOARD, London, UK),
Swedish Medical Research Council (Nr 2710-HSS)
Swedish Strategic Research Foundation, Stockholm, Sweden
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
Society for study on Neuroprotection and Neuroplasticity, Romania
Grants from the Alzheimer's Association (IIRG-09- 132087),

Title: Sleep deprivation induced exacerbation of Parkinson's disease pathophysiology is attenuated by co-administration of nanowired cerbrolysin and serotonin-3 receptor antagonist ondansetron

Authors: *A. OZKIZILCIK[1], A. SHARMA[2], A. NOZARI[3], H. MOESSLER[4], D. F. MURESANU[5], J. V. LAFUENTE[6], R. J. CASTELLANI[7], R. TIAN[8], R. PATNAIK[9], P. K. MENON[10], H. S. SHARMA[2];
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Abstract: Sleep deprivation (SD) is a serious problem in military personnel that affects mental functions. Moreover, neurodegenerative diseases like Alzheimer’s disease (AD) and Parkinson’s disease (PD) are also prevalent in veterans either due to post-traumatic stress disorders (PTSD) or following mild traumatic brain injury (TBI). Previous reports from our laboratory showed that TBI exacerbates PD induced brain pathology. However, it is still uncertain whether SD could also affect brain pathology in PD. In this investigation we explored effects of SD on PD induced brain pathology. Furthermore, we examined effects of nanowired delivery of ondansetron that was capable to induce neuroprotection in SD cases effectively. In addition, co-administration of cerebrolysin using nanodelivery was evaluated in PD that for superior neuroprotection. SD was

induced by inverted flowerpot methods surrounded by water (30±1°C) that disturbs continuous sleep.
PD like symptoms were induced in normal or SD mice by administration of 1-metyl-4-fenyl-1,2,3,6-tetrahydropyridin (MPTP, 20 mg/kg, i.p.) daily within 2-h intervals for 5 days induced PD like symptoms. This is confirmed by significant decreases in tyrosine hydroxylase (TH) positive cells in the substantia niagra pars Compacta (SNpc) and striatum (STr) together with dopamine (DA) and its metabolites 3,4-Dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) on the 8th day. At this time, alpha-synuclein (ASNC) and tau proetins increased profoundly in the CSF. We observed that 24 to 48 h SD mice when received MPTP loss of TH positive cells and reduction in DA, DOPAC an HVA were further potentiated. The levels of SNC and p-tau in the CSF were 80 to 109 % increased in PD cases with SD. Brain pathology in PD after SD was also 2- to 3-fold enhanced.
Treatment with TiO2-nanowired ondansetron (1 mg/kg, i.p. daily for 3 days) together with cerebrolysin (5 ml/kg, i.v. daily from day 5 to 8) resulted in significant reduction in brain pathology, and restored DA and DOPAC levels and TH immunoreactivity in the SNpc, STr by more than 78 to 90 % than the normal values. Interestingly, CSF levels of ASNC, and p-tau were also decreased by 70 to 85 % from the untreated PD mouse. When cerebrolysin or ondansetron were given alone in PD, the magnitude of biochemical or immunohistochemical changes together with brain pathology were much less evident in SD mice. Taken together our observations are the first to point a prominent role of SD in the pathophysiology of PD, not reported earlier.

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Poster

561. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 561.06/D17

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Air Force Material Command, USAF, under grant number FA8655-05-1-3065
Air Force Office of Scientific Research (EOARD, London, UK),
Swedish Medical Research Council (Nr 2710-HSS)
Swedish Strategic Research Foundation, Stockholm, Sweden
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
Alzheimer's Association (IIRG-09- 132087),
Dr. Robert M. Kohrman Memorial Fund (MAS, RJC);

Title: Nanodelivery of neuronal nitric oxide synthase antibodies with cerebrolysin thwarted methamphetamine induced aggravation of brain pathology in Parkinson's disease

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Abstract: Previous reports from our laboratory shows that methamphetamine (METH) intoxication exacerbates traumatic brain injury induced brain pathology that is most marked at high altitude (HA). METH or substance abuse is quite common at high altitude leading to a variety of CNS disease and a well-known risk factor for Parkinson’s disease (PD). Thus, in this investigation we examined role of METH in PD induced brain pathology at HA as compared to sea level (SL).
Rats were exposed to chronic METH intoxication (3 mg/kg, s.c.) for 1 week at HA chamber mimicking 5000 M. In these rats PD like symptoms were induced 1-metyl-4-fenyl-1,2,3,6-tetrahydropyridin (MPTP, 20 mg/kg, i.p.) administration daily within 2-h intervals for 5 days. This treatment results in PD symptoms such as decrease in tyrosine hydroxylase (TH) positive cells in the substantia niagra pars Compacta (SNpc) and striatum (STr) together with dopamine (DA) and its metabolites 3,4-Dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) on the 8th day. At this time, alpha-synuclein (ASNC) and tau proetins increased profoundly in the CSF. The magnitude and intensity of these PD symptoms were 150 to 230 % higher in METH treated rats exposed to HA. At SL METH treated rats showed only 50 to 80 % greater changes in these symptoms as compared to MPTP alone treated animals at SL. In our hands MPTP induced PD also upregulated neuronal nitric oxide synthase (nNOS) immunoreactivity in the cerebral cortex that was also exacerbated by METH treatment both at HA and SL. MPTP indexed biochemical and immunochemical changes were significantly attenuated by nanowired delivery of cerebrolysin (NWCBL).
When NWCBL is administered (5 ml/kg, i.v.) with antibodies to nNOS (1:20, 50 µl into lateral cerebral ventricle) on 5th day for 3 consecutive days, brain pathology and breakdown of the blood-brain barrier (BBB) was considerably reduced in METH treated PD rats at HA. In these groups TH positive cells were significantly restored and the levels of DA, DOPAC and HVA is enhanced markedly. On the other hand nNOS antibodies or NWCBL alone were effective in METH treated PD rats at SL only. These observations for the first time show that METH can exacerbate PD symptoms that are further aggravated at HA. Combined treatment with nNOS

antibodies and NWCBL is needed to thwart brain pathology and PD symptoms in METH treated group at HA, not reported earlier.

Disclosures: **J.V. Lafuente:** None. **A. Sharma:** None. **H. Moessler:** None. **A. Nozari:** None. **D.F. Muresanu:** None. **R. Patnaik:** None. **P.K. Menon:** None. **R.J. Castellani:** None. **A. Ozkizilcik:** None. **R. Tian:** None. **H.S. Sharma:** None.

Poster

561. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 561.07/D18

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Air Force Material Command, USAF, under grant number FA8655-05-1-3065
Air Force Office of Scientific Research (EOARD, London, UK),
Swedish Medical Research Council (Nr 2710-HSS)
Swedish Strategic Research Foundation, Stockholm, Sweden
society for Study on Neuroprotection & Neuroplasticity (SSNN), Cluj-Napoca, Romania
Grants from the Alzheimer's Association (IIRG-09- 132087),
the National Institutes of Health (R01 AG028679)

Title: Nanowired delivery of cerebrolysin with antioxidant methylene blue induces superior neuroprotection following ischemia-reperfusion injury in experimental cardiac arrest

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Abstract: Several lines of evidences suggest that oxidative stress plays an important role in neuronal injuries after cardiac arrest. Oxidative stress is known to induce increased production of

carbon monoxide (CO) like nitric oxide (NO) and damage blood-brain barrier (BBB) inducing brain edema and cellular injuries.
Rats were anesthetized and an alternating transthoracic current induced 3 min cardiac arrest. Then, 8 min of cardiac pulmonary resuscitation (CPR) followed that often-resulted in return of spontaneous circulation (ROSC). After a monitoring period of 3 hours the rats were sacrificed and the brain was collected. Some rats were given nanowired methylene blue (MB) dye (3 ml/kg, i.v.) initially during CPR either alone or together with nanowired cerebrolysin (5 ml/kg, i.v.). ELISA analysis together with immunohistochemical studies was used to determine HO-1 and HO-2 enzymes content in the parietal cerebral cortex, hippocampus and cerebellum.
Our observations show that cerebral tissue from rats subjected to cardiac arrest (CA), CPR and surviving the monitoring period resulted in 150 to 230 % increase in HO-1 enzyme and 78 to 103% in HO-2 enzyme levels in the cerebral cortex, hippocampus and cerebellum together with BBB breakdown and cellular injuries. Interestingly hippocampus and cerebellum showed significantly higher increase in HO-1 and HO-2 as compared to cerebral cortical tissues. These biochemical changes were further confirmed by increased immunostaining of HO-1 and HO-2 in the parietal cortex especially in layer III as well as in the hippocampus CA1, CA3 and dentate gyrus. In cerebellum both Purkinje cells and granule cells showed increased immunostaining of HO-1 and HO-2 in untreated group. MB was able to slightly but markedly reduce HO-1 and HO-2 staining that was potentiated when combined with cerebrolysin. In general HO-1 expression was greater than HO-2 upregulation in all cases of cardiac arrest examined.
Our observations are the first to show that an experimental CA of long duration followed by successful CPR results in significant alteration of cerebral concentrations of HO-1 and HO-2 levels indicating role of CO in brain pathology after CA that was significantly reduced by nanowired methylene blue and cerebrolysin together with brain pathology.
1.Sharma HS, Miclescu A, Wiklund L. Cardiac arrest-induced regional blood-brain barrier breakdown, edema formation and brain pathology: a light and electron microscopic study on a new model for neurodegeneration and neuroprotection in porcine brain. J Neural Transm (Vienna). Jan;118(1):87-114.

Disclosures: **A.K. Pandey:** None. **A. Sharma:** None. **D.F. Muresanu:** None. **H. Moessler:** None. **J.V. Lafuente:** None. **A. Nozari:** None. **A. Ozkizilcik:** None. **R. Tian:** None. **R. Patnaik:** None. **R.J. Castellani:** None. **H.S. Sharma:** None.

Poster

561. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 561.08/D19

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Air Force Material Command, USAF, under grant number FA8655-05-1-3065

Air Force Office of Scientific Research (EOARD, London, UK),
Swedish Medical Research Council (Nr 2710-HSS)
Swedish Strategic Research Foundation, Stockholm, Sweden
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
Alzheimer's Association (IIRG-09- 132087),
National Institutes of Health (R01 AG028679)

Title: Spinal cord injury induced exacerbation of Alzheimer's disease pathophysiology in rhe cord is reduced by topical application of nanowired cerebrolysin and antibodies to tumor necrosis factor alpha

Authors: *P. K. MENON[1], A. SHARMA[2], A. NOZARI[3], R. J. CASTELLANI[4], D. F. MURESANU[5], R. PATNAIK[6], J. V. LAFUENTE[7], A. OZKIZILCIK[8], R. TIAN[9], H. MOESSLER[10], H. S. SHARMA[11];
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Abstract: Military personnel are prone to development of Alzheimer's disease (AD) largely due to either post-traumatic stress disorder (PTSD) or lifetime mild to moderate traumatic brain injury. Spinal cord injury (SCI) is also quite frequent in military due to motor vehicle accident, missile of gunpowder explosion or direct insult to the spinal cord. Although, AD is well known to induce brain pathology, damage or deposition of amyloid beta peptide (ABP) in the cord is still not well known. Recent clinical studies showed that patients with SCI lead to 37 % higher episodes of AD than non-SCI patients. This suggests that SCI and AD pathology are somehow inter-related.
We explored effects of SCI on AD induced spinal cord pathophysiology. Previous reports from our laboratory showed that topical application of cerebrolysin-a multimodal drug is able to reduce SCI induced cord pathology up to 24 and 48 h. Also topical application of monoclonal antibodies to tumor necrosis alpha over the injured cord 30 to 1 h after is able to reduce cord pathology. Thus, we investigated role of SCI in ABP infusion induced AD pathology in the cord and also evaluated effects of combined nanowired delivery of cerebrolysin and TNF-alpha on cord neuroprotection.
AD like symptoms were produced in rats by intraventricular (i.c.v.) administration of AβP (1-40) in the left lateral ventricle (250 ng/10 µl, once daily) for 4 weeks in normal or spinal cord traumatized animals. SCI was inflicted in anesthetized rats after laminectomy at T10-11

segments by making a longitudinal incision of 2 mm deep and 4 mm long of the right dorsal horn. In these ABP infused animals spinal cord pathology, ABP radioimmunoassay and blood-spinal cord barrier (BSCB) was examined.
Our observations showed that ABP deposits in AD rats after SCI was 85 to 98 % higher than normal intact AD group. BSCB breakdown to radioiodine or Evans blue was 250 and 340 % higher in AD rats with SCI as compared to normal AD group. Neuronal, glial and axonal injuries were 2- to 4-fold higher in the cord of ABP infused rats after SCI as compared to non-SCI rats. Topical application of nanowired cerebrolysin (50 µl/day) for 3 weeks resulted in significant reduction in the BSCB breakdown, cell injury and ABP deposition. These effects were further enhanced when TNF-alpha antibodies (1:20, 50 µl) was co-administered with cerebrolysin in identical manner. Significant reduction in nNOS activity was also seen in combined administration of TNF-alpha and cerebrolysin in AD cases within SCI. This suggests that co-administration of cerebrolysin with TNF-alpha antibodies potentiates neuroprotection in AD with SCI, probably via nitric oxide mediated mechanisms, not reported earlier.

Disclosures: **P.K. Menon:** None. **A. Sharma:** None. **A. Nozari:** None. **R.J. Castellani:** None. **D.F. Muresanu:** None. **R. Patnaik:** None. **J.V. Lafuente:** None. **A. Ozkizilcik:** None. **R. Tian:** None. **H. Moessler:** None. **H.S. Sharma:** None.

Poster

561. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 561.09/D20

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Air Force Material Command, USAF, under grant number FA8655-05-1-3065
Air Force Office of Scientific Research (EOARD, London, UK),
Swedish Medical Research Council (Nr 2710-HSS)
Swedish Strategic Research Foundation, Stockholm, Sweden
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
Society for study on Neuroprotection and Neuroplasticity, Romania
Grants from the Alzheimer's Association (IIRG-09- 132087),

Title: Engineered nanoparticles from metals aggravate brain pathology following traumatic brain injury is reduced by nanodelivery of antibodies to dynorphin A (1-17) with a multimodal drug cerebrolysin

Authors: *A. NOZARI[1], A. SHARMA[2], H. MOESSLER[4], R. PATNAIK[5], P. K. MENON[6], D. F. MURESANU[7], R. J. CASTELLANI[8], R. TIAN[9], A. OZKIZILCIK[10], J. V. LAFUENTE[11], H. S. SHARMA[3];
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Injury & Repair (IECNSIR), Univ. Hospital, Anesthesiol. & Intensive Care Medici, [3]int. Exp. CNS Injury & Repair (IECNSIR), Univ. Hospital, Anesthesiol. & Intensive Care Medici, Uppsala Univ., Uppsala, Sweden; [4]Drug design & Develop., Ever NeuroPharma, Mondsee, Austria; [5]Sch. of Biomed. Engin., Indian Inst. of Technology,Banaras Hindu Univ., Varanasi, India; [6]biomaterials, Biomed. Engin., Banaras Hindu Univ., Varanasi, India; [7]Neurology, ''RoNeuro'' Inst. for Neurolog. Res. and Diagnos., The Fndn. of the Society for the Study of NEU, Cluj Napoca, Romania; [8]Pathology, Univ. of Maryland Med. Sch., Baltimore, MD; [9]Chem. & Biochem., Univ. of Arkansas Fayetteville, Fayetteville, AR; [10]Biomed. Engin., Univ. of Arkansas, Fayetteville, AR; [11]Neurosciences, Univ. of Basque Country, Bilbao, Spain

Abstract: Traumatic brain injury (TBI) is one of the biggest challenges in military personnel during combat operations. TBI is also one of the predisposing factors for development of Alzheimer's disease (AD) and Parkinson' disease (PD). In addition, exposure to nanoparticles (NPs) from gun power explosion, environment and industrial hazards could further complicate TBI cases in military. Previous reports from our laboratory show that engineered NPs from metals e.g., Au, Cu, Al exposure to naïve rats exacerbates spinal cord injury (SCI) induced pathology and functional disabilities. In such cases of NPs exposure with SCI nanowired delivery of cerebrolysin (CBL)-a multimodal drug with balanced composition of several neurotrophic factors is able to thwart exacerbation of cord pathology and functional disturbances. However, NPs exposure and TBI is not well investigated. In this investigation, we examined Ag, Cu and Al NPs exposure (20-30 nm, 50 mg/kg, i.p.) on TBI induced brain pathology and functional disturbances in a rat model. Since SCI pathology was also attenuated by administration of dynorphin A (1-17) antibodies (Dyn Abs), we also evaluated effects of nanowired Dyn Abs together with nanowired CBL (NWCBL) in our TBI rat model.
TBI was performed in anesthetized rats by making an incision on the right parietal cerebral cortex (2 mm deep and 4 mm long) and animals were allowed to survive 24 and 48 after injury using standard procedures. In separate group TBI was inflicted in rats on the 8th day that were either exposed to Ag, Cu or Al daily (50 mg/kg, i.p.) for 1 week. Our observations show that NPs exposed rats exhibited 150 to 213 % higher blood-brain barrier (BBB) breakdown, 4 to 6 % greater edema formation and 120 to 230 % higher neuronal injuries than control TBI. These effects are most pronounced in Ag and Cu NPs treated injured rats as compared to Al exposed TBI group. Radioimmunoassay (RIA) of Dyn A showed 189 to 208 % increase after TBI in the cortex in NPs treated group from naïve rats after injury. The magnitude and intensity of these changes were significantly higher at 48 h after TBI as compared to 24 h injury. Intracerebroventricular (i.c.v.) administration of nanowired Dyn A abs (1:20, 50 µl) daily for 1 week followed by intravenous NWCBL (5 ml/kg) 4, 8 and 12 h after TBI significantly attenuated brain pathology, BBB breakdown and edema formation in NPs exposed TBI group at 48 h. Dyn a concentration was also reduced significantly in this group. These observations are the first to show that NPs exposure enhance brain pathology in TBI and NWCBL together with Dyn A abs could induce remarkable neuroprotection, not reported earlier.

Disclosures: **A. Nozari:** None. **A. Sharma:** None. **H. Moessler:** None. **R. Patnaik:** None. **P.K. Menon:** None. **D.F. Muresanu:** None. **R.J. Castellani:** None. **R. Tian:** None. **A. Ozkizilcik:** None. **J.V. Lafuente:** None. **H.S. Sharma:** None.

Poster

561. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 561.10/D21

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Air Force Material Command, USAF, under grant number FA8655-05-1-3065
Air Force Office of Scientific Research (EOARD, London, UK),
Swedish Medical Research Council (Nr 2710-HSS)
Swedish Strategic Research Foundation, Stockholm, Sweden
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
Society for study on Neuroprotection and Neuroplasticity, Romania
Alzheimer's Association (IIRG-09- 132087), the National Institutes of Health (R01 AG028679)

Title: Prior heat exposure exacerbates brain blast injury-neuroprotection by nanodelivery of cerebrolysin with serotonin 6 receptor antagonist SB-399885

Authors: *D. F. MURESANU[1,2], A. SHARMA[3], A. OZKIZILCIK[4], A. NOZARI[5], I. MANZHULO[6,7], J. V. LAFUENTE[8], R. TIAN[9], R. J. CASTELLANI[10], H. MOESSLER[11], H. S. SHARMA[12];
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Abstract: Brain blast injury (bBI) is quite frequent in military personnel often caused by several factors such as high blast pressure waves, penetrating injuries together with chemical explosives. Tissue losses, laceration, hemorrhage, destruction of neuronal networks, edema and neuronal, glial and axonal injury altogether lead to lifetime disability. There are reasons to believe that environmental temperature could affect the pathophysiology of bBI. In this investigation we explored the role of prior heat exposure on bBI and compared the results with normal

thermoneutral ambient temperature as controls.
Rats were heat exposed (HE) in a biological Oxygen Demand (BOD) incubator at 34°C for 1 h daily for 2 weeks without any brain pathology. Control rats were placed at 21±1°C. A shock tube blast devise in which compressed helium-driven membrane rupture induced pressure waves simulate bBI was used in a rat model. Equithesin anesthetized rat's head from HE and control group was subjected to overpressure blast (100, 150 or 200 kPa) in the shock-tube (shockwave velocity 400 to 450 m/sec). After 4 and 8 h bBI, breakdown of the blood-brain barrier (BBB) permeability to Evans Blue albumin (EBA) and Radioiodine ([^{131}-I]) was measured in 8 brain regions. Regional cerebral blood flow (rCBF) using radiolabelled microspheres was measured. Morphological examination for neuronal, glial, myelin changes and albumin leakage was examined. Profound progressive increase in the BBB permeability to EBA and radioiodine in the cerebral cortex, hippocampus, cerebellum, thalamus, hypothalamus and brain stem was seen that is progressive in time and blast overpressure strength. Severe reduction in the rCBF and brain edema also seen in these brain areas associated with neuronal, glial and myelin damages. Activation of astrocytes and albumin leakage were most pronounced in the areas associated with cellular injuries. These changes were 3- to 4-fold higher in HE rats after bBI. Cerebrolysin (a multimodal drug comprising neurotrophic factors and active peptide fragments) together with 5-HT receptor antagonist (SB-399885, 2 mg/kg, i.v.) given 30 min to 1 h after bBI (5 to 10 ml/kg, i.v.) significantly reduced brain pathology following 4 h trauma in normal and HE rats. However, TiO2 nanodelivery of cerebrolysin (5 ml/kg, i.v.) together with SB-399885 (1 mg/kg, i.v.) induce superior neuroprotection in HE rats after 8 h and 12 h after bBI. These results are the first to show that cerebrolysin together with 5-HT 6 receptor antagonist has the potential to enhance and prolong neuroprotection in rain pathology in HE group after bBI, not reported earlier.

Disclosures: D.F. Muresanu: None. **A. Sharma:** None. **A. Ozkizilcik:** None. **A. Nozari:** None. **I. Manzhulo:** None. **J.V. Lafuente:** None. **R. Tian:** None. **R.J. Castellani:** None. **H. Moessler:** None. **H.S. Sharma:** None.

Poster

561. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 561.11/D22

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Air Force Material Command, USAF, under grant number FA8655-05-1-3065
Air Force Office of Scientific Research (EOARD, London, UK),
Swedish Medical Research Council (Nr 2710-HSS)
Swedish Strategic Research Foundation, Stockholm, Sweden
Government of Basque Country and UFI 11/32 (JVL) University of Basque Country, Spain

Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
India-EU Co-operation Program (RP/AS/HSS)

Title: Nanodelivery of histamine H3 receptor inverse agonist BF-2549 with clobenpropit a H3 receptor antagonist and H4 receptor agonist induced neuroprotection in spinal cord injury is potentiated by antioxidant compound H-290/51

Authors: *R. PATNAIK[1], A. SHARMA[2], P.-O. SJOQUST[3], D. F. MURESANU[4], A. NOZARI[5], R. J. CASTELLANI[6], P. K. MENON[7], R. TIAN[8], A. OZKIZILCIK[9], H. S. SHARMA[2];
[1]Biomaterials, Biomed. Engin., Indian Inst. of Technology,Banaras Hindu Univ., Varanasi, India; [2]Int. Exp. CNS Injury & Repair (IECNSIR), Univ. Hospital, Anesthesiol. & Intensive Care Medici, Uppsala Univ., Uppsala, Sweden; [3]Drug design & Develop., Astra Zaneca, Mölndal, Sweden; [4]Neurology, ''RoNeuro'' Inst. for Neurolog. Res. and Diagnos., The Fndn. of the Society for the Study of NEU, Cluj Napoca, Romania; [5]Anesthesia and Critical Care, Beth Israel Deaconess Med. Ctr., Boston, MA; [6]Pathology, Univ. of Maryland Med. Chool, Baltimore, MD; [7]biomaterials, Biomed. Engin., Banaras Hindu Univ., Varanasi, India; [8]Chem. & Biochem., Univ. of Arkansas Fayetteville, Fayettevillie, AR; [9]Biomed. Engin., Univ. of Arkansas, Fayetteville, AR

Abstract: We reported that histamine H3 and H4 receptors are involved in modulating brain pathology of Alzheimer's disease (AD) and Parkinson's disease (PD). Also, involvement of histamine H1 and H2 receptors participate in traumatic brain injury (TBI) and spinal cord injury (SCI). Thus, potent H2 receptor antagonists cimetidine or ranitidine reduced brain or spinal cord pathology after trauma whereas, H1 receptor antagonist mepyramine aggravated cell injury in TBI or SCI. This suggests that histamine plays key roles in CNS injury and repair. Since SCI or TBI is associated with oxidative stress and cell injuries, we observed that pretreatment with a chain breaking antioxidant compound H-290/51 is highly neuroprotective. However, role of histamine H3 and H4 receptors in SCI is still not well known.
In this investigation, we used TiO2 nanodelivery of BF-2549 and clobenpropit administration together and also investigated combination of nanowired delivery of H-290/51 for superior neuroprotection in a rat model of SCI.
SCI was inflicted in Equithesin anesthetized rats by making a longitudinal lesion (2 mm deep and 4 mm long) of the right dorsal horn of the T10-11 segment after laminectomy. The animals were allowed to survive 15 days after the primary injury sealed wound and routine care. The animals develop hind leg disturbances but other autonomic functions were quite under control. Separate group of rats were treated with TiO2-nanowired BF 2649 (1 mg/kg, i.p.) and Clobenpropit (1 mg/kg, i.p.) once daily for 1 week after 12 h of SCI. Another group of SCI rats also received nanowired H-290/51 (50 mg/kg, i.p. /day for 7 days) besides histaminergic drugs. Control animals with SCI received saline instead of any drug. Our observations show that SCI at 30 days resulted in profound hind limb paralysis with significant edema formation extended to the C4 to L5 regions of the spinal cord. Cellular damage to motor neurons and sensory nerve cells were also present in remote areas as well as in the vicinity of the lesion. Treatment with histaminergic agents and H-290/51 together results in significant improvement in hind limb

function and the cell injuries were markedly reduced and confined to the injury side only at the T10-11 segments. Edema formation and leakage of plasma proetins were minimized to the inured segment only. However, treatment with either histaminergic agents or H-290/51 alone the neuroprotective effect was much less evident on after 2 weeks of SCI. These results are the first to point out that histamine H3 and H4 receptors are regulating SCI induced pathophysiology and a combination of antioxidant induces superior neuroprotection in chronic SCI, not reported earlier.

Disclosures: R. Patnaik: None. **A. Sharma:** None. **P. Sjoqust:** None. **D.F. Muresanu:** None. **A. Nozari:** None. **R.J. Castellani:** None. **P.K. Menon:** None. **R. Tian:** None. **A. Ozkizilcik:** None. **H.S. Sharma:** None.

Poster

561. Neurotoxicity, Inflammation, and Neuroprotection: Advances in Nanomedicine

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 561.12/D23

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Air Force Material Command, USAF, under grant number FA8655-05-1-3065
Ministry of Science & Technology, People Republic of China
Air Force Office of Scientific Research (EOARD, London, UK),
Swedish Medical Research Council (Nr 2710-HSS),
Swedish Strategic Foundation, Stockholm, Sweden (HSS/AS)
Göran Gustafsson Foundation, Stockholm, Sweden (HSS),
Alzheimer's Association (IIRG-09- 132087), the National Institutes of Health (R01 AG028679)

Title: Nanowired delivery of dl-3-n-butylphthalide with antibodies to alpha synuclein potentiated neuroprotection in Parkinson's disease

Authors: *L. FENG[1], A. SHARMA[2], F. NIU[3], D. F. MURESANU[4], A. NOZARI[5], J. V. LAFUENTE[6], A. OZKIZILCIK[7], R. TIAN[8], R. J. CASTELLANI[9], H. S. SHARMA[10]; [1]Neurol., Bethune Intl. Peace Hosp., Shijiazhuang, China; [2]Int. Exp. CNS Injury & Repair (IECNSIR), Univ. Hospital, Anesthesiol. & Intensive Care Medici, Uppsala Univ. Hosp., Uppsala, Sweden; [3]Drug design & Develop., CSPC Zhongnuo Pharmaceut. Shijiazhuang Co Ltd, Hebei Province, China, China; [4]Neurol., The Fndn. of the Society for the Study of NEU, CLUJ NAPOCA, Romania; [5]Anesthesia and Critical Care, Beth Israel Deaconess Med. Ctr., Boston, MA; [6]Neurosciences, Univ. of Basque Country, Bilbao, Spain; [7]Biomed. Engin., Univ. of Arkansas, Fayetteville, AR; [8]Chem. & Biochem., Univ. of Arkansas Fayetteville, Fayetteville, AL; [9]Pathology, Univ. of Marymand Med. Sch., Baltimore, MD; [10]Int. Exp. CNS Injury &

Repair (IECNSIR), Univ. Hospital, Anesthesiol. & Intensive Care Medici, Uppsala Univ., Uppsala, Sweden

Abstract: Parkinson's disease (PD) induces large social burden in the society for which no suitable therapeutic agents are available so far to reduce miserly of patients across the Globe. Military personnel are often quite prone to develop PD in later phase of their life in association with post-traumatic stress disorder (PTSD). In PD alpha synuclein (ASNC) plays a major role in developing PD pathology. Antibodies to ASNC are able to neutralize some of PD induced brain pathology.
dl-3-n-butylphthalide (NBP) a synthetic drug (CSPC Pharma China) is an antioxidant and neuroprotective agents in stroke and traumatic brain injury. The drug is also capable to induce neuroprotection in Alzheimer's disease (AD). Since brain pathology of AD and PD are quite similar, we investigated the role of NBP and ASNC in brain pathology of PD in a mouse model. To enhance the efficacy of these agents we also used TiO2 nanowired delivery of these agents in our PD model.
PD like symptoms appeared on the 8^{th} day after 1-metyl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP, 20 mg/kg, i.p.) daily within 2-h intervals for 5 days in male mice. A significant decrease in dopamine (DA) and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) along with a marked decrease in the number of tyrosine hydroxylase (TH) positive cells in the Substantia Nigra Pars Compacta (SNpc) and striatum (STr) confirms the validity of this model. Measurement of ASNC showed 150-220 % increase in CSF in PD mice as compares to saline administered control group. Neuronal, glial cell and myelin damages examined using Nissl stain, glial fibrillary acidic protein (GFAP) and myelin basic protein (MBP) immunoreactivities respectively using standard protocol. Our observations show that NBP (60 mg/kg, i.p.) either alone or together with antibodies to ASNC (1:20, 100 µg in 10 µl sterile saline) given after 2-days of MPTP daily for 5 days resulted in a marked increase in TH-positive cells in the SNpc and STr as compared to untreated PD mice. Also NBP and ASNC antiserum therapy significantly increased DA, DOPAC and HVA in SNpc and STr on the 8^{th} day. Behavioral function was also significantly improved in MPTP-treated animals that received NBP and ASNC antibodies therapy together. Interestingly, nanowired delivery of NBP (40 mg/kg) with antibodies to ASNC (1:20, 50 µg in 10 µl) significantly enhanced neuroprotection in PD. Neuronal, glial and axonal damages were also considerable reduced in nanowired delivery group of NBP and ASNC abs in PD. These observations are the first to demonstrate that NBP and ASNC abs together when given using nanowired delivery has superior neuroprotection in PD, not reported earlier.

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Poster

562. Alzheimer's Disease: Tau Biochemistry and Physiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 562.01/D24

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: 1R21AG051820

Title: Hyperphosphorylated tau aggregation as a platform for Alzheimer's disease therapeutics and risk factors identification

Authors: *M.-H. KUO[1], M. LIU[2], S. HOVDE[1], D. SUI[1];
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Abstract: Alzheimer’s disease (AD) is an irreversible neurodegenerative disease that has no cure or prevention to date. A defining feature of AD is neurofibrillary tangles (NFTs) composed of fibrils of hyperphosphorylated tau. Here we show a novel AD drug screening methodology based on the aggregation of hyperphosphorylated tau (p-tau). P-tau expressed by the PIMAX approach possesses clinically relevant sites of phosphorylation, fibrillizes autonomously, and causes cell death at sub-micromolar concentrations. This inducer-free p-tau aggregation assay was applied to a 1280-compound library screen, in which we identified two brain permeant prescription drugs as potent p-tau aggregation inhibitors that also counteract p-tau cytotoxicity. Conversely, selective benzodiazepines were found to enhance p-tau aggregation and cytotoxicity, lending molecular support to the epidemiological association of benzodiazepines and increased risks of dementia. These results pave the way for high-throughput screening for therapeutics candidates as well as for the identification of potential risk factors of AD and tauopathies.

Disclosures: M. Kuo: None. **M. Liu:** None. **S. Hovde:** None. **D. Sui:** None.

Poster

562. Alzheimer's Disease: Tau Biochemistry and Physiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 562.02/D25

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R15AG058197-01
PSC/CUNY Grant PSC CUNY 49

Title: Alzheimer's disease-like tau toxicity is enhanced by its nuclear localization

Authors: R. CANDIA[1], *A. ALONSO[2];
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Abstract: Abnormal hyperphosphorylation of the microtubule associated protein tau is a common feature that links several neurodegenerative disorders known as tauopathies. Hyperphosphorylated tau is known to bind to itself and form aggregates rather than associate with microtubules. This loss of cytoskeletal support interferes with neuronal signaling and is thought to underlie the neurodegenerative process. Mutations in tau have been causally linked with familial forms of certain tauopathies, most notably frontotemporal dementia. The mutated tau involved in familial frontotemporal dementia (R406W) has been shown to form aggregates at an accelerated rate. In order to better characterize tau-mediated toxicity, our group has developed PH-tau, which is full-length human tau that has been pseudophosphorylated by the mutations S199E, T212E, T231E, and S262E. When human embryonic kidney (HEK-293) cells are transfected with PH-tau, either with or without the R406W mutation, the protein is found localized to the nucleus. In both cases, there appear to be morphological changes associated with tau overexpression as cells expressing PH-tau are more rounded. In addition, there was an overall decrease in the number of surviving cells post-transfection with PH-Tau-R406W, and a lower number of cells expressing either type of pseudophosphorylated tau compared to cells transfected with wildtype tau. Cells expressing PH-Tau-R406W also exhibit markedly less mitochondrial staining than cells expressing other forms of tau, and this loss of staining extends to nearby un-transfected cells. Elimination of the importin binding site from these constructs prevents the expressed tau from entering the nucleus. The changes in cell morphology and survival also seem to be prevented. However, the loss of mitochondrial staining does not appear to be prevented by removal of PH-Tau-R406W from the nucleus. These initial results suggest that PH-tau is a toxic species, and this toxicity is enhanced by the presence of the R406W mutation. In addition, the toxicity of these pseudophosphorylated tau constructs appears to be at least partially linked to entry into the nucleus. Further investigation will examine how the structure of the actin cytoskeleton, mitochondrial health, and overall cell viability are affected by the presence of pseudophosphorylated tau.

Disclosures: **A. Alonso:** None. **R. Candia:** None.

Poster

562. Alzheimer's Disease: Tau Biochemistry and Physiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 562.03/D26

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association Grant
Virginia Center on Aging Grant

Title: Key sequences within isoforms of human tau protein drive aggregation in Alzheimer's and related tauopathies

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Abstract: Alzheimer's Disease (AD) is the sixth leading cause of death in the United States, and leaves characteristic trademarks in the brain, one being neurofibrillary tangles (NFTs). NFTs form as tau proteins are hyperphosphorylated and become insoluble, ultimately creating highly ordered aggregates that strangle and kill brain cells. Failures in clinical trials on other AD-related proteins make tau a major target for AD drug discovery. In the human brain, tau has six alternatively spliced isoforms, containing 0, 1, or 2 N-terminal inserts, and 3 or 4 C-terminal repeat regions, referred to as 0N3R, 1N3R, 2N3R, 0N4R, 1N4R, and 2N4R. Currently, how tau isoforms aggregate and induce neurotoxicity is largely unknown. Using the largest isoform, 2N4R, as a template, we expressed, purified, and systematically characterized three series of truncation mutants using molecular biology, biochemical, and biophysical techniques. These series included 8 N-terminal truncation mutants, 5 C-terminal truncation mutants, and 3 C-terminal truncation mutants with attached peptide sequences. Detailed aggregation analysis of the truncation mutants revealed the critical role of the second and third repeat regions (R2 and R3) in tau aggregation. Deletion of both R2 and R3 repeat regions prevented protein aggregation. Interestingly, truncation mutants regained aggregation competency when a hexapeptide sequence from the beginning of R2 (VQIINK) or R3 (VQIVYK) was added, but not if a shorter tripeptide sequence shared between R2 and R3 was added (VQI). Our work highlights the importance of R2 and R3 derived hexapeptide sequences (VQIINK and VQIVYK) for human tau isoform aggregation, and provides a possible target for pharmacological intervention.

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Poster

562. Alzheimer's Disease: Tau Biochemistry and Physiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 562.04/D27

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JSPS Grant 17H05703
A research award from the Hoan-sha Foundation

Takeda Science Foundation

Title: An Alzheimer's disease-related mutation in MARK4 promotes tau accumulation and exacerbates tau-induced neurodegeneration in a *drosophila* model of tau toxicity

Authors: *T. OBA[1], T. SAITO[1], A. ASADA[1], K. M. IIJIMA[2], K. ANDO[1];
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Abstract: Alzheimer's disease (AD) is the primary cause of age-dependent dementia. Accumulation of microtubule-associated protein tau is associated with AD and related neurodegenerative disorders. Tau in disease brains are abnormally phosphorylated at a number of sites, and phosphorylation at Ser262 and Ser356 is known to stabilize tau and trigger accumulation of hyperphosphorylated tau in disease brains. Microtubule Affinity Regulating Kinase (MARK) 4 is a kinase that phosphorylates tau at Ser262 and Ser356. Expression of MARK4 is increased in AD brains and colocalizes with tau lesions. A mutation in MARK4, $MARK4^{\Delta Gly316Glu317InsAsp}$, has been associated with an elevated risk of AD. However, it is not well understood how this mutation affects tau metabolism and tau-induced neurodegeneration. Here we report that the introduction of ΔGly316Glu317InsAsp mutation in MARK4 enhances its effects on tau accumulation and tau-induced neurodegeneration by using a *Drosophila* model. We established a transgenic *Drosophila* expressing human MARK4 ($MARK4^{WT}$) or a mutant version of MARK4 ($MARK4^{\Delta Gly316Glu317InsAsp}$). Co-expression of $MARK4^{WT}$ has been reported to increases total tau levels via its phosphorylation at Ser262 and Ser356 and enhances tau-induced neurodegeneration. Co-expression of $MARK4^{\Delta Gly316Glu317InsAsp}$ also increased total tau levels and enhanced tau-induced neurodegeneration, and these effects of $MARK4^{\Delta Gly316Glu317InsAsp}$ on tau were higher than those of $MARK4^{WT}$. The effects of $MARK4^{WT}$ on tau accumulation and toxicity is depending on Ser262 and Ser356, and blocking tau phosphorylation at those sites by substitution of Ser262/356 to unphosphorylatable alanines (S2A) protects tau from the effects of $MARK4^{WT}$. In contrast, we found that co-expression of $MARK4^{\Delta Gly316Glu317InsAsp}$ increased the levels of S2A tau, suggesting that $MARK4^{\Delta Gly316Glu317InsAsp}$ promotes tau accumulation and enhances its toxicity through additional mechanisms. Further studies would shed light on the mechanisms by which $MARK4^{\Delta Gly316Glu317InsAsp}$ increases the risk of AD as well as dysregulation of MARK4 in disease pathogenesis.

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Poster

562. Alzheimer's Disease: Tau Biochemistry and Physiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Japan Agency for Medical Research and Development (AMED) JP19dm0307030
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Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS) JP18dm0207014

Title: Photooxygenation inhibits tau amyloid formation

Authors: *Y. HORI[1], T. SUZUKI[1], T. SAWAZAKI[2], Y. SHIMIZU[2], Y. NEMOTO[1], A. TANIGUCHI[3], S. OZAWA[1], Y. SOHMA[2], M. KANAI[2], T. TOMITA[1];
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Abstract: Alzheimer Disease (AD) is the most common neurodegenerative disorder, which is characterized by two types of depositions of amyloidogenic proteins, amyloid β peptide (Aβ) and tau with cross-β-sheet structure. Several lines of evidence suggest that the aggregation and deposition of these amyloidogenic proteins are associated with the pathogenesis in AD. Therefore, it is important to suppress the formation and the spread of these amyloid depositions, especially via regulation of the seeding activity because it plays an important role in the spreading of pathology in the human brain. Previously, we have reported photooxygenation catalyst which could selectively oxygenate amyloids under light irradiation by binding to cross-β-sheet structure and photooxygenation could suppress the aggregation and the toxicity of Aβ *in vitro* and *in vivo* (Taniguchi et al., Nat Chem 2016; Ni et al., Chem 2018). However, the effect of photooxygenation on tau amyloid was unclear. To investigate this issue, we first developed the new catalyst that was able to oxygenate tau amyloid more effectively than previous catalysts. Oxygen adducts in recombinant tau amyloid by the photooxygenation reaction were detected using MALDI-TOF-MS. Next, to examine the effect of the photooxygenation on the tau aggregation, we performed the *in vitro* aggregation assay measured by Thioflavin-T, which is a selective probe for cross-β-sheet structure. We revealed that the photooxygenation markedly inhibited the seeding activity of tau, thereby suppressing its aggregation. Finally, we showed that the photooxygenation significantly reduced the induction of the tau aggregation in the cellular tauopathy model by seed transfection, indicating that the photooxygenated tau lost its seeding activity in the intracellular milieu. These results indicates that catalytic photooxygenation markedly suppresses the tau seeding activity and inhibits the tau amyloid formation, both *in vitro* and in cultured cells. Thus, photooxygenation for tau amyloid would have the potential for AD therapy by attenuating the seed activity.

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Poster

562. Alzheimer's Disease: Tau Biochemistry and Physiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's association grant 2018-AARF-591935
NIH Grant 1RF1AG058674-01
NIH Grant RF1AG059789
Eli Lilly and Company Research Funded agreement

Title: Tau propagation is dependent on the genetic background in multiple mouse strains

Authors: *S. DUJARDIN[1], M. B. DE LOS SANTOS[2], R. N. BANNON[2], C. COMMINS[2], T. V. KAMATH[2], B. T. HYMAN[3];
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Abstract: The hyperphosphorylation and deposition of tau protein in insoluble aggregates inside neurons are hallmarks of around 20 pathologies called tauopathies including the well-known Alzheimer’s disease (AD). In AD and other tauopathies, histopathological studies have shown that tau lesions appear progressively and hierarchically in the brain along anatomical connections. The mechanisms underlying such evolution had remained unexplained for many years, but recent evidence support the idea that the spread across brain areas is the result of the active propagation of tau aggregation within the brain. We and others previously demonstrated in in vitro and in vivo models that tau assemblies are transferred from cell-to-cell and, by being taken up by a second cell, seed the aggregation of endogenous tau leading to the propagation of tau lesions in the brain. We hypothesized here that the genetic background of mice influences the propagation of tau across neural networks. We used a model of tau propagation that we previously described in which adeno-associated viral vectors (AAV) encoding the eGFP-2A-Tau construct are injected into the entorhinal cortex of mice. The 2A peptide is a self-cleaving peptide resulting in the equimolar independent expression of the eGFP and human tau. Using this model, we can therefore discriminate the neurons expressing the AAVs (GFP and tau positive) from the tau propagation recipient neurons (tau positive only). We injected mice from multiple strains (n = 5 males and 5 females per strain), with diverse genetic backgrounds with this construct and subsequently quantified the number of neurons positive for tau propagation in each condition. In a blinded analysis we found that the propagation of tau in vivo is highly dependent of the genetic background with strains (such as C57BL/6) that are mostly resilient to tau propagation whereas other strains (such as CD-1 or A/J) show a high degree of tau propagation.In conclusion, these results provide an important insight to the idea that tau

propagates from neuron-to-neuron in the human pathology. This could explain part of the human clinical heterogeneity and must be investigated further to understand the genetic factors responsible for such drastic differences.

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Poster

562. Alzheimer's Disease: Tau Biochemistry and Physiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 562.07/D30

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: PRIN2015W729WH_001
PRIN2015W729WH_005
PRIN20179JHAMZ_006

Title: Role of extracellular vesicles in HSV-1-driven brain damage

Authors: *V. PROTTO[1], O. KOLESOVA[2], L. PILENZI[2], G. NAPOLETANI[2], M. L. POTENZA[2], R. PIACENTINI[3,4], C. GRASSI[3,4], M. E. MARCOCCI[2], A. T. PALAMARA[2,5], G. DE CHIARA[1];
[1]Inst. of Translational Pharmacol., Natl. Res. Council of Italy, Rome, Italy; [2]Dept. of Publ. Hlth. and Infectious Diseases,Lab affiliated to Pasteur Inst. Italy, Sapienza Univ. of Rome, Rome, Italy; [3]Inst. of Human Physiology, Univ. Cattolica, Rome, Italy; [4]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [5]San Raffaele Pisana, IRCCS, Telematic Univ., Rome, Italy

Abstract: Extracellular vesicles (EVs) are involved in cell-to-cell communication, spreading of intracellular proteins and miRNA, as well as used by viruses to pass from a cell to another one. Microvesicles shed from plasma membrane whereas exosomes are smaller vesicles, generated from multivesicular bodies and released by neurons and glial cells. A growing body of evidence supports the role of EVs in transferring neurotoxic proteins such as Aβ and Tau, key players in Alzheimer’s disease (AD). Recent studies reported that aggregated forms of Tau can be transmitted among neurons and that exogenous aggregates of Tau could enter inside cells acting as seeds for the aggregation of the endogenous protein, thus propagating Tau-dependent damages in the brain. Several data support the role of Herpes Simplex Virus-1 (HSV-1) infection in AD pathogenesis. We recently demonstrated the effect of multiple viral reactivations on the accumulation of Tau-related brain damages in an *in vivo* mouse model. Interestingly, brain slices from HSV-1 infected animals showed a higher number of phosphorylated Tau (pTau) positive cells with respect to virus positive ones. Here, we investigated whether HSV-1 infection in the

brain could promote Tau spreading among neurons via EVs, as well as virus spreading. To this aim, EVs were isolated from supernatants of human neuroblastoma and primary cultures of rat neurons following 24-48h of HSV-1- or Mock-infection, analysed in western blotting (WB) or incubated on uninfected neurons for 24h following UV-treatment. Cell lysates were then analysed in WB for pTau content and compared to untreated cells. Results showed that EVs derived from HSV-1-infected cells contained: a) viral proteins, suggesting that the virus exploits them for its spreading among cells; b) increased levels of pTau, indicating that the virus can promote pTau propagation among neurons via exosomes. Accordingly, cells incubated with EVs isolated from HSV-1-infected cells showed: a) the occurrence of HSV-1 productive infection, as visualized by the use of fluorescent recombinant HSV-1 virus; b) higher levels of pTau with respect to those detected in untreated cells, indicating that exosomes derived from infected cells can promote Tau phosphorylation and likely its aggregation. Overall, these data indicate that the virus can promote pTau propagation among neurons via EVs, as well as virus spreading, and support the hypothesis that repeated HSV-1 reactivations into the brain may concur to neurodegeneration.

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Poster

562. Alzheimer's Disease: Tau Biochemistry and Physiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 562.08/D31

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG054018

Title: The role of annealing and fragmentation in human tau aggregation dynamics

Authors: C. J. HUSEBY[1], R. BUNDSCHUH[2], ***J. KURET**[3];
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Abstract: Alzheimer’s disease pathogenesis is associated with the conversion of monomeric tau protein into filamentous aggregates. Because toxicity and prion-like spread of tau pathology depend in part on aggregate size, the processes that underlie filament formation and size distribution are of special importance. Here we investigate human 2N4R tau fibrillation dynamics using a combination of biophysical and computational approaches. We find that tau filaments engage in a previously uncharacterized secondary process involving end-to-end annealing, and that rationalization of empirical aggregation data composed of total protomer

concentrations and fibril length distributions requires inclusion of this process along with fragmentation. Annealing of 2N4R tau filaments is robust, with an intrinsic association rate constant of similar magnitude to that mediating monomer addition, and consistent with diffusion-mediated protein-protein interactions in the absence of long-range attractive forces. In contrast, secondary nucleation on the surface of tau filaments makes no detectable contribution to tau aggregation dynamics. These data demonstrate that tau filament ends engage in a range of homotypic interactions involving monomers, oligomers and filaments. They further indicate that in the case of tau protein, annealing and fragmentation along with primary nucleation and elongation are the major processes controlling filament size distribution.

Disclosures: C.J. Huseby: None. **R. Bundschuh:** None. **J. Kuret:** None.

Poster

562. Alzheimer's Disease: Tau Biochemistry and Physiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 562.09/D32

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Public Health Service NS07741
Public Health Service AG045018
C.N.H. Molecular Biophysics Training Grant T32 GM118291

Title: Quantification of lysine methylation on tau protein in aging and Alzheimer's disease

Authors: *C. J. HUSEBY[1], C. N. HOFFMAN[2], J.-C. COCURON[4], A. P. ALONSO[4], J. KURET[3];
[1]Ohio State University, Wexner Med. Ctr., Columbus, OH; [2]Ohio State Biochem. Program, [3]Ohio State Univ., Columbus, OH; [4]BioDiscovery Inst., Univ. of North Texas, Denton, TX

Abstract: Tau is a microtubule-associated protein that normally interacts in monomeric form with the neuronal cytoskeleton. In Alzheimer’s disease, however, it aggregates to form the key structural component of neurofibrillary lesions. The transformation is thought to be controlled in part by age and disease-associated post-translational modifications. Recently we showed that tau is modified on lysine residues by methylation, and that high-stoichiometry methylation can depress the aggregation propensity of recombinant tau *in vitro*. However, whether methylation site occupancy changes with aging and disease or reaches levels needed to influence aggregation is unknown. Here we address this problem using liquid chromatography-tandem mass spectrometry approaches. Results revealed that lysine methylation was present in soluble tau isolated from cognitively normal elderly cases at multiple sites that only partially overlapped with cognitively normal middle aged and AD cohorts. Furthermore, aging and disease also were accompanied by a shift from predominantly dimethyl-lysine to monomethyl-lysine forms.

However, the bulk mol methylation/mol tau stoichiometry did not exceed 1 mol methyl group/mol tau protein in any cohort. We conclude that lysine methylation is a physiological post-translational modification of tau protein that varies with aging and disease. Although basal modification stoichiometries are low, artificial elevation of tau methylation may provide a means for protecting against pathological tau aggregation in disease.

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Poster

562. Alzheimer's Disease: Tau Biochemistry and Physiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 562.10/D33

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH RO1AG056603

Title: Identifying unique sites of tau phosphorylation during hyperexcitation

Authors: *A. K. SCHNEEWEIS[1], J. MA[2], E. ANDRE[1], W. ZHU[3], D. PAK[1];
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Abstract: Alzheimer’s Disease (AD) is the sixth leading cause of death. Current therapies address the symptoms of AD, but not disease progression. There are two pathological hallmarks of AD, aggregation of amyloid beta and hyperphosphorylated tau, and amyloid beta is the major target of current therapeutic studies. However, it has been shown that tau hyperphosphorylation, resulting in synaptic simplification and neuronal death, correlate more closely with dementia. In fact, amelioration of tau pathology can rescue dementia, even with amyloid plaques present. Tau is a microtubule associated protein that has been well-characterized as an axonal protein but has also been reported in the dendrites and synapses. Although tau has over 80 phosphorylation sites, many studies rely heavily on a few sites of phosphorylation to broadly determine hyperphosphorylation of tau in a specific condition or disease. Unfortunately, this methodology tends to be biased due to the exclusion of many other phosphorylation sites in tau. Currently, there lacks a comprehensive atlas identifying phosphorylation sites that may be different during specific cellular conditions, including homeostatic synaptic plasticity. I hypothesize that specific pattern of phosphorylation occurs during hyperexcitation which leads to downregulation of AMPA receptors. To test this hypothesis, DIV21 primary hippocampal neurons were treated with 100μM picrotoxin to induce hyperexcitation. Using mass spectrometry, I observed sites with unique tau phosphorylation compared to control. Additionally, using recombinant tau and Polo-like kinase 2 (Plk2), a kinase upregulated during hyperexcitation and known to phosphorylate Amyloid Precursor Protein, two additional sites were identified to be directly phosphorylated by

Plk2. Using mass spectrometry, I have shown that I can characterize tau phosphorylation during homeostatic synaptic plasticity in a way that is unbiased. Creating an atlas of tau phosphorylation sites involved in homeostatic synaptic plasticity could be useful as a biomarker and could also aid in the development of therapies for Alzheimer's Disease and other tauopathies.

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Poster

562. Alzheimer's Disease: Tau Biochemistry and Physiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 562.11/D34

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Development of new ultra sensitive assays to quantify tau aggregation and pathological tau conformation using digital immunoassay technology

Authors: *A. FRANCOIS, G. DAS DORES, F. IOP, R. BILLIRAS, V. PASTEAU, F. PANAYI, R. JEGGO;
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Abstract: As clinical trials aimed at clearing neurotoxic β-amyloid species have so far been largely unsuccessful, interest in tau-based treatments, including tau-aggregation inhibitors is increasing. Therefore, the validation of assays sensitive enough to measure onset/progression of tau pathology in preclinical rodent models, as well as biomarkers to measure therapeutic efficacy in patients is increasingly important. The recent introduction of digital ELISA has highly improved the sensitivity of immunoassays. In this context, we have developed digital ELISA assays using the SIngle MOlecular Array (SIMOA™) technology from Quanterix to quantify total tau aggregation and the pathological tau conformation, MC1. The detection of total tau aggregation is based on the principle that the same monoclonal antibody is used for both capture and detection to selectively quantify aggregated tau forms over monomeric form. The screening of commercially available monoclonal tau antibodies was performed with tau-5, tau-2, tau-12, tau-14, tau-46, HT7, SP70, D1M9X, DA9 (provided by Dr. Peter Davis) and using heparin aggregated tau as calibrator. HT7 was identified as having the lowest limit of quantification (7.86 pg/ml of equivalent monomeric tau) and the largest dynamic range (up to ~3 logs). In parallel, two SIMOA™ assays, one to detect MC1 (provided by Dr. Peter Davis) positive aggregates and another to evaluate the total level of tau MC1 conformation were developed. These three SIMOA™ assays were applied to characterize the tau pathology in postmortem samples of frontal cortex of Alzheimer's disease (AD) patients and healthy controls and the progression of tau pathology in a tau transgenic mouse model overexpressing the mutated P301S tau. As expected, levels of total tau aggregation, MC1 positive aggregates and total MC1 levels were

significantly higher in AD patients compared to healthy controls. Interestingly, MC1 positive aggregates in AD brain samples represent approximately 50% of the total tau aggregation. In the P301S mouse model the tau pathology time-course showed a significant increase of total tau aggregation and MC1 positive aggregates at 9 months compared to 3 and 6 months. MC1 positive aggregates represent approximately 12% of the total tau aggregation in this model and total MC1 levels increased progressively in a time-dependent manner.These three new ultra-sensitive assays provide new tools to investigate the progression of tauopathy in transgenic models, to evaluate the efficacy of different tau-targeting treatments and to determine the optimal treatment window with the best estimated translatability to the human situation.

Disclosures: **A. Francois:** A. Employment/Salary (full or part-time):; full time employee of SERVIER. **G. Das Dores:** A. Employment/Salary (full or part-time):; full time employee of SERVIER. **F. Iop:** A. Employment/Salary (full or part-time):; full time employee of SERVIER. **R. Billiras:** A. Employment/Salary (full or part-time):; full time employee of SERVIER. **V. Pasteau:** A. Employment/Salary (full or part-time):; full time employee of SERVIER. **F. Panayi:** A. Employment/Salary (full or part-time):; full time employee of SERVIER. **R. Jeggo:** A. Employment/Salary (full or part-time):; full time employee of SERVIER.

Poster

562. Alzheimer's Disease: Tau Biochemistry and Physiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 562.12/D35

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AG050471
NS089544
AG056318
BrightFocus Foundation
Alzheimer Association
Cure Alzheimer’s Fund

Title: The dynamics of MAPT liquid-liquid phase separation are regulated by RNA binding proteins

Authors: P. E. ASH[1], S. LEI[1], S. BOUDEAU[1], L. JIANG[1], L. AL-MOHANNA[1], M. KNOBEL[1], N. M. KANAAN[3], *B. L. WOLOZIN[1,2];
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[3]Translational Sci. & Mol. Med., Michigan State Univ., Grand Rapids, MI

Abstract: Microtubule-associated protein tau (tau), the hallmark aggregating protein of Alzheimer’s disease (AD), interacts with RNA binding proteins (RBPs) in the pathogenesis of

disease. Previously, we demonstrated that depletion of Tia1 (a core nucleating RBP of stress granules) in transgenic PS19 P301S tau mice results in behavioural recovery and increased life span. Recovery in PS19; Tia1+/- mice correlates with increased fibrillary tau pathology but reduced levels of oligomeric tau. Recombinant TIA1 interacts with tau, inhibits the elongation of fibrillary tau and stabilizes oligomeric tau, promoting its accumulation. Both RBPs and tau undergo liquid-liquid phase separation (LLPS).We hypothesized that the interaction of tau with RBPs would promote phase separation which would modulate production of pathogenic tau. LLPS of tau and RBPs, conjugated with DyLight fluorophores, was assayed by epifluorescent and super resolution microscopy. The dynamics and distribution of Tau LLPS were differentially affected by diverse RBPs. The rate of formation of tau droplets was strikingly increased in the presence of TIA1 in a dose dependent fashion. Initially, both tau and TIA1 were diffusely distributed in droplets, however over time, tau became concentrated into microdomains within the TIA1 droplets. Microdomains of tau show reduced diffusion suggesting conversion to gels. In contrast, Tau exhibits no phase separation with proteins, such as eIF4E. Tau microdomains are spherical, appear to exclude TIA1 and are sensitive hexandiol, suggesting LLPS within TIA1 droplets is governed by differential hydrophobicity. Introduction of pseudo phosphorylation into tau (E14) dramatically changes the dynamics of co-LLPS with TIA1. E14-tau forms amorphous microdomains within TIA1 droplets, suggesting that phosphorylation alters charge distribution in tau that changes the biophysical properties by which tau undergoes LLPS in the presence of TIA1. Progression of AD is characterized by increasing accumulation of phosphorylated-tau. Our results suggest that tauopathy results from the interaction of hyper-phosphorylated tau with RBPs as part of the protein translation stress response. This interaction is mediated by phase separation of tau with RBPs. The concentration of tau in the RNA granules accelerates oligomerization and then fibrillization, resulting in formation of pathological aggregates. As such, phase separation of phospho-tau with RBPs may be the focal point for generation of tau pathology.

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Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.01/D36

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NC TraCS ECBR004
UNC Department of Neurology

Title: Neuroprotective effects of cannabinoid ligands in a model of early Alzheimer pathogenesis

Authors: *E. BOESCH[1], T. B. DEMARSE[2], B. HARRIS[3], A. DOMBROSKI[3], A. SUCHY[3], A. AMIN[3], R. B. MEEKER[3];
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Abstract: Alzheimer disease (AD) is a devastating neurodegenerative disorder with no disease-modifying therapies currently available. Since AD pathology is preceded by inflammation and neural dysfunction, control of these early manifestations has the potential to modify the course of the disease. Cannabidiol (CBD) has both anti-inflammatory and network stabilizing effects that could offer early protection. To determine if CBD has neuroprotective properties in the context of early AD pathogenesis, we evaluated its effects on regulation of intracellular calcium in primary neurons challenged with conditioned medium from microglia treated with amyloid beta oligomers ($A\beta_o$). Since microglia are potential targets, we also investigated the "anti-inflammatory" properties of CBD by pretreating microglia with CBD before exposure to $A\beta_o$. Network stabilizing properties were measured through electrophysiological recordings of neurons cultured on microelectrode arrays. In neurons, CBD partially decreased the aberrant neuronal calcium accumulation in response to microglial conditioned medium while also increasing the intensity of individual calcium signaling events. CBD also stabilized neuronal network activity and facilitated synchronous activity while decreasing the frequency of synchronous firing events. CBD treatment of microglia robustly decreased secretion of neurotoxic factors suggesting a strong effect on microglial secretory phenotype. Since the pharmacology underlying the potential benefits of CBD is still poorly understood, we examined potential signaling through CB_2 and GPR55. The GPR55 antagonist, ML193, and the CB_2 agonist, JW133, but not CBD, decreased the frequency of intrinsic neuronal calcium signaling in neurons. The GPR55 agonist, LPI, induced a prominent facilitation of mononuclear phagocyte calcium signaling but had a marginal effect on neurons indicating that microglia and macrophages may be prominent targets. Different effects of CBD versus CB_2 and GPR55 ligands indicated a complex pharmacology that needs to be explored in greater depth. The suppression of neural calcium dysregulation, "anti-inflammatory" effects on the microglial secretome and stabilization of neural network activity support the hypothesis that CBD has disease modifying potential for AD.

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Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.02/D37

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: .Teacher Research Support Foundation of Jining Medical University Grant JY2017JS001
Research Fund for Lin He's Academician Workstation of New Medicine and Clinical Translation in Jining Medical University Grant JYHL2018MS07

Title: Regulatory effect of resveratrol on neuronal apoptosis in Alzheimer's disease

Authors: *X. WANG[1], F. JIAO[1], Q. ZHAO[2], S. ZHANG[3], Y. ZHANG[3], Y. ZAI[3], Y. WU[1]; [1]Shandong Key Lab. of Behavioral Medicine, Inst. of Mental Health,Jining Med. Univ., [2]shool of Mental Health,Jining Med. Univ., [3]Jining Med. Univ., Jining, China

Abstract: Alzheimer's disease is achronic neurodegenerative disorder. It's one of observably characters is progressive loss of cognitive and behavioral abilities. AD shares the same pathological hallmarks in the brain, including extraneuronal neuritic plaques,intraneuronal neurofibrillary tangles and synaptic/neuronal loss leading to brain atrophy. In the past few years, many studies have reported interesting in sights about the neuroprotective properties of the poly phenolic compound resveratrol when used with in vitro and in vivo models of AD.Resveratrol(3,5,4_-trihydroxy-*trans*-stilbene)is widely found in skin and seeds of more than 70 different plant species, including hellebore, grapes, berries, grains, tea, peanuts. Resveratrol as a natural herbal extracts in many Chinese herbal medicine has been reported that Resveratrol play an important biological role in protective against oxidative stress, inflammation, and the development of cardiovascular diseases, diabetes, neurodegenerative diseases and cancer. Recent studies reported that resveratrol protects neurons against peroxide (H_2O_2), 1-methyl-4-phenylpyridine ion (MPP) and Aβ injury. A rat model of AD suggests that resveratrol can prevent the cognitive impairment. However, the neuroprotection of resveratrol against Aβ cytotoxicity, oxidative stress or endoplasmic reticulum stress,especially the underlying mechanism, remains largely unknown due to its widely pharmacological actions. Therefore, our study devoted ourselves to the protective effect of resveratrol against oxidative stress or endoplasmic reticulum stress and explored the possible underlying mechanisms.***Results:***1) Resveratrol can increase SH-SY5Y cell viability in oxidative stress/ Ca^{2+} overexpress.2) Resveratrol reduces the oxidative stress/ Ca^{2+} overexpress which induced Ca^{2+}level in SH-SY5Y cell. 3) Resveratrol downregulates the RCAN1 ,BACE1,PSN1,GRP78,CHOP expression in oxidative stress/ Ca^{2+} overexpress cells.

Disclosures: **X. Wang:** None. **F. Jiao:** None. **Q. Zhao:** None. **S. Zhang:** None. **Y. Zhang:** None. **Y. Zai:** None. **Y. Wu:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.03/D38

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH GRANT R01 DK104363
NIH GRANT R01 NS050465

Title: The interaction between fructose and DHA consumption on Alzheimer's disease (AD) pathogenesis

Authors: *V. PALAFOX-SANCHEZ[1], Z. YING[1], X. YANG[1], F. GOMEZ-PINILLA[1,2]; [1]Integrative Biol. and Physiol., UCLA, Los Angeles, CA; [2]Dept. of Neurosurg., UCLA Brain Injury Res. Ctr., Los Angeles, CA

Abstract: It is becoming an alarming public health issue that a large portion of the American population is affected by some degree of metabolic disorder such as diabetes and obesity with subsequent risk for the pathogenesis of AD. Although AD is getting recognition as a metabolic disorder, how dysfunctional metabolism exacerbates the pathogenesis of AD is poorly understood. Fructose is the most consumed sugar in our society in soft drinks and processed foods and is a major contributor to the epidemic of metabolic disorders. Fructose explains a remarkable 20% increase in diabetes, and the connection between diabetes and dementia is increasingly recognized. We are embarked in studies to examine the effects of the metabolic perturbation posed by fructose and the potential of the omega-3 fatty acid DHA to counteract these effects on the AD pathogenesis using the 5xFAD mice. We started treatment when the 5xFAD mice were 2 month-old and found that the mice developed peripheral insulin resistance by 3 months old. The capacity to manage glucose was further altered in the 5xFAD mice treated with fructose. The insulin resistance has been related with alteration in the progression of DA and is becoming an important hallmark in the AD pathogenesis. Fructose ingestion disrupts cognitive performance in the Barnes Maze and open field center time starting by 8 weeks after treatment and continued progression by 12 weeks after fructose ingestion, compared to the 5xFAD+water consumption group. Most of the effects elicited by fructose were counteracted by DHA. Most of these alterations were counteracted by DHA supplemented in the diet. Fructose is metabolized differently to glucose favoring pathogenic pathways and posing additional toll to AD pathogenesis. Our results indicate that metabolic dysfunction carried by fructose increased predisposition to AD pathology. These results are important for the design of public health programs to counteract the effects of AD pathology.

Disclosures: **V. Palafox-Sanchez:** None. **Z. Ying:** None. **X. Yang:** None. **F. Gomez-Pinilla:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.04/D39

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 1R01AG057555-01A1
NIH Grant R25NS80686-08

Title: Therapeutics to target amyloid beta and tau in fibroblasts from a familial Alzheimer's disease patient: Relevance to drug repurposing

Authors: *J. SEPULVEDA[1], E. FELDMAN[1], L. XIE[2], P. ROCKWELL[1], P. A. SERRANO[3], M. E. FIGUEIREDO-PEREIRA[1];
[1]Dept. of Biol. Sci., [2]Computer Sci. Dept., [3]Dept. of Psychology, Hunter Col., New York City, NY

Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that accounts for 60-70% of dementia cases. In AD, the Aβ42 fragment of the amyloid precursor protein (APP) and hyperphosphorylation of the microtubule associated protein Tau, play important roles in disease pathology. Moreover, familial AD is associated with higher levels of Aβ42. Drug discovery for AD has had limited success. Repurposing of FDA-approved drugs could streamline the identification of AD therapeutics. Our *in silico* studies predicted the following: (1) Diazoxide (DZ), which is FDA-approved for hypertension, is a potassium channel activator that could activate multiple AD-relevant kinases. (2) The anti-inflammatory Ibudilast (IBU) and the antidepressant Rolipram (ROL) could inhibit AD-relevant phosphodiesterases. (3) The cancer-preventing Dibenzoylmethane (DIB) could induce the expression of antioxidant enzymes. We investigated the therapeutic potential of these four drugs against Aβ42 and Aβ40 production in skin fibroblasts from a familial AD patient carrying the A246E mutation in the presenilin 1 gene, and human neuroblastoma SY5Y cells overexpressing APP695 (APP695-SY5Y). Cell viability (MTT) assays established that DZ, DIB and ROL are not toxic, but DIB is in both fibroblast and neuroblastoma. Assessing Aβ42 and Aβ40 secretion with ELISAs demonstrated that DZ and IBU decrease Aβ42 production, suggesting that these drugs may reduce AD pathology. The effect of these drugs on tau hyperphosphorylation is also being determined. Moreover, we are testing whether the *in vitro* anti-AD effects of IBU will be reproduced in a transgenic rat model of AD, thus offering a new treatment strategy for this disease.

Disclosures: **J. Sepulveda:** None. **E. Feldman:** None. **L. Xie:** None. **P. Rockwell:** None. **P.A. Serrano:** None. **M.E. Figueiredo-Pereira:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.05/D40

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: IWT SBO iPSCAF – 150031
IWT SB [141228]
IWT-VIND project - 135043

Title: Disease model for progranulin-linked frontotemporal dementia using patient and engineered stem cells

Authors: ***J. TERRYN**[1], F. NAMI[1], M. GAJJAR[1], W. DECRAENE[1], L. ORDOVAS VIDAL[1], S. RAITANO[1], P. VAN DAMME[2], C. VERFAILLIE[1];
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Abstract: INTRODUCTION: Frontotemporal lobar degeneration (FTLD) is a progressive neurodegenerative disease, characterized by behavior and language problems. FTLD is related to the progressive motor neuron disease Amyotrophic Lateral Sclerosis on a clinical, genetic and pathophysiological level. We focus on FTLD linked to mutations in the progranulin gene (*GRN*) and use stem cell technology to model the disease. Provoked by the great clinical heterogeneity seen in these patients, we sought to study the specific contribution of the progranulin (*GRN*) mutation versus its genetic background and disease modifiers.
METHODS: We seamlessly inserted the *GRN* gene mutation (*IVS1 +5G>C*) into an iPSC line and an embryonic stem cell line. In addition, we created patient iPSC lines that conditionally overexpress a copy of the *GRN* gene with the aim to create a flexible inducible correction of the PGRN haploinsufficiency. Genome engineering to introduce the $GRN^{IVS1\ +5G>C}$ gene mutation was performed using TALE nucleases and the Piggybac transposon system. To create the flexible PGRN overexpression system, two patient iPSC lines first underwent site specific targeting of the *AAVS1* locus, using zinc-finger mediated integration of a donor cassette, to create master cell lines suitable for Flippase (FLPE) mediated recombinase mediated cassette exchange (RMCE). We next performed RMCE to create doxycycline inducible progranulin $GRN^{IVS1+5G>C}$ iPSC lines. Patient- and engineered stem cells were characterized, differentiated into cortical neurons using published methods (Shi et al. Nature protocols 2012; 7 1836-1846) and subjected to RNA-sequencing.
RESULTS: We successfully introduced the $GRN^{IVS\ +5G>C}$ gene mutation in an iPSC and ESC line. Sequencing confirmed the introduction of the $GRN^{IVS1+5G>C}$ mutation and *GRN* expression

levels, assessed by RT-qPCR, confirm *GRN* haploinsufficiency throughout cortical neuron differentiation. Conditional overexpression of PGRN to correct PGRN haploinsufficiency in patient derived iPSC lines was confirmed by qRT-PCR and Western blot. Functional characterization of the PGRN haploinsufficient stem cells revealed possible cytoskeletal dysfunction. Transcriptome analysis of the patient derived and engineered lines supported this possibility and revealed the presence of a disease-related transcriptional signature in the pluripotent stem cells that persisted throughout neuronal differentiation. In conclusion, by investigating patient derived and genome engineered $GRN^{IVS\ +5G>C}$ PSC and cortical neurons, we could unequivocally link disease related phenotypes to progranulin haploinsufficiency.

Disclosures: **J. Terryn:** None. **F. Nami:** None. **M. Gajjar:** None. **W. Decraene:** None. **L. Ordovas Vidal:** None. **S. Raitano:** None. **P. Van Damme:** A. Employment/Salary (full or part-time):; UZ Leuven. **C. Verfaillie:** A. Employment/Salary (full or part-time):; KU Leuven.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.06/D41

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Novel NAMPT activators attenuate neurotoxicity and neuroinflammation associated with neurodegeneration

Authors: *J. GORDON-BLAKE, K. RATIA, B. KARUMUDI, K. DYE, R. C. KNOPP, M. BEN AISSA, K. TAM, G. THATCHER;
Medicinal Chem. and Pharmacognosy, Univ. of Illinois at Chicago, Chicago, IL

Abstract: Background: Therapies directly targeting amyloidβ (Aβ) and hyperphosphorylated tau in Alzheimer’s disease (AD) have been unsuccessful, so an alternative drug target is desperately needed. One potential strategy to prevent or reverse the course of the disease is to target the NAD/NAMPT pathway, proposed largely with reference to dietary supplements. Increasing catabolism of NAD with age, leading to NAD depletion, impacts cellular energy pathways crucial to neuronal function. In combination with protein misfolding associated AD pathophysiology, NAD depletion can drive disease progression. An efficient way to increase NAD is to activate nicotinamide phosphoribosyltransferase (NAMPT), which catalyzes the rate limiting step in NAD biosynthesis. We hypothesize that by activating NAMPT, increased NAD levels will support neuroprotective pathways that will prevent neurodegenerative progression. **Method:** To test our NAMPT activation hypothesis, we employed a high throughput screen (HTS) of 10,000 compounds measuring NMN production and ATP depletion. Structural analogs of hits were synthesized to generate cocrystal structures with NAMPT. Neuroprotection by the hit and analogs against oxygen-glucose deprivation (OGD) was measured, in addition to effects

on neuroinflammation. Cellular NAD was also measured.
Result: Our HTS campaign produced several hits that increased NAMPT activity. Novel NAMPT activators were shown to activate NAMPT with nanomolar potency and binding was validated by surface plasmon resonance (SPR) and X-ray crystal structure diffraction. In contrast, the reported NAMPT activator, P7C3, showed no activity in NAMPT assays. Several analogs showed concentration-dependent neuroprotection and reduced neuroinflammation. Cellular NAD was partially restored in models of oxidative stress, and ATP consumption was greatly attenuated by activators in enzyme assays.
Conclusion: These results provide a proof-of-concept for the first small molecule activators of NAMPT, with a detailed mechanism of action supported by enzymology and structural biology. The use of NAMPT activators in treatment of ADRD, possibly in combination with NAD supplements, is proposed.

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Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.07/D42

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG048205
VA Merit Award I01BX002477
VA Research Career Scientist Award

Title: Glia maturation factor knockdown and gene editing attenuates microglial activation

Authors: *S. P. RAIKWAR[1,2], G. P. SELVAKUMAR[1,2], M. E. AHMED[1,2], I. DUBOVA[1,2], R. THANGAVEL[1,2], K. DURAISAMY[1,2], S. ZAHEER[1], S. IYER[1,2], A. ZAHEER[1,2];
[1]Dept. of Neurol., Univ. of Missouri-Columbia, Sch. of Med., Columbia, MO; [2]Harry S. Truman Mem. Veterans' Hosp., Columbia, MO

Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that causes an irreversible cognitive decline in elderly people. Towards fulfillment of the unmet need for an effective AD therapy, our ultimate goal is to develop a robust AD patient-specific personalized precision-guided targeted gene knockdown and gene editing therapy. Glia maturation factor (GMF), a brain specific pro-inflammatory molecule discovered in our laboratory plays a crucial role in neuroinflammation and AD pathogenesis. We hypothesized that GMF knockdown by short-hairpin RNA (shRNA) and CRISPR/Cas9-mediated GMF gene editing in microglia is a novel approach to reduce neuroinflammation. To achieve GMF knockdown and gene editing, we

developed and tested recombinant lentiviral vectors (LVs) expressing either GMF-specific shRNAs or recombinant adeno-associated viral (AAV) vectors and LVs expressing CRISPR/Cas9 and GMF-specific sgRNAs. LV-mediated GMF knockdown by GMF-specific shRNAs in BV2 microglial cell line was confirmed by western blot analysis. Confocal microscopy of BV2 cells transduced with an AAV simultaneously co-expressing SaCas9 and a GMF specific sgRNA revealed a small subset of BV2 cells expressing SaCas9 while completely lacking GMF expression, thereby confirming successful biallelic GMF gene editing. Further, sequential transduction of BV2 cells with LV-SpCas9 and LV-GMF-sgRNAs was used to generate stable GMF-edited clones. Confocal microscopy revealed reduced GMF expression in GMF-edited BV2 cells as compared to non-edited BV2 cells. DNA sequencing of GMF-edited clones revealed indels in the exons 2 and 3 of GMF coding sequence thereby conclusively proving SpCas9-mediated GMF gene editing in BV2 cells. Treatment of wild type non-edited and GMF-edited BV2 cells with LPS revealed differences in basal p38 MAPK as well as LPS-induced phosphorylation of p38 MAPK. In wild type non-edited BV2 cells, LPS treatment induced significant upregulation of pp38 MAPK; however, in GMF-edited BV2 cells the pp38 MAPK levels were significantly lower, thereby indicating that GMF gene editing leads to attenuation of microglial activation. Overall, our data suggest that GMF knockdown and GMF gene editing represent novel approaches to develop precision-targeted AD patient-specific therapy.

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Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.08/D43

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Triple therapy with masupirdine (SUVN-502), donepezil and memantine in moderate Alzheimer's disease: Topline results of phase-2a study

Authors: *R. V. NIROGI, J. RAVULA, S. JETTA, V. GOYAL, S. PANDEY, G. BHYRAPUNENI, P. JAYARAJAN, A. SHINDE, K. MUDIGONDA, V. JASTI;
Suven Life Sci., Hyderabd, India

Abstract: Pharmaceutical companies are currently revisiting palliative therapies for Alzheimer’s disease (AD) because of the setbacks observed in the development of a disease-modifying therapy. The current greatest interest is to exploit the therapeutic potential of 5-HT_6 receptor. SUVN-502, a 5-HT_6 receptor antagonist, was evaluated using a novel approach for the

symptomatic treatment of AD dementia. SUVN-502 was added to background dual combination treatment of donepezil and memantine (triple therapy). The trial was a phase-2a proof-of-concept, randomized, double-blind, placebo-controlled, multicenter, parallel groups study conducted in the United States (NCT02580305). Total trial duration was 30- weeks i.e., 26-weeks double-blind treatment period followed by a 4- weeks placebo washout. A total of 558 subjects aged between 50-85 years, received double-blind oral treatment of SUVN-502 (50 or 100 mg) or placebo once daily in a ratio of 1:1:1. The primary efficacy endpoint was evaluated using Alzheimer's Disease Assessment Scale for Cognition (ADAS-Cog 11). Secondary endpoints include change in the Clinical Dementia Rating Scale - Sum of Boxes Score (CDR-SB), the Alzheimer's Disease Co-operative Study - Activities of Daily Living Scale (ADCS-ADL), the Neuropsychiatric Inventory (NPI), the Cornell Scale for Depression & Dementia (C-SDD) and Mini-Mental State Examination (MMSE). For primary and secondary analyses, SUVN-502 (50 or 100 mg) was compared with the placebo. Treatment groups were compared in terms of mean change from baseline for all the endpoints. Between-group comparisons were based on the intent-to-treat population using a mixed effects model for repeated measures using the z-score last observation carried forward approach prior to analysis. No adjustments for multiple comparisons were made. Topline efficacy results will be presented in the meeting.

Disclosures: **R.V. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **J. Ravula:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Jetta:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Goyal:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Pandey:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **G. Bhyrapuneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **K. Mudigonda:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Jasti:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.09/D44

Topic: C.02. Alzheimer"s Disease and Other Dementias

Title: Triple therapy with masupirdine (SUVN-502), donepezil and memantine in moderate Alzheimer's disease: Baseline patient characteristics in phase-2a study

Authors: R. NIROGI, J. RAVULA, S. JETTA, V. GOYAL, S. PANDEY, G. BHYRAPUNENI, *P. JAYARAJAN, A. SHINDE, K. MUDIGONDA, V. JASTI;
Suven Life Sci. Ltd, Hyderabad, India

Abstract: A novel symptomatic therapy that addresses the limitations of current standard of care is needed for the treatment of Alzheimer's disease (AD). Central antagonism of the 5-HT_6 receptor may provide a mechanistically distinct palliative treatment for AD that works through cholinergic and glutamatergic neuronal systems. SUVN-502, a promising 5-HT_6 receptor antagonist, is evaluated as a novel approach for the management of AD dementia: triple therapy with SUVN-502 added to background treatment with donepezil and memantine. This study is a phase-2a proof-of-concept, 26-weeks, randomized, double-blind, placebo-controlled, multicenter, parallel groups study conducted in the United States (NCT02580305). The study involves a 2 to 4- weeks screening period followed by a 26- weeks double-blind treatment which is followed by a 4-weeks placebo washout period. Total of 558 subjects, aged 50-85 years, received double-blind oral administration of one of three treatments once daily; SUVN-502 (50 mg), SUVN-502 (100 mg), or placebo in a 1:1:1 ratio. The primary efficacy endpoint was evaluated using Alzheimer's Disease Assessment Scale for Cognition (ADAS-Cog 11). Secondary endpoints were change in the Clinical Dementia Rating Scale - Sum of Boxes Score (CDR-SB), the Alzheimer's Disease Co-operative Study - Activities of Daily Living Scale (ADCS-ADL), the Neuropsychiatric Inventory (NPI), the Cornell Scale for Depression & Dementia (C-SDD) and Mini-Mental State Examination (MMSE). The baseline patient characteristics of the enrolled population were analyzed using customary summary statistics and comparisons. Subject characteristics are highly consistent with moderate AD clinical trial populations in the U.S.

Disclosures: R. Nirogi: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **J. Ravula:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Jetta:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Goyal:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Pandey:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **G. Bhyrapuneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **K. Mudigonda:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Jasti:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.10/D45

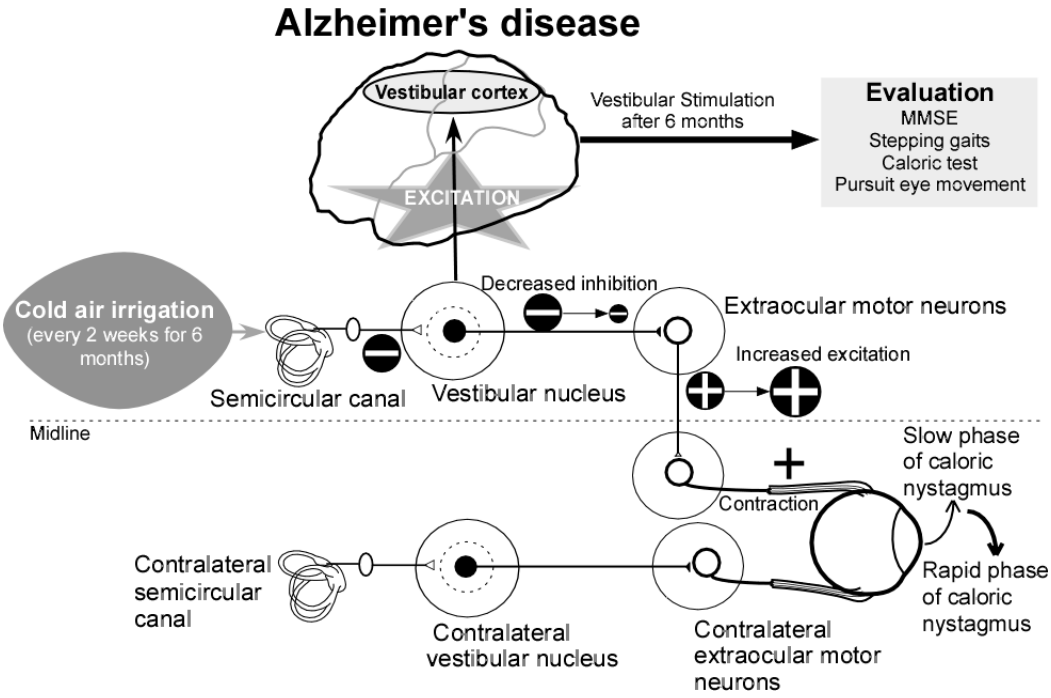
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JSPS KAKENHI grant number JP 26460901

Title: The effect of clinical vestibular repeating stimulation on Alzheimer's disease by air caloric device

Authors: *K. NAKAMAGOE[1], S. YAMADA[1], R. KAWAKAMI[1], T. KOGANEZAWA[2], A. TAMAOKA[1];
[1]Dept. of Neurology, Div. of Clin. Medicine, Fac. of Medicine, Univ. of Tsukuba, Tsukuba, Japan; [2]Dept. of Physiology, Div. of Biomed. Science, Fac. of Medicine, Univ. of Tsukuba, Tsukuba, Ibaraki, Japan

Abstract: Objective and rationale: We have previously demonstrated that cortical vestibular dysfunction with Alzheimer's disease (AD) is one cause of balance disorders with dementia (Nakamagoe et al. *J Alzheimers Dis* **47**:185-196, 2015). The present clinical study is the first to explore the prevention of balance disorder progression in patients with AD through vestibular stimulation with an air caloric device. The purpose of this study was to delay the progression of balance disorders by inducing vestibular compensation by utilizing the effects of vestibular stimulation on cerebral activation. **Methods:** Eight AD patients underwent vestibular stimulation every two weeks for six months as a "stimulation group." As a control group, 7 AD patients participated as the "non-stimulation group." Both groups were subsequently evaluated with a higher function test, stepping test, a caloric test, and a smooth-pursuit eye movement test just before and 6 months after starting the study. The rate of decline of these test parameter values of both groups were compared. **Results:** Vestibular stimulation was performed on all patients without dropouts. The stimulation group's rate of decline in their Mini-Mental State Examination (MMSE) scores decreased more than in the non-stimulation group (P=0.02). Those tests, except for MMSE scores, did not show any significant differences. **Conclusion:** From the MMSE results, repeating vestibular stimulation is suggested to delay the progression of functional impairment of the cerebrum. On the other hand, we were unable to prove the effect for vestibular and eye movement control. Future clinical application will require an increased number of cases. *Research projection*: Dr. Nakamagoe, Conception. Dr. Nakamagoe and Dr. Tamaoka, Organization. Dr. Nakamagoe, Ms. Kawakami, and Ms. Yamada, Execution. *Statistical Analysis*: Dr. Nakamagoe, Ms. Kawakami, and Dr. Koganezawa, Design. Dr. Nakamagoe, Ms. Yamada, Dr. Koganezawa, and Ms. Kawakami, Execution. Dr. Nakamagoe, Dr. Tamaoka, and Dr. Koganezawa, Review and Critique. The all authors report no conflicts of interest.



Disclosures: **K. Nakamagoe:** None. **S. Yamada:** None. **R. Kawakami:** None. **T. Koganezawa:** None. **A. Tamaoka:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.11/D46

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: VA Merit 121RX001889

Title: Repetitive transcranial magnetic stimulation as an emerging treatment of cognitive dysfunction in Alzheimer’s disease

Authors: ***M. W. MCNERNEY**[1,2], J. CHENG[1], A. NODA[1], B. HERNANDEZ[1], L. SHERE[1], J. YESAVAGE[1,2];
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Abstract: Alzheimer’s disease (AD) and mild cognitive impairment are debilitating neurodegenerative conditions characterized primarily by loss of memory. Although medications can be used to help alleviate symptoms, current treatments are insufficient. We therefore aimed to determine if an emerging therapy, repetitive transcranial magnetic stimulation (rTMS), can be utilized to help individuals suffering from Alzheimer’s symptoms. rTMS is a noninvasive brain

stimulation technique which can be used to target magnetic fields into the brain, thereby inducing changes in cell singling and plasticity. In the current study, 13 patients received sham stimulation and 10 received magnetic stimulation directed at the dorsolateral prefrontal cortex. The treatment consisted of 20 sessions of 10Hz stimulation. Prior to and following treatment, patients were given a battery of cognitive tests and a blood draw to test for changes in circulating brain-derived neurotrophic factor (BDNF), a protein which underlies plasticity and is decreased in AD. The treatment group showed a modest improvement in both the Trails B test and the California Verbal Learning test while no difference was found for the sham controls. There was a small increase in circulating BDNF levels compared to sham controls, but the was also high variability between samples in both conditions. These results show preliminary evidence that rTMS can help the cognitive deficits seen in AD, but more research needs to be done to determine if BDNF is reliably responding to treatment. Another future step will be to incorporate brain imaging results.

Disclosures: **M.W. McNerney:** F. Consulting Fees (e.g., advisory boards); Tahoe Institute for Rural Health Research. **J. Cheng:** None. **A. Noda:** None. **B. Hernandez:** None. **L. Shere:** None. **J. Yesavage:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.12/E1

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: A possible role of Palmitoylethanolamide combined with Luteoline in Frontotemporal Dementia treatment: A clinical and neurophysiological study

Authors: *M. ASSOGNA[1], E. CASULA[2], C. MOTTA[1], S. BONNÌ[2], I. BORGHI[2], F. DI LORENZO[2], M. MINEI[2], A. MARTORANA[1], G. KOCH[2];
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Abstract: Frontotemporal dementia (FTD) is a frequent cause of presenile neurodegenerative dementia and there is no effective pharmacological treatment to slow its progression. A link has been proposed between neuroinflammation and specific forms of FTD, suggesting that neuroinflammation is an important component of the disease since the early phases. We aim to investigate efficacy and safety of Palmitoylethanolamide combined with Luteoline (PEA-LUT) in a sample of FTD patients to reduce behavioral disturbances. We enrolled ten patients with a diagnosis of probable FTD. We performed cognitive and neurophysiological evaluations at baseline (T0) and after 4 weeks (T1) treatment with PEA-LUT 700 mgx2/day. To evaluate the cognitive effects of PEA-LUT administration we used a battery of tests including the MMSE, the Frontal Assessment Battery (FAB), the Neuropsychiatric Inventory (NPI), the screening for

aphasia in Neurodegeneration (SAND), the Activity of daily living inventory (ADCS/IADL) and the FTD modified Clinical Dementia Rating (FTD-CDR). We measured change on synaptic transmission using SICI-ICF, LICI and SAI paired-pulse TMS protocols over the primary motor cortex. We used iTBS protocol to measure changes in cortical plasticity. We used combined TMS/EEG methods to evaluate changes in DLPFC cortical oscillatory activity. We observed an improvement in NPI mean score (p=0.018) and FAB score (p=0.038). Neurophysiological evaluation showed a restoration of LICI (p=0.040), in particular at ISI 100ms (post-hoc p=0.035), suggesting a modulation of GABA(B) activity. We observed an increase of LTP-like cortical plasticity (p=0.079) and of DLPFC oscillatory activity in beta/gamma range. PEA-LUT could reduce behavioural disturbances and improve executive function in FTD patients through the modulation of cortical excitability and GABAergic transmission.

Disclosures: **M. Assogna:** None. **E. Casula:** None. **C. Motta:** None. **S. Bonnì:** None. **I. Borghi:** None. **F. Di Lorenzo:** None. **M. Minei:** None. **A. Martorana:** None. **G. Koch:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.13/E2

Topic: C.02. Alzheimer"s Disease and Other Dementias

Title: Role of Akt2 in activity dependent protein translation in Alzheimer's disease pathology

Authors: *V. RAVINDRANATH[1], **R. D. GOWAIKAR**[2];
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Abstract: The clinical stage of Alzheimer’s disease is characterized by memory and cognitive impairments leading to severe dementia. This however is the culmination of a long series of physiological events, that may have their origins decades prior to the manifestation of the symptoms. One such physiological process to be affected in early stage of AD is activity dependent translation at the synapse. Work in our lab has shown that this process of activity dependent translation which is responsible for maintenance of normal synaptic function and consolidation of long-term changes at the synapse is affected in young AD mice. This process is regulated by intracellular signaling cascades like Akt-mTOR signaling cascade. Akt also known as Protein Kinase B which plays a central role in this signaling cascade is a Serine-Threonine kinase.There are 3 known forms of Akt kinase: Akt1,Akt2,Akt3. Akt1 is implicated in cell growth and survival. Akt2 is expressed in muscles and adipocytes and has a role in glucose homeostasis. Akt3 is expressed in the brain and testes. Despite sharing a high degree of amino acid identity, phenotypes observed in knockout mice suggest that Akt kinases are not functionally redundant. However, the functional roles of the individual kinases are not completely understood and require further investigation, especially in the brain in general and at

the synapse, in particular. Our study first focused on characterization of Akt isoforms in the brain, and the study of their individual contribution to activity dependent synaptic translation. To this effect we measured the RNA and protein levels of Akt isoforms in C57 mice of different age groups. We observed that Akt2 is the most abundant protein in the brain. Next, we measured the activity of Akt isoforms in a transgenic mouse model of AD, APPswe/PS1ΔE9(APP/PS1). We did this by measuring phosphorylated levels of Akt isoforms and by performing kinase assays. We observed that Akt1 & Akt2 show a decrease in activity in 1 month old APP/PS1 mice. The decrease in activity of Akt2 is the most while Akt3 isn't affected at all. We therefore, downregulated each isoform in primary cultures using shRNA. A protein translation assay based on puromycin uptake was performed on these cells. Our results indicate that downregulation of Akt2 has the most substantial negative effect on activity dependent protein translation in cultured hippocampal cells. In conclusion, our study has revealed the differential distribution of Akt isoforms in the brain and also differential regulation by them of activity dependent protein translation.We also observed Akt2 activity to be reduced in young AD mice thus indicating a role of Akt2 in AD disease progression.

Disclosures: V. Ravindranath: None. **R.D. Gowaikar:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.14/E3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: This work was supported by a grant from Tata Trusts. Dr. Kommaddi is a Ramalingaswami Fellow of the Department of Biotechnology (BT/RLF/Re-entry/50/2014).

Title: Sex specific differences in synaptic dysfunction and behavioral deficit in Alzheimer's disease mouse model

Authors: *R. KOMMADDI[1], K. CHITHANATHAN[1], R. D. GOWAIKAR[1], S. KARUNAKARAN[2], V. RAVINDRANATH[1,2];
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Abstract: The occurrence of Alzheimer's disease (AD) is greater in women than in men. Several processes such as brain development, adult brain structure and function, molecular and biochemical signatures differ by sex. Sex differences in the brain are initiated through sex-determining genes and hormonal factors and these differences have important clinical implications for AD risk. However, the molecular mechanisms underlying the higher burden of AD in women remain unknown. Thus, we are interested in looking at sex-specific differences in

terms of the progression of the disease and that we studied younger ages because the disease starts early. Associative learning and memory test was assessed by contextual fear conditioning (cFC). Male APP/PS1 mice, but not female mice showed deficient recall upon contextual fear conditioning at 2, 4 and 6 months of age. Female APP/PS1 mice started showing deficient recall upon contextual fear conditioning only after the age of 8 months after onset of menopause and this was sustained as the mice aged. Further, we found significant decrease in synaptosomal F-actin levels in male (indicative of dendritic spine dysfunction), but not in female, APP/PS1 mice at 4 months of age. Intriguingly, synaptosomal F-actin levels also started decreasing in female APP/PS1 mice at the age of 8 months. Activity dependent synaptic protein translation (^{35}S-methionine incorporation) was affected only at 8 months of age and no deficits were seen in 3-4 months old APP/PS1 female mice. Synaptosomal Akt1-mTOR signaling pathway , which is significantly down-regulated in male APP/PS1 mice was actually upregulated in female mice at 4 months and declined as they aged and entered menopause. We conclude that the appearance of cognitive deficits, loss of synaptosomal F-actin and perturbation of Akt1-mTOR pathway occurred in females only as they aged, specifically as they entered menopause. These findings indicate that the neuroprotective effects of estrogen may play an important role in protecting from β-amyloid induced toxicity at the synapse and estrogen plays a critical protective role in preventing synaptic dysfunction during early stages of AD progression.

Disclosures: R. Kommaddi: None. **K. Chithanathan:** None. **R.D. Gowaikar:** None. **S. Karunakaran:** None. **V. Ravindranath:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.15/E4

Topic: C.02. Alzheimer"s Disease and Other Dementias

Title: Cortical synaptic transcriptomic profile of a mouse model of Alzheimer’s disease

Authors: *R. D. GOWAIKAR[1], A. VERMA[2], V. RAVINDRANATH[3];
[2]Ctr. for Neurosci., [1]Indian Inst. of Sci., Bangalore, India; [3]Ctr. for Neurosci., Indian Inst. of Sci., Bangalore North, India

Abstract: One of the most debilitating aspect of Alzheimer’s disease (AD) at the pathophysiological level is the degeneration of neurons. But increasing evidence points to synaptic dysfunction as one of the earliest events in the cascade of events of this progressive disease. Synaptic dysfunction observed at early stages of AD can be both structural and functional in nature; for example, dysfunction in actin cytoskeleton, and activity dependent synaptic protein translation respectively. Substantial evidence of presence of functional protein translation machinery at the synapse has accumulated over the past decade. We characterized the

synaptic transcriptome of a widely used AD mouse model, APPswe/PS1ΔE9 (APP/PS1). To this effect we prepared synaptosomes using sucrose density gradient method from cortex of 3-month-old wild type and AD mice. We then isolated RNA from the synaptospmes, after ribo-depletion we proceeded to library preparation. We performed paired -end (100X2 bp, 45 million reads) RNA sequencing on the Illumina HiSeq2500 platform. Raw RNA seq reads were quality controlled and adapter trimmed and then aligned to reference mouse genome using TopHat2. Differential gene expression analysis was performed using DESeq2 normalization followed by pathway analysis. Cell type enrichment analyses of the total 4509 differentially expressed genes revealed that 209 were unique to astrocytes, 243 to microglia, 129 to oligo-dendrocytes, while 3928 genes were unique to synaptic compartment. Of the differentially expressed genes, 2630 genes were up regulated, and 1879 genes were down- regulated in the APP/PS1 mice. Pathway analysis of the differentially expressed genes revealed that genes involved with proteasome machinery, protein translation, glycolysis, oxidative phosphorylation, and glutathione metabolism were upregulated. Our analysis suggeststhat in early stages of AD in a transgenic mouse model various cellular processes are perturbed at the synapse and that is reflected in the local transcriptome.

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Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.16/E5

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: Human Brain Tissue Bank, Semmelweis University
TATA Trusts

Title: Transcriptomic profiling in young AD transgenic (APPswe/PS1ΔE9) mice reveals a novel candidate gene

Authors: A. VERMA[1], :. V. RUPANAGUDI[4], *A. RAMACHANDRAN[2], V. RAVINDRANATH[3];
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Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by deposition of amyloid β (Aβ) and hyperphosphorylated tau, loss of neurons and cognitive deficit. While cognitive deficit characteristic to AD is most often manifested in late stages of life, studies from our lab have shown that synaptic dysfunction and associated molecular changes

occur at early, pre-symptomatic stage in APPswe/PS1ΔE9 (APP/PS1) mouse model of AD indicating that the disease pathogenesis starts early in AD. Understanding early mechanisms in the disease course can help in timely intervention through design of strategies that may impede disease progression. We, therefore aimed to investigate changes in transcriptomic profiles in the entorhinal cortex (EC) and hippocampus (HP) in adolescent (1-month old) and young adult (3-months old) APP/PS1 mice using RNA sequencing. Total RNA was isolated from EC and HP from male APP/PS1 transgenic (Tg) and wild type (WT) control mice at 1 month and 3 months of age. Total RNA was processed for depletion of ribosomal RNA, cDNA library preparation followed by Illumina paired end sequencing. The raw reads were quality controlled to remove reads with low quality and adapters. The reads were aligned to mouse genome and read counts were generated and normalized using DESeq2 to obtain information on differential gene expression. In both EC and HP at 1 month and 3 months of age in APP/PS1 mice, APP was found to be upregulated, which served as a positive control. A single gene was consistently down-regulated in EC and HP at both 1 and 3 months of age. The gene is a regulator of calmodulin (CaM) signalling. Further, splice variant analysis of RNA sequencing data revealed specific down-regulation of a specific isoform of this gene. We further validated the down-regulation of this gene in entorhinal cortex and hippocampus from transgenic mice using qRT-PCR. We also observed down-regulation of this gene in fronto-polar prefrontal cortex from AD human autopsy samples. In conclusion, our results indicate the identification of this gene as a novel gene candidate that may be involved in AD pathogenesis early in the disease.

Disclosures: A. Verma: None. **:.V. Rupanagudi:** None. **A. Ramachandran:** None. **V. Ravindranath:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.17/E6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: UF T32 AG061892
CAO K99 DA041493
BS/JLB RF1 AG60778

Title: Aging is associated with risk-averse decision making in fischer 344 x Brown Norway F1 hybrid rats

Authors: *R. J. DRAGONE[1], C. A. ORSINI[2], M. POMPILUS[2], A.-R. WHEELER[2], M. FEBO[2], B. SETLOW[2], J. L. BIZON[3];
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Abstract: The ability to make adaptive decisions among options that vary in both risks and rewards is critical for managing finances, health care, and other activities of daily living necessary to maintain personal independence. Such risky decision making can be compromised at advanced ages, however, which can lead to maladaptive choices and reduced quality of life. Optimizing decision making could broadly benefit functional outcomes and promote independent living among older adults; however, development of interventions is currently hindered by limited understanding of the neural mechanisms underlying maladaptive decision making in aging. To begin to address this issue, we used a rat model to determine how performance on a risk-based decision-making task changes as a function of age, and to investigate the neurobiological mechanisms that may underlie these changes. Young adult (6 mo, n=12) and aged (24 mo., n=15) Fischer 344 x Brown Norway F1 hybrid rats were trained in a risky decision-making task in which they made discrete trial choices between a small (1 food pellet) "safe" reward and a large (2 food pellets) "risky" food reward accompanied by varying probabilities of mild footshock punishment. Aged rats exhibited an attenuated preference for the large, risky reward in comparison to young adult rats. This age difference in choice behavior was not due to compromised behavioral flexibility, nor was it readily attributable to altered shock reactivity, as young and aged rats had similar shock sensitivity thresholds. Importantly, this risk averse pattern of behavior in aged rats is consistent with findings of elevated risk aversion in older humans. To begin to investigate the neural mechanisms mediating age changes in risky decision making, a subset of the rats (young n=10, aged n=5) underwent resting state functional magnetic resonance imaging to assess functional connectivity among brain regions implicated in decision making including basolateral amygdala, nucleus accumbens, prefrontal cortex, and ventral hippocampus.

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Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.18/E7

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: McKnight Brain Research Foundation
NIH RO1 NIA AG055544
NIH T32 NIA AG061892

Title: Age-related decreases in CA3-CA1 ripple coordination

Authors: *N. M. DICOLA[1], A. L. LACY[2], O. J. BISHR[2], K. M. KIMSEY[3], K. DIBA[4], S. N. BURKE[1], A. P. MAURER[1];

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Abstract: Local field potential oscillations are mainly generated by the superposition of synaptic activity (G. Buzsáki, *et al.*, 2012). Therefore, changes in hippocampal oscillations are capable of providing insights into the synaptic alterations that occur during aging and neurodegenerative diseases such as Alzheimer's disease. In the hippocampus, high-frequency oscillations known as ripples can be detected in the pyramidal layer and are observed most frequently during rest and 'offline' periods. Ripples are thought to support several cognitive functions including reactivation and memory consolidation (GM. van de Ven, *et al.*, 2016; G. Girardeu, *et al.*, 2009); however, most of these studies have focused on ripples in CA1. Ripples can also be detected in the CA3 pyramidal cell layer and these events, along with their associated sharpwave, are thought to initiate ripple events in CA1 through a large, transient, excitatory drive to the stratum radiatum of CA1 (G. Buzsáki, 1986; D. Sullivan, *et al.*, 2011). During aging, the hippocampus exhibits several synaptic alterations including CA3 hyperexcitability (MA. Yassa, ML. Tugan, CE. Stark, 1986; IA. Wilson, *et al.*, 2005), loss of Schaffer collateral synaptic efficacy (CA. Barnes, G. Rao, J. Shen, 1997), and hilar interneuron functional loss (AM. Spiegel, *et al.*, 2013). Moreover, the frequency of CA1 ripples has been shown to be reduced in aged compared to young rats (SL. Cowen, *et al.*, 2018). Each of these age-associated changes could impact ripple dynamics across the hippocampus, but CA3-CA1 ripple co-occurrence has not been interrogated in the context of age-related cognitive decline. The current study recorded from the right CA1 and CA3 hippocampal subregions of young (4 month) and aged (24 month) rats using two different 64 channel silicon probes. We recorded extracellular local field potentials and examined ripples during rest periods that flanked an epoch of behavior on a hippocampal-dependent task. CA1-CA3 ripple co-occurrence probability was measured as the portion of the time CA1 ripples occurred within a 100 ms time window of CA3 ripples. Preliminary data showed that the probability of CA3-CA1 ripple co-occurrence is decreased in aged animals, suggesting that the aged CA3 has less influence over CA1 than the young CA3. Further studies are required to determine if the aged CA1 receives a greater proportion of influence from cortical input or if the overall activity level is decreased.

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Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.19/E8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA R01AG055798
Barbara's Dream Fund
Florida Department of Health (7AZ25)
NIA T32AG061892
McKnight Brain Institute

Title: Neuropathological outcomes in a mouse model of amyloid beta and tau

Authors: *E. J. KOLLER, K. R. IBANEZ, E. GONZALEZ DE LA CRUZ, T. A. MACHULA, D. RYU, C. JANUS, B. I. GIASSON, D. R. BORCHELT, P. CHAKRABARTY;
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Abstract: Amyloid β (Aβ) and tau neurofibrillary tangles (NFTs) are the two hallmark pathologies of Alzheimer's disease (AD), but how these two pathological components of AD influence each other is unclear. It has been hypothesized that tau and Aβ synergize to produce the AD pathological cascade which results in neurodegeneration and cognitive impairment, but it remains unknown whether insoluble NFT tau or soluble form(s) of tau synergize with Aβ to produce the pathological effects. To examine the consequences of tau and Aβ in mouse brains, we used adeno-associated virus (AAV)-mediated delivery of human tau variants in the TgCRND8 mouse model of Aβ plaques. These tau variants were delivered via intracerebral injection of AAV in neonatal TgCRND8 litters. Expression of these different tau variants results either in accumulation of abundant soluble hyperphosphorylated tau (WT tau or P301L tau variants) or primarily NFT-type tau (P301L/S320F tau variant) in nontransgenic mice.
At 3 months of age, AAV-tau expression in TgCRND8 mice led to the accumulation of phosphorylated tau in all the experimental groups, with NFT-type tau and robust widespread astrogliosis observed exclusively in the P301L/S320F tau expressing mice. While expression of WT tau or P301L tau expression did not alter Aβ plaques, surprisingly, expression of AAV-P301L/S320F tau lowered Aβ plaque burden. We also observed modest levels of tau in the sarkosyl-insoluble cellular fraction of P301L tau expressing TgCRND8 mice (not observed in nontransgenic mice), indicating that presence of Aβ plaques can modify solubility of P301L tau protein. When investigating synaptic protein profiles, we found that expression of both P301L tau and P301L/S320F tau resulted in increased amounts of GluR1, vGlut1, and spinophilin. Overall, we conclude that tau variants affect neuroinflammation, Aβ burden, self-aggregation and synaptic alterations to differential degrees in the presence of Aβ plaques, leading to the concept that these variants might represent different tau conformers.

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Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.20/E9

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: CTSI non-patient Pilot Award UL1TR001427
Barbara's Dream Foundation F019659

Title: Progranulin deficiency causes structural abnormalities in the periphery of knockout mice

Authors: *A. WALKER[1], S. RAYAPROLU[4], J. GASS[5], J. HOWARD[2], L. JAMES[2], C. DUFFY[2], J. M. LEWIS[3];
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Abstract: Progranulin (PGRN) is a secreted glycoprotein that can be cleaved into granulin motifs depending on the biological needs of the body, with full-length PGRN acting as an anti-inflammatory molecule. Mutations within the granulin gene (*GRN*) exert pleiotropic effects as heterozygous loss-of-function mutations cause frontotemporal lobar dementia with TDP-43 pathology (FTLD-TDP43) and homozygous loss-of-function mutations cause a rare form of neuronal ceroid lipofuscinosis (NCL). Mice deficient of *Grn*, develop excessive intraneuronal accumulations of lipofuscin throughout the brain, a pathological hallmark of NCL. Current studies of NCL pathology have been mainly focused in the brain, but PGRN is also expressed throughout the periphery; therefore, we sought to determine whether *Grn*-deficient mice develop NCL relevant pathology in organs peripheral to the brain. We assessed the liver, kidney, lung, and heart from 7 and 12-month-old *Grn*-knockout (KO) (N=4) and wild-type (WT) (N=4) mice per age using immunohistochemical stains and immunoblotting. The livers of the KO mice show abnormal hepatocyte structure, glycogen deposits, and enlarged lysosomes and macrophages at 7 and 12 months compared to the WTs. Cathepsin Z and TFEB are both elevated in 7-month-old KO kidneys compared to 7-month-old WT kidneys. Lastly, the lungs and hearts of the KO mice do not have any overt differences in pathology compared to the WTs at 7 and 12-months of age. These data highlight the presence of peripheral pathologies due to PGRN loss and raise the potential that peripheral symptoms may be overlooked in patients with PGRN deficiency. Although obtaining brain tissue is rare from individuals carrying homozygous *GRN* mutations, peripheral tissue biopsies, such as liver or kidney, can be taken in relatively non-invasive procedures and peripheral pathology could then serve as a peripheral marker for disease progression and treatment.

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Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.21/E10

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: FL Dept of Health Ed and Ethel Moore Alzheimer’s Disease Research Program Grant 7AZA1

Title: Mediation of periventricular white matter hyperintensity burden, cognition, depression, and quality of life in older adults with amnestic mild cognitive impairment

Authors: *B. DEFEIS[1], J. TANNER[1], D. O'SHEA[1], L. DE WIT[1], A. MEJIA[1], P. AMOFA[1], S. MAYEWKSI[2], M. CHANDLER[3], G. SMITH[1];
[1]Univ. of Florida, Gainesville, FL; [2]Tallahassee Mem. HealthCare, Tallahassee, FL; [3]Mayo Clin., Jacksonville, FL

Abstract: Introduction: Periventricular white matter hyperintensities (PVWMH) have been previously associated with the development of depression in older adults, contributing to a vascular theory of late-life depression. Progression of these hyperintensities through development of new clusters or increasing volume has been also associated with cognitive decline and poor depression outcomes, which may impact overall quality of life. Previous studies have suggested that varying numbers and sizes of clusters may indicate specific etiologies and clinical symptoms. The aim of this study is to examine the relationship of the number and sizes of PVWMH clusters on general cognition, depression, and quality of life in older adults with amnestic Mild Cognitive Impairment (aMCI).
Methods: Data for the present study were obtained from 35 older adults with aMCI who completed the baseline assessment as part of a larger ongoing intervention study. PVWMH were extracted using UBO Detector, a cluster-based, automated pipeline which extracts white matter hyperintensities from FLAIR and T1-weighted scans using SPM12 and FSL functions. In this analysis, PVWMH were qualified as total number of clusters (NoC) of various sizes (punctuate [$<10.125mm^3$], focal [$<30.375mm^3$], medium [$<50.625mm^3$], and confluent [$>50.625mm^3$]), and total volume. Mediation analyses were performed predicting whether the impact of PVWMH on quality of life was mediated by cognition and depression when controlling for age, gender, and education.
Results: Participants were, on average, 75.05(.50) years old, 58% women, and had 16.82 (2.8) years of education. Average cognitive performance on the DRS was 130.49 (8.64), and the average depression score was 10.28 (6.89). Quality of life scores ranged from 33 to 50 (M=40.62; SD=4.66). The number of focal white matter hyperintensity clusters was significantly associated with lower quality of life and higher depressive symptoms. Mediation analyses

revealed that the indirect effect of white matter on quality of life as mediated by depression was statistically significant (Effect= -.321; Boot CI= -.684 to -.092). No association between PVWMH and general cognition was detected.
Discussion: Depression fully mediated the relationship between PVWMH and quality of life. There was no relationship found between PVWMH and general cognition, which can be expected given conflicting findings in the literature. The association between the number of PVWMH clusters, rather than total volume, and depression may warrant consideration of etiological differences, and represent more evidence towards the vascular hypothesis for late-life depression.

Disclosures: B. DeFeis: None. **J. Tanner:** None. **D. O'Shea:** None. **L. De Wit:** None. **A. Mejia:** None. **P. Amofa:** None. **S. Mayewksi:** None. **M. Chandler:** None. **G. Smith:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

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Program #/Poster #: 563.22/E11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: MRC Grant GO501263
ARUK

Title: Investigating the neuroprotective mechanisms of the presubiculum in a knock-in App mouse model of Alzheimer’s disease

Authors: *J. SHI, *A. B. ALI;
Sch. of Pharm., Univ. Col. London, London, United Kingdom

Abstract: Alzheimer’s disease (AD) pathogenesis is correlate with dramatic changes of network homeostasis attributed to the altered astrocyte-neuron interactions. During the progression of the disease, astrocytes adopt a hyperactive phenotype, leading to up-regulated glial fibrillary acidic protein (GFAP) and purinoreceptors, P2Y1 receptors. These cellular changes are evidenced in various cortical regions, but interestingly, it has been shown that the presubiculum is preserved from these pathological changes in AD.
To investigate the neuroprotective mechanisms of presubiculum, we employed a knock-in mouse model of AD that harbors mutant form of amyloid precursor protein (App), (App^{NL_F/NL_F}) (Saito et al., 2014), and the wild-type (C57BL/6) mice were used as control. The presubiculum and CA1 tissue was also obtained from post-mortem AD patients and age-matched healthy controls. Previously, we have shown that there is a preservation of calretinin (CR)-expressing interneurons in CA1 in the presence of the age-dependent cellular phenotypical changes of AD, including amyloid beta accumulation, pyramidal neuron loss and neuroinflammatory markers such as

astrocytes and microglia. In the present study, analysis from z-stack images obtained with confocal microscopy reveals that the expression of P2Y1 receptors was apparent in astrocytes (GFAP), CR-expressing interneurons and pyramidal cells, and the CR-expressing interneurons showed the highest level of P2Y1 receptors, followed by GFAP, while pyramidal cells expressed the lowest level in both control and in AD human and mice tissue. Interestingly, in CA1 of App^{NL_F/NL_F} mice and AD patients, CR-expressing interneurons and astrocytes expressed significantly higher levels of P2Y1 receptors, which is not present in the presubiculum of control or AD tissue. In vitro whole-cell electrophysiological recordings were performed in the App^{NL_F/NL_F} mice age matched to wild-type mice (9-12 months) to investigate whether there was any aberrant excitatory-inhibitory imbalance in the presubiculum reported in CA1 (Petrache et al., 2019). The pyramidal cells in the presubiculum seems to display “normal” biophysical and synaptic properties consistent with control wild-type mice.
In summary, our data suggests that astrocytes and CR-expressing interneurons preserved in CA1 region of App^{NL_F/NL_F} mice and AD patients up-regulate P2Y1 receptors, which may contribyte to the enhanced purinergic signaling. The absence of these cellular changes in the presubiculum may underlie the neuroprotective mechanisms of the presubiculum.

Disclosures: **J. Shi:** None. **A.B. Ali:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.23/E12

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: MRC Grant MR/N013867/1
ARUK Network
MRC GO501263

Title: Alpha5 subunit-containing $GABA_A$ receptors are preserved on resilient calretinin interneurons in the AppNL-F/NL-F mouse model of Alzheimer’s disease

Authors: *A. L. PETRACHE, A. B. ALI;
Sch. of Pharm., Univ. Col. London, London, United Kingdom

Abstract: The hippocampus, important in memory formation and consolidation, is significantly affected in Alzheimer’s disease (AD). The cells of the hippocampus consist of excitatory neurons and diverse inhibitory interneurons that release gamma-aminobutyric acid (GABA) neurotransmitter to control these excitatory networks.
Evidence suggests a preservation of the α5-containing $GABA_A$ receptors, which play a crucial role in memory in human brain areas most affected by AD (Howell *et al.*, 2000). This is despite

the early stage synaptic hyperexcitability observed in mouse models of AD (Petrache et al., 2019) prior to the manifestation of the cellular symptoms of AD such as amyloid beta (Aβ) accumulation and neuroinflammation.
To investigate the underlying mechanisms that causes the synaptic imbalances preceding the symptoms of AD, we investigated whether the α5 subunit-containing $GABA_A$ receptors were restricted to specific cell-types and whether they were performing their intended functions using the $App^{NL-F/NL-F}$ knock-in mouse model of AD age-matched to wild-type control mice.
Using immunohistochemistry and confocal microscopy we investigated 3 sub-types of modulatory inhibitory interneurons co-expressed with GAD67 (enzyme that indicates GABA synthesis), $Aβ_{42/40}$, or α5 $GABA_A$ receptors in the CA1 region of the hippocampus. We show that α5 $GABA_A$ receptors are selectively expressed at a the highest levels on calretinin- (CR) expressing interneurons compared to the other two interneuron subtypes, and on pyramidal cells, in both age-matched wild-type and $App^{NL-F/NL-F}$ mice. Interestingly, this pattern of expression correlated with the selective penetration of Aβ in somatostatin- (SST) and cholecystokinin- (CCK) expressing cells, which reduced significantly in cell density in the later stages of AD. In contrast, there was a lack of Aβ presence in CR interneurons consistent with their anatomical preservation. Furthermore, using whole-cell recordings we find that CR cells were synaptically hyperinhibited correlated with the excess GAD67 expressed in these cells in the $App^{NL-F/NL-F}$ mice compared to the age-matched wild-type mice (Shi et al., 2019).
In summary, our data suggests that α5 subunit-preservation is correlated with interneuron resilience in AD. Therefore, we propose that pharmacological modulation of α5 subunit-containing $GABA_A$ receptor networks is a potential therapeutic target, which we are investigating using behavioural learning memory paradigms for cognitive impairment.

Disclosures: **A.L. Petrache:** None. **A.B. Ali:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.24/E13

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant 2R01AG037637-07
NSF Grant 1606833

Title: Maternal choline supplementation ameliorates Alzheimer’s disease pathology by reducing brain homocysteine levels across multiple generations

Authors: *R. VELAZQUEZ, Jr[1], E. FERREIRA[1], W. WINSLOW[1], I. S. PIRAS[2], N. DAVE[1], M. NAYMIK[2], M. J. HUENTELMAN[2], A. TRAN[1], S. ODDO[1,3];

[1]Arizona State Univ. - Banner Neurodegenerative Dis. Res. Ctr., Biodesign Inst. At Arizona State Univ., Tempe, AZ; [2]Translational Genomics Res. Inst., Phoenix, AZ; [3]Sch. of Life Sci., Arizona State Univ., Tempe, AZ

Abstract: The lack of effective treatments for Alzheimer's disease (AD) is alarming, considering the number of people currently affected by this disorder and the projected increase over the next few decades. Elevated homocysteine (Hcy) levels double the risk of developing AD. Choline, a primary dietary source of methyl groups, converts Hcy to methionine and reduces age-dependent cognitive decline. Here, we tested the transgenerational benefits of maternal choline supplementation (ChS; 5.0 g/kg choline chloride) in two generations of APP/PS1 mice. We first exposed 2.5-month-old mice to the ChS diet and allowed them to breed with each other to generate generation-1 mice. Generation-1 mice were exposed to the ChS diet only during gestation and lactation; once weaned at postnatal day 21, generation-1 mice were then kept on the control diet for the remainder of their life. We also bred a subset of generation-1 mice to each other and obtained generation-2 mice; these mice were never exposed to ChS. We found that ChS reduced Aβ load and microglia activation, and improved cognitive deficits in old generation-1 and generation-2 APP/PS1 mice. Mechanistically, these changes were linked to a reduction in brain Hcy levels in both generations. Further, RNA-Seq data from APP/PS1 hippocampal tissue revealed that ChS significantly changed the expression of 27 genes. These genes were enriched for inflammation, histone modifications, and neuronal death functional classes. Our results are the first to demonstrate a transgenerational benefit of ChS and suggest that modifying the maternal diet with additional choline reduces AD pathology across multiple generations.

Disclosures: R. Velazquez: None. **E. Ferreira:** None. **W. Winslow:** None. **I.S. Piras:** None. **N. Dave:** None. **M. Naymik:** None. **M.J. Huentelman:** None. **A. Tran:** None. **S. Oddo:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.25/E14

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AS-IA-108-L06

Title: Adenosine augmentation evoked by an ENT1 inhibitor ameliorates the dysregulated protein phosphorylation and impaired neuronal plasticity in a mouse model of tauopathy

Authors: *Y. CHERN[1], C.-P. CHANG[2], Y.-G. CHANG[3], S.-J. CHENG[4], D. BLUM[5], L. BUEE[6], H.-M. CHEN[3];

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Abstract: Alzheimer's disease (AD) is the most prominent neurodegenerative disease in aging societies with no effective treatment at this time. The major pathogenic hallmarks of AD include extracellular amyloid plaques and intracellular neurofibrillary tangles. Adenosine is a nucleoside that modulates many pathophysiological functions and the bioenergetic network in the brain. We have previously demonstrated that augmentation of adenosine tone in the brain using an orally active inhibitor (J4) of the equilibrative nucleoside transporter 1 (ENT1) improved the impairment of cognitive functions and neuronal plasticity in a mouse model of AD (APP/PS1). In the present study, we reported that chronic treatment of a mouse model of tauopathy (THY-Tau22) also provided significant beneficial effects. Briefly, J4 treatment ameliorated spatial memory deficiency, synaptic plasticity impairment, and the level of hyperphosphorylated Tau in THY-Tau22 mice. Phosphoproteomic analysis of the hippocampus of THY-Tau22 mice further demonstrated that chronic J4 treatment normalized 24% of the total 170 proteins (including kinases, transcription regulators, phosphatases and ion channels) with altered phosphorylation levels in THY-Tau22 mice. Collectively, our findings suggested that adenosine augmentation induced by an ENT1 inhibitor (J4) provides a new therapeutic strategy for Tauopathy, and may contribute to the development of therapeutic treatment for AD.

Disclosures: Y. Chern: None. **C. Chang:** None. **Y. Chang:** None. **S. Cheng:** None. **D. Blum:** None. **L. Buee:** None. **H. Chen:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.26/E15

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: the SENSHIN Medical Research Foundation
JSPS KAKENHI
AMED JP16dm0107056h0001

Title: Utilization of γ-secretase trimming activity for proper evaluation of Aβ targeting compounds

Authors: *S. TAGAMI[1], K. YANAGIDA[1], M. IKEDA[1], T. KUDO[2], M. OKOCHI[1];
[1]Osaka Univ. Grad. Sch. of Med., Suita, Japan; [2]Dept Mental Hlth. Promoion, Osaka Univ. Grad. Sch. of Med., Toyonaka-Shi, Japan

Abstract: Introduction: Beta-amyloid (Aβ), which accumulates in the brain of Alzheimer's disease, is generated from its precursor protein, βAPP. βAPP is first shed by BACE followed by sequential intramembrane cleavages of the transmembrane remnant by presenilin/γ-secretase. Following an initial ε-cleavage at the border between cytosol and transmembrane domain, γ-secretase cleaves the remaining membrane-bound long Aβ with stepwise trimming by every 3 to 4 amino-acids. These small peptides such as ITL, VIV, and IAT termed γ-byproducts were identified not only in *in vitro* γ-secretase cleavage assay but also inside cultured cells and in brain of βAPP transgenic mice. Unlike Aβ, γ-byproducts are not secreted and thus could serve as a more direct indicator of γ-secretase activity than secreted Aβ.
Objective: By quantification of γ-byproducts generated during sequential cleavages upon Aβ production, we aimed to properly evaluate effects of Aβ targeting compounds such as γ-secretase modulators and BACE inhibitors.
Methods: The γ-byproducts extracted from cells treated with each compound were measured using LC/MS/MS (Quattro Premier XE tandem quadrupole mass spectrometer equipped with UPLC, Waters).
Results: Previously, we reported that non-transition state analogue γ-secretase inhibitors did not decrease but rather increased the levels of γ-byproducts. In addition to the increased level of γ-byproducts, we found accumulation of Aβ inside neurons derived from human iPS cells, although non-transition state analogue γ-secretase inhibitors decreased secreted Aβ as reported. In this study, we investigated whether other Aβ targeting compounds might cause unexpected increase in the levels of γ-byproducts.
Conclusions: We propose that γ-secretase activity should also be evaluated in terms of the levels of γ-byproducts in development of Aβ targeting compounds.

Disclosures: S. Tagami: None. **K. Yanagida:** None. **M. Ikeda:** None. **T. Kudo:** None. **M. Okochi:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.27/E16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG061800
NIH Grant AG054719
NIH Grant AG043552
NIH Grant P30NS055077
NIH Grant T32 NS 061788

Title: Lim kinase inhibition provides dendritic spine resilience against amyloid-β

Authors: *J. H. HERSKOWITZ, B. HENDERSON, K. M. GREATHOUSE, R. RAMDAS, T. RAO, S. BACH, C. WALKER, K. CURTIS, J. DAY, A. MATTHEYSES;
The Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Alzheimer's disease (AD) therapies predominantly focus on amyloid-β (Aβ), but Aβ effects may be maximal before clinical symptoms. Downstream of Aβ, dendritic spine loss correlates most strongly with cognitive decline in AD. Rho-associated kinases (ROCK1 and ROCK2) regulate the actin cytoskeleton and ROCK1 and ROCK2 protein levels are increased in early AD. We show that expression of ROCK1 in hippocampal neurons reduces dendritic spine length through a myosin-based pathway, while expression of ROCK2 induces spine loss through LIMK1. Aβ42 oligomers can activate ROCKs, and using static imaging studies combined with multi electrode array analyses we show that the ROCK2-LIMK1 pathway mediates Aβ42-induced spine degeneration and neuronal hyperexcitability. Living cell microscopy revealed that pharmacologic inhibition of LIMK1 renders dendritic spines resilient to Aβ42 oligomers. Treatment of hAPP mice with a LIMK1 inhibitor rescued Aβ-induced hippocampal spine loss and morphologic aberrations. Our work suggests that therapeutic targeting of LIMK1 may provide dendritic spine resilience to Aβ, benefitting cognitively normal patients at high risk for dementia.

Disclosures: **J.H. Herskowitz:** None. **B. Henderson:** None. **K.M. Greathouse:** None. **R. Ramdas:** None. **T. Rao:** None. **S. Bach:** None. **C. Walker:** None. **K. Curtis:** None. **J. Day:** None. **A. Mattheyses:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.28/E17

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG061800
NIH Grant AG054719
NIH Grant AG043552
NIH Grant P30NS055077

Title: Synergistic analysis of dendritic spine morphology and the synaptic proteome in human entorhinal cortex uncovers mechanisms of synapse loss in Alzheimer's disease

Authors: *C. K. WALKER[1], B. D. BOROS[1], K. M. GREATHOUSE[1], E. B. DAMMER[2], K. A. CURTIS[1], H. M. MUHAMMAD[1], R. RAMDAS[1], I. CHAUDHARY[1], D. M. DUONG[2], N. T. SEYFRIED[3], J. H. HERSKOWITZ[1];

[1]Univ. of Alabama At Birmingham, Birmingham, AL; [2]Emory Univ., Atlanta, GA; [3]Human Genet., Emory Sch. Med., Atlanta, GA

Abstract: Amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs) of the microtubule-associated protein tau are the pathological hallmarks of AD; however, synapse or dendritic spine loss correlates more strongly with cognitive impairment than plaques or NFTs. Approximately one-third of individuals that come to autopsy in their eighties have Aβ plaques and tau NFTs, yet did not have dementia in life. These cognitively normal individuals with AD pathology (CAD) were likely in preclinical stages of AD. Unlike individuals with AD dementia, CAD cases do not exhibit dendritic spine loss in the prefrontal cortex. NFT burden negatively correlates with dendritic spine loss, suggesting that tau contributes to synapse loss in AD. In this study, we asked whether the entorhinal cortex (EC), one of the earliest regions to exhibit tau pathology, shows alterations in dendritic spine density and morphology in AD. Dendrites in postmortem human EC samples from 20 normal controls, 6 CAD cases, and 24 AD cases were visualized using the Golgi–Cox technique and spines were imaged using high-resolution brightfield microscopy. Neurolucida 360 was employed for three-dimensional dendrite reconstruction and dendritic spine morphometry analysis. CAD cases maintained spine density at levels similar to healthy controls, while spine density was reduced in AD patients. To begin to understand the mechanisms of EC synapse loss in AD, we undertook a systems approach to identify synaptic proteins that are differentially expressed in AD and associated with dendritic spine density and morphology. EC synaptosomal fractions were isolated from 20 normal controls, 7 CAD cases, and 31 AD cases. Liquid chromatography coupled with tandem mass spectrometry-based proteomics was performed on synaptosomes, followed by weighted protein co-expression network analysis. Resulting modules were correlated with numerous traits, including clinical data, spine density and morphology, and neuropathology to reveal protein targets that associate with EC synapse loss in AD.

Disclosures: C.K. Walker: None. **B.D. Boros:** None. **K.M. Greathouse:** None. **E.B. Dammer:** None. **K.A. Curtis:** None. **H.M. Muhammad:** None. **R. Ramdas:** None. **I. Chaudhary:** None. **D.M. Duong:** None. **N.T. Seyfried:** None. **J.H. Herskowitz:** None.

Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.29/E18

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: EC Horizon 2020 grant # 689592

Title: My active and healthy ageing (My-AHA), an ICT-based project for risk detection and prevention

Authors: *A. E. VERCELLI[1,2], I. RAINERO[2], G. AUMAYR[3], M. SUMMERS[4];
[1]Neurosci. Inst. Cavalieri Ottolenghi, Orbassano (TO), Italy; [2]Neurosci. R.L.Montalcini, Univ. of Torino, Torino, Italy; [3]Johanniter Austria, Vienna, Austria; [4]Sunshine Coast Mind & Neurosci. – Thompson Inst., Univ. of the Sunshine Coast, Birtinya, Australia

Abstract: Stemming from a holistic view of interrelated frailties, cognitive decline, physical frailty, depression and anxiety, social isolation and poor sleep quality, My-AHA proposes an ICT platform for early detection of pre-frailty and intervention to sustain active and healthy ageing and slowing or reversing further decline. The main aim of My-AHA is to reduce frailty risk by improving physical activity and cognitive function, psychological state, social resources, nutrition, sleep and overall well-being in older adults with pre-frailty symptoms. It empowers older citizens to better manage their own health, providing new ways of health monitoring and disease prevention through individualized profiling and personalized recommendations, feedback and support. An ICT-based platform detects defined risks in the frailty domains early and accurately via non-stigmatising embedded sensors and data readily available in the daily living environment of older adults. When risk is detected (pre-frail), My-AHA provides targeted ICT-based interventions. These interventions follow an integrated approach to motivate users to participate in physical exercise, cognitively stimulating games and social networking to achieve long-term behavioural change, sustained by continued end user engagement with My-AHA. A randomized controlled study (RCT), involving 150 subjects receiving intervention, and 150 controls from many EU and non EU countries, to evaluate intercultural aspects, is ongoing in order to evaluate efficacy of the my-AHA platform. The ultimate aim is to deliver significant innovation in the area of active and healthy ageing through cooperation between European health care organizations, SMEs, and NGOs.On behalf of the My-AHA ConsortiumMy Active and Healthy Ageing is supported by the European Union with a Horizon 2020 (PHC-21-2015) grant, Contract # 689592.

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Poster

563. Alzheimer's Disease and Related Disorders: Preclinical Models

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 563.30/E19

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Thailand Research Fund (IRN-58W0004)

Title: Neuroprotective effects of a novel lipoic acid-dl-3-n-butylphthalide hybrid

Authors: *K. UPPAKARA[1], S. B. WAN[3], W. SAENGSAWANG[2];
[1]Toxicology Grad. Program, [2]Physiol., Fac. of Sci. Mahidol Univ., Bangkok, Thailand; [3]Sch. of Med. and Pharm., Ocean Univ. of China, Qingdao, China

Abstract: Neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) are progressive and irreversible damage of the nervous system. The pathogenesis of these diseases is still unclear but several evidences suggest that oxidative stress is one of major causes of the degeneration. In this study, series of new alpha lipoic acid hybridized dl-3-n-butylphthalide were synthesized and tested for their antioxidant activity and protective effects against oxidative damages to neuronal cells. An analogue combination, dlx-23, showed strong antioxidant activity in *in vitro* DPPH scavenging assay. To determine the protective effect of dlx-23 in neuronal cells we used Cath. a differentiated (CAD) cells as a model. Dlx-23 effectively prevented H_2O_2-induced neuronal cells death. Using antioxidant assay, we found that intracellular ROS level after exposure to H_2O_2 was significantly reduced when the cells were pretreated with dlx-23. Dlx-23 also increased the level of glutathione in the cells. These activities are more potent than the parent compounds alone. In addition, Live imaging of the neuronal growth cone demonstrated that dlx-23 protected the growth cone of primary cortical neurons from damages induced by H_2O_2. Taken together these results suggest the potential of dlx-23 to be further developed into a novel neuroprotective agent.

Disclosures: K. Uppakara: None. **S.B. Wan:** None. **W. Saengsawang:** None.

Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 564.01/E20

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: BrightFocus A2018128F
AbbVie

Title: Therapeutic effects of human LDLR overexpression on ApoE-related tau pathology and brain dysfunction

Authors: *C. WANG[1], A. LI[1], S. NATHAN[1], R. SPELLMAN[1], M. MANIS[1], M. FINN[1], Y. SHI[1], M. XIONG[1], J. REMOLINA SERRANO[1], P. SULLIVAN[2], D. HOLTZMAN[1];
[1]Washington Univ. In St. Louis, St. Louis, MO; [2]Dept. of Med., Duke Univ., Durham, NC

Abstract: Apolipoprotein E gene (*APOE*) is the strongest genetic risk factor for late-onset Alzheimer's disease (AD) with the ε4 allele increasing risk in a dose-dependent fashion and the ε2 allele decreasing risk relative to the ε3 allele. Although the mechanisms are not fully

elucidated, apoE appears to influence AD at least in part via influencing amyloid β (Aβ) aggregation and clearance. In addition, our lab has recently reported that apoE isoforms also directly affect tauopathy and tau-mediated neurodegeneration in P301S tau transgenic mice expressing different human apoE isoforms. Specifically, apoE4 results in significant loss of brain volume and increase in glial inflammatory response compared to other apoE isoforms. The absence of apoE alleviated both neurodegeneration and the inflammatory response. Low-density lipoprotein receptor (LDLR) is a cell surface glycoprotein that plays a pivotal role in maintaining plasma cholesterol homeostasis. In the brain, abundant evidence reveals that LDLR is one of the main apoE receptors that regulate apoE levels, but LDLR has very few identified ligands compared to other apoE receptors. LDLR overexpression in the brain can dramatically lower apoE and Aβ levels, as well as decrease Aβ accumulation and deposition. Therefore, we propose to evaluate whether AAV-mediated overexpression of human LDLR (hLDLR) is an efficient way to reduce apoE levels, tau pathology, and neurodegeneration. To study the effect of LDLR overexpression on apoE4-related tau pathology and neurodegeneration, P301S Tau/ApoE4 (TE4) male mice received a bilateral intracerebroventricular injection with AAV expressing hLDLR or GFP-control, starting before the onset of tau pathology development. Brains were isolated after 9 months, divided into hemispheres, and analyzed by histological and biochemical techniques. Widespread expression of hLDLR throughout the brain was observed and apoE levels were significantly decreased. Furthermore, mouse nest-building impairment was rescued after hLDLR overexpression. Strikingly, there is a significant decrease in brain atrophy, phosphorylated tau deposition in TE4 mice overexpressing hLDLR. In summary, these data suggest that LDLR may be a promising target to lower apoE levels and decrease neurodegeneration.

Disclosures: **C. Wang:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; This work was funded by a grant from BrightFocus (CW). **A. Li:** None. **S. Nathan:** None. **R. Spellman:** None. **M. Manis:** None. **M. Finn:** None. **Y. Shi:** None. **M. Xiong:** None. **J. Remolina Serrano:** None. **P. Sullivan:** None. **D. Holtzman:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; This work was funded by a grant from AbbVie (DMH). F. Consulting Fees (e.g., advisory boards); DMH co-founded and is on the scientific advisory board of C2N Diagnostics, LLC. DMH is on the scientific advisory board of Denali and Genentech..

Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 564.02/E21

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Synaptic tau targeted immunotherapy for Alzheimer's disease

Authors: *C.-Y. TAI, H.-T. MA, S.-C. HUANG, C.-L. LI, M.-F. WU, C.-L. WU, S.-H. LIN, M.-K. JANG;
APRINOIA Therapeut. Inc., Taipei, Taiwan

Abstract: Alzheimer’s disease (AD) is the most common form of dementia in aging population. Propagation of tau aggregates along the synaptically connected brain regions tightly correlates with pathophysiological changes such as neuronal loss and cognitive impairment of the disease. We propose here an immunotherapeutic approach to block the tau pathology in AD by an anti-tau antibody specifically targeting synaptic tau species. We ranked order the synaptic tau specificity of our anti-tau antibodies using dot-blot assay, and synaptic preferred antibodies were highly specific to sarkosyl-insoluble tau aggregates extracted from AD brains. Immunohistochemistry study with brain slices obtained from 3-mo-old rTg4510 mice showed distinct patterns of localization in either somatic or axodendritic space, indicating diverse tau species identified by our tau antibodies. Some of the tau species seem to be actively transported/segregated in specific sub-cellular compartments. Moreover, a few synaptic preferred antibodies labeled tau aggregates in the entorhinal cortex of early Braak stage I-II subjects before clinical symptoms onset, and removal of tau aggregates by the antibody drastically blocked the seeding ability of rTg4510 brain lysate in a HEK cell-based assay. Membrane depolarization of rTg4510 synaptoneurosomes enhanced the release of several tau species that were recognized by our antibodies, suggesting a therapeutic utility of our antibodies by blocking the releasable tau in the extracellular space. These results imply a role for synaptically localized AD tau species in disease causing mechanism. They also profile the molecular and cellular properties of these tau species and suggest an immunotherapy by blocking the releasable tau at the synapse.

Disclosures: **C. Tai:** A. Employment/Salary (full or part-time):; APRINOIA Therapeutics Inc. **H. Ma:** A. Employment/Salary (full or part-time):; APRINOIA Therapeutics Inc. **S. Huang:** A. Employment/Salary (full or part-time):; APRINOIA Therapeutics Inc. **C. Li:** A. Employment/Salary (full or part-time):; APRINOIA Therapeutics Inc. **M. Wu:** A. Employment/Salary (full or part-time):; APRINOIA Therapeutics Inc. **C. Wu:** A. Employment/Salary (full or part-time):; APRINOIA Therapeutics Inc. **S. Lin:** A. Employment/Salary (full or part-time):; APRINOIA Therapeutics Inc. **M. Jang:** A. Employment/Salary (full or part-time):; APRINOIA Therapeutics Inc..

Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 564.03/E22

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: Shah Philanthropic Fund to NEOMED for Alzheimer's Research

Title: Neuroprotective effects of peripherally-administered irisin in a tauopathy model of Alzheimer's

Authors: *K. A. BRETLAND[1], L. LIN[1], K. M. BRETLAND[2], C. M. DENGLER-CRISH[1]; [1]Pharmaceut. Sci., Northeast Ohio Med. Univ., Rootstown, OH; [2]Kent State Univ., Kent, OH

Abstract: As clinical trials for single-target therapies continue to fail, there is a critical call for developing complete treatments that address the multifactorial nature of Alzheimer's disease (AD) pathology. One emerging candidate is the recently discovered hormone irisin, which is cleaved from the fibronectin type III domain-containing protein 5 (FNDC5) transmembrane protein. A small but increasing number of studies show that irisin may protect against AD by a) ameliorating peripheral inflammation associated with metabolic disease, b) inhibiting neuroinflammatory responses, and c) reducing production of amyloid beta. However, the mechanisms by which irisin provides direct neuroprotective effects are not well-understood, and nothing is known about how it interacts with AD-related tauopathy. Studies have shown that peripheral enhancement of irisin (either exercise-induced or by exogenous administration of recombinant irisin protein) can elevate central levels of this hormone. Therefore, we sought to determine whether exogenous administration of irisin would reduce brain levels of hyperphosphorylated tau (ptau) in htau mice, a transgenic model that develops age-related tauopathy and cognitive deficits akin to the clinical presentation of AD. We treated female and male htau mice with weekly injections of 100 ug/kg (i.p.) recombinant human irisin or saline vehicle for 4 weeks and then sacrificed animals for fresh or fixed tissue collection. Using capillary-based western blotting (Wes; ProteinSimple) and fluorescent immunohistochemistry, we measured ptau, FNDC5/irisin, neuroinflammation, and additional pathological indicators within the hippocampus, cortex, and brainstem. We found that irisin treatment significantly reduced hippocampal ptau in female htau mice, whereas male htau mice only trended towards a similar reduction. These results indicate that irisin may be neuroprotective against tauopathy, increasing its potential as a multi-target therapeutic in AD.

Disclosures: K.A. Bretland: None. **L. Lin:** None. **K.M. Bretland:** None. **C.M. Dengler-Crish:** None.

Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 564.04/E23

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH

CNPq
CAPES
FAPERJ
ISN
INNT/CNPq

Title: FNDC5/irisin links physical exercise to neuroprotection in mouse models of Alzheimer's disease

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Abstract: Alzheimer’s disease (AD) is a disorder characterized by synapse and memory failure, which has been closed linked to impaired hormonal action in the brain. Irisin is an exercise-induced myokine released on cleavage of the precursor protein fibronectin type III domain-containing protein 5 (FNDC5), which is also expressed in the hippocampus. We examined whether FNDC5/irisin would display neuroprotective properties in animal models of AD and whether it mediates the beneficial actions of exercise in the degenerating brain. We found that brain or peripheral overexpression of FNDC5/irisin rescued synapse and memory defects in AD mice. Recombinant irisin stimulated cAMP/PKA-mediated signaling and prevented translational repression induced by soluble amyloid-beta in primary neurons. In mice, blockade of either peripheral or brain FNDC5/irisin attenuated the neuroprotective actions of physical exercise on AD-linked synaptic plasticity and memory failure. Our results provide a novel mechanism of neuroprotection by physical exercise and suggest a novel potential target for effective therapeutics in AD.

Disclosures: M.V. Lourenco: None. **O. Arancio:** None. **S.T. Ferreira:** None. **F.G. De Felice:** None.

Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

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Program #/Poster #: 564.05/E24

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: John and Patricia Beckler Fellowship in Alzheimer's and Cognitive Diseases
NIH R01AG050518
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Office of the Vice President for Research at USC
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Title: Dose-dependent neurochemical, molecular, and behavioral effects of intranasal insulin

Authors: *J. M. ERICHSEN[1], J. L. WOODRUFF[1], H. E. BURZYNSKI[1], C. A. GRILLO[1,2], L. P. REAGAN[1,2], J. R. FADEL[1];
[1]Pharmacology, Physiology, and Neurosci., Univ. of South Carolina Sch. of Med., Columbia, SC; [2]WJB Dorn VA Med. Ctr., Columbia, SC

Abstract: Cognitive dysfunction with aging is a dreaded and costly (both economically and personally) aspect of growing old. Unfortunately, there is no therapeutic strategy to date that effectively treats age-related cognitive decline (ARCD). It is plausible that intranasal insulin (INI) could fill this gap, as a number of studies have demonstrated that INI improves memory. However, the mechanistic basis for these pro-cognitive changes has yet to be elucidated. Behavioral, neurochemical, and molecular techniques were employed in adult Sprague-Dawley and Fischer 344/Brown Norway F1 hybrid rats following INI with the goal of beginning to understand this mechanism. In order to determine the optimal dose for the molecular and behavioral effects of INI, several doses of insulin were explored in these experiments. First, feeding behavior was assessed for 18 hours following INI or IN vehicle to examine if the insulin elicited a behavioral effect. INI produced dose-dependent effects on food intake post-administration. Next, cholinergic transmission and insulin receptor signaling in the brain were assessed. Probes were inserted into the medial prefrontal cortex and hippocampus of the rats for *in vivo* microdialysis. Levels of acetylcholine, glutamate, and GABA varied in the three hours after IN vehicle compared to different doses of insulin. On a separate day, the rats were euthanized 30 minutes post-INI. Olfactory bulb and hippocampal extracts were processed for immunoblot analysis to determine if changes in central insulin signaling in response to IN vehicle vs. different doses of insulin could be seen. The results of these experiments provide a potential molecular/neurochemical basis for the pro-cognitive effects of INI. It is important to understand the mechanism of action, as INI could eventually be used in the broader clinical setting to treat ARCD. Further, this could initiate the development of other treatments for ARCD that exploit the same mechanism of action. More studies are needed to fully understand the neurochemical, molecular, and behavioral changes following INI and to determine the most effective clinical dose, but these results demonstrate the ability of INI to rapidly target the brain and influence neurotransmission, central insulin signaling, and feeding behavior.

Disclosures: **J.M. Erichsen:** None. **J.L. Woodruff:** None. **H.E. Burzynski:** None. **C.A. Grillo:** None. **L.P. Reagan:** None. **J.R. Fadel:** None.

Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 564.06/E25

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Insulin sensitizers and the risk of incident dementia: A meta-analysis using real-world evidence

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Abstract: Several epidemiological studies considered diabetes as a risk factor for developing dementia. Published clinical studies found insulin resistance as a culprit for developing dementia. So, this study is aimed to explore the effects of insulin sensitizers (biguanides, thiazolidinediones and DPP-4 inhibitors) on the incidence of dementia. An electronic search was performed in PubMed and Cochrane central to identify the suitable articles using Mesh term related to "insulin sensitizers" and "dementia." The search period was from inception to December 2018. Risk of bias was assessed using an appropriate tool based on the study design of articles qualified for inclusion. The primary outcome was to quantify the effects of insulin sensitizers on the incidence of dementia. The secondary outcome was to assess the dementia risk based on subgroups like drug class, dementia types. All the analysis was performed using Review Manager v5.3. This meta-analysis comprised of total 102,580 patients of which 95,968 belongs to biguanide (metformin) and 6,612 belongs to thiazolidinediones (TZD) group. Majority of the studies were of high quality as reflected on the score attainment in Newcastle-Ottawa Scale. Insulin sensitizers (pooled effect of each drug class) has no effect on the incidence of dementia with a relative risk (RR) of 1.02 (95% CI: 0.87 to 1.20, p = 0.78). Only drugs belong to TZD group was found to have statistically significant protective effects for the dementia incidence with RR of 0.74 (95% CI: 0.56 to 1.0, p = 0.05). None of the subgroups has statistically significant effects on dementia incidence. This meta-analysis concludes that only the use of thiazolidinediones was associated with a significant reduction in the risk of developing dementia. However, well-designed randomized controlled trials are warranted to generalize the evidence.

Disclosures: M. Hussain: None. **A. Habib:** None. **A. Najmi:** None.

Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 564.07/E26

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH 2-R37-NS051874-22

Title: A novel Cdk5 inhibitory peptide attenuates pathological features in human and mouse models of Alzheimer's disease

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[1]Picower Inst. for Learning and Memory, [2]Picower Inst. for Learning and Memory, Brain and Cognitive Sci., MIT, Cambridge, MA; [3]The Picower Inst. for Learning and Memory, MIT, Cambridge, MA

Abstract: Cyclin-dependent kinase 5 (Cdk5), a serine/threonine kinase, plays a critical role in many aspects of neuronal function such as neuronal migration and positioning, cytoskeletal regulation, presynaptic neurotransmitter release, and synaptic plasticity and learning. However, it has also been reported that Cdk5 becomes hyperactive in neurodegenerative diseases such as Alzheimer’s due to increased levels of p25, a proteolytic fragment of the regulatory subunit p35. We previously showed that inhibition of p25 generation by replacing endogenous p35 with a non-cleavable mutant p35 (Δp35) ameliorated amyloid and tauopathic phenotypes in familial Alzheimer’s disease and frontotemporal mouse models, respectively. Here we show that a modified, truncated peptide (Cdk5 inhibitory peptide- Cdk5i), derived from Cdk5, effectively and specifically inhibits aberrant Cdk5 hyperactivity in vitro. In addition, Cdk5i-TAT peptide penetrates blood-brain barrier in mice after an intraperitoneal injection, rendering it a potentially small and readily diffusible therapeutic agent to combat pathological features of neurodegeneration.

Disclosures: O. Kritskiy: None. **J. Seo:** None. **L. Tsai:** None.

Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 564.08/E27

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH RF1 AG058081
NIH RF1 AG056976
NIH R21 AG056025
College of Pharmacy, Academic Health Center of the University of Minnesota

Title: The HDL mimetic peptide 4F mitigates cerebral amyloid angiopathy in transgenic APPswDI mice

Authors: *R. ZHONG[1], D. S. CHERNICK[2], D. A. HOTTMAN[1], L. LI[1];
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Abstract: Cerebral amyloid angiopathy (CAA) features amyloid-β (Aβ) deposition in small arteries and capillaries of the cerebral cortex and the leptomeninges, and constitutes one of the pathological hallmarks of Alzheimer's disease (AD) along with senile plaques and neurofibrillary tangles. CAA is associated with intracerebral hemorrhage, cerebrovascular dysfunction and cognitive impairment. There is currently no effective clinical therapy for CAA or AD. Substantial evidence has shown that high levels of high-density lipoprotein (HDL), and its main protein component, apoA-I, are associated with superior cognitive function in the elderly; in animal models, our previous studies have shown that overexpression of human apoA-I rescues cognitive function in AD mice by attenuating CAA and neuroinflammation. 4F is an 18 amino acid HDL mimetic peptide that has advanced into clinical trials for cardiovascular disease. Our preliminary data have shown that 4F inhibits Aβ aggregation and enhances Aβ efflux across the blood-brain barrier. The present study was undertaken to investigate whether acute or chronic treatment with the HDL mimetic peptide 4F mitigates CAA and associated cognitive deficits and neuropathologies in the transgenic APPswDI mouse model of CAA/AD. APPswDI mice were treated with i.p. injections of D-4F, the D-isomer of 4F that exhibits higher bioavailability and longer half-life. Two cohorts of age- and sex-matched APPswDI mice received either a 1 week (acute) or 12 week (chronic) daily treatments of D-4F or vehicle (PBS), respectively. In the acute treatment study, soluble Aβ levels were significantly reduced in the brain of D-4F treated APPwDI mice; consistently, D-4F treatment trends toward decreased amyloid deposition and microglia recruitment in cortical and hippocampal regions. In the chronic study, D-4F administration was shown to rescue CAA-associated memory deficits in male APPswDI mice, suggesting a sex-dependent effect in this mouse model of CAA/AD. Additional analyses are underway to unravel the molecular mechanisms underlying the effects of D-4F treatment in these mice. These findings suggest that HDL memetic peptides could be a potential therapeutic agent to mitigate CAA/AD.

Disclosures: R. Zhong: None. **D.S. Chernick:** None. **D.A. Hottman:** None. **L. Li:** None.

Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 564.09/E28

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: the National Natural Science Foundation of China No. U1803281
he National Natural Science Foundation of China 81673411
the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences 2018RC350013

Title: LC1405 prevents beta-amyloid peptide-induced toxicity by regulating histamine H3 receptor signaling pathway

Authors: *R. LIU[1], L. WANG[2], H. JIANG[2], Q. WANG[1];
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Abstract: In studies on the treatment of Alzheimer’s disease (AD), in which cognition is enhanced even modestly or selectively, it has been considered that the histamine H3 receptor (H3R) may be a potential target. In this study, we aimed at evaluating the ability of 7-pyrrolidinethoxy-4'-methoxyisoflavone (indicated as LC1405), a novel potential H3R antagonist identified from our H3R antagonist screening system, to ameliorate amyloid β (Aβ)-induced cognitive deficits, and to explore the underlying mechanisms that are related to H3R-modulated signaling. Our results demonstrated that LC1405 effectively reduced the progression of Aβ-associated disorders, such as improved learning and memory capabilities, preserved tissues from suffering neurodegeneration and ultrastructural abnormalities, and ameliorated cholinergic dysfunction in an APP/PS1 double transgenic mouse model of AD. In an *in vitro* model, LC1405 protected neuronal cells against copper-induced Aβ toxicity, as demonstrated by the improvement in cell viability and decrease in neuronal apoptotic ratio. In addition, treatment with LC1405 resulted in the up-regulation of acetylcholine (ACh) or histamine release and provided neuroprotection through cellular signaling cascades involving H3R-mediated cAMP/CREB and AKT/GSK3β pathways. Furthermore, the beneficial effects of LC1405 on Aβ-mediated toxicity and H3R-mediated cAMP/CREB and AKT/GSK3β axes were reversed after pharmacological activation of H3R. In conclusion, our results demonstrated that LC1405 blocked Aβ-induced toxicity through H3R-modulated signaling transduction both *in vitro* and *in vivo*. The results also suggested that LC1405 might have translational potential as a complementary therapy to control disease progression in AD patients who developed cognitive deficits with H3R-related ACh neurotransmission abnormality.

Disclosures: R. Liu: None. **L. Wang:** None. **H. Jiang:** None. **Q. Wang:** None.

Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 564.10/E29

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 1RF1AG051514
NIH Grant 5T32ES012870
NIH Grant 1RF1AG057247

Title: Soluble TNF mediates obesogenic diet-induced alterations in peripheral and brain immunophenotype in a mouse model of Alzheimer's disease

Authors: *M. G. T. TANSEY[1], K. P. MACPHERSON[2], L. N. EIDSON[3], M. K. HERRICK[3], M. DE SOUSA RODRIGUES[4], L. SNIFFEN[4], S. D. KELLY[3], A. M. HAMILTON[3], D. L. OLIVER[3], Y. YANG[3], J. CHANG[3];
[1]Physiol., Emory Univ. Sch. of Med., Atlanta, GA; [2]Indiana Univ. Sch. of Med., Indianapolis, IN; [3]Physiol., [4]Emory Univ., Atlanta, GA

Abstract: Increasing evidence indicates that neurodegenerative disease, such as Alzheimer's disease (AD), is the product of an individual's genetic risk in the context of their environmental exposures. A major contributor in mediating the gene-environment effect in AD is the immune system. Peripheral immune cell signaling plays an important role in AD through regulating immune cell interactions within the microvasculature and meninges of the CNS, as well as mediating effects at the Blood-Brain Barrier (BBB) and Gut. A diet high in fat and sugar dysregulates several signaling pathways that trigger immune and metabolic responses that can result in metabolic syndrome and is linked to increased risk for AD. Among these, cytokine and chemokine mechanisms regulate peripheral immune cell trafficking to inflamed tissues, including the gut and brain. The cytokine, tumor necrosis factor (TNF), is elevated in AD patients, regulates brain and gut barrier permeability, and is produced by central and peripheral immune cells. Further, TNF mediates conditions involved in metabolic syndrome. We hypothesize that soluble TNF (sTNF) is a key mediator of peripheral immune cell contributions to AD-like pathology and metabolic dysfunction. Here we aim to determine the effect of chronic high-fat-high-carbohydrate (HFHC) diet-induced peripheral inflammation on neuroinflammation and neuronal health in a model of AD. Two-month old female 5xFAD mice were fed a HFHC or a control diet (CD) for 8 weeks. After 4 weeks of diet, XPro1595, a BBB-permeant peptide, was used to selectively inhibit sTNF signaling. XPro1595 ameliorated HFHC diet-induced increased hippocampal Abeta and Iba1 protein levels as well as TNF and ZO-1 mRNA. 5xFAD mice had increased T cell populations in the brain when fed HFHC, and in HFHC diet-fed Tg mice as compared with HFHC non-Tg mice. An increase in Ly6C+ T cells was observed in HFHC diet-

fed Tg mice versus CD fed mice. Tg mice fed a HFHC diet had decreased PBMC T cell expression. Experiments are ongoing to assess additional effects of sTNF in AD pathogenesis gut permeability and inflammation, and alterations in the gut microbiome. Together, these data suggest that diet -induced obesity alters immune cell populations in 5xFAD mice and promotes BBB associated alterations that may enhance neuroinflammation, amyloid burden, and neurodegeneration.

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Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 564.11/E30

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01 NS088192
NIH Grant R21 NS107897
NIH Grant R56NS105632

Title: Suppression of ATAD3A aberrant activation attenuates neuropathology and cognitive deficits in experimental models of Alzheimer's disease

Authors: *Y. ZHAO, X. SUN, X. QI;
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Abstract: Alzheimer’s disease is the most common age-dependent neurodegenerative disease, which is featured by accumulation of amyloid deposition, neurofibrillary tangles, loss of synapses and progressive loss of memory and other cognitive functions. So far, there is no effective treatment available for AD. ATAD3A (ATPase family AAA-domain containing protein 3A) is a nuclear-encoded mitochondrial protein that regulates mitochondrial morphology and controls cholesterol trafficking at mitochondrial contact sites. Our recent study demonstrates that ATAD3A oligomerization elicits mitochondrial bioenergetics failure and neuronal dysfunction under stress and pathological condition. In AD cell culture, animal brains and patient postmortem brains, we observe an increase in ATAD3A oligomerization, suggestive of ATAD3A aberrant activation. We developed a peptide blocker, DA1, that binds to ATAD3A to block its oligomerization. Treatment with DA1 reduces the production of mitochondrial reactive oxygen species, improves the cholesterol metabolism and decreases the expression of APP level

in both mouse hippocampus neuronal HT-22 cells exposed to oligomeric $A\beta_{1-42}$ and neuro2a cells stably expressing APP. Notably, sustained treatment with DA1 peptide inhibitor attenuates the cognitive deficits and memory loss, and reduces Aβ accumulation and neuro-inflammation in the brains of 5xFAD AD transgenic mice. Our findings suggest that ATAD3A oligomerization may contribute to the pathogenesis and cognitive decline in AD and that DA1-like reagent might be useful for therapeutic development of AD and aging-related dementia.

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Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

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Program #/Poster #: 564.12/E31

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH NS047229
NIH AG005138
NIH AG008200

Title: A rationally designed peptide based on the ɣ-secretase cleavage product of ephrinB2 promotes angiogenesis *in vitro*

Authors: *S. Z. VANCE[1], Y. YOON[2], N. WARREN[3], N. K. ROBAKIS[3], A. GEORGAKOPOULOS[4];
[1]Psychiatry, Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Psychiatry and Neurosci., [3]Icahn Sch. of Med., New York, NY; [4]Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Presenilin1 (PS1) is part of the γ-secretase complex which cleaves type I transmembrane proteins. Previous studies have shown its role in regulation of vascular function in addition to linking it to familial Alzheimer's disease (fAD). Vascular impairment is commonly observed in Alzheimer's disease. Our lab has previously shown PS1 participates in ephrinB2 (efnB2) signaling by creating a cytoplasmic peptide (efnB2/CTF2) that promotes angiogenic activity *in vitro* through a PDZ-domain. In order to develop therapeutics to treat vascular dysfunction in both AD and related conditions such as ischemic stroke, we aim to develop a deliverable angiogenic peptide *in vivo* based on the PDZ-binding domain from the efnB2/CTF2 sequence. A small peptide (NCB2) was designed based on the PDZ-binding domain of efnB2/CTF2 and fused with the HIV TAT sequence to enhance delivery. Peptides lacking either TAT or PDZ sequence or a scrambled sequence served as controls. Bovine adrenal microvascular endothelial cells (BAMEC) were used to test angiogenic function. NCB2 delivery was confirmed via fluorescent microscopy. To assess the ability of NCB2 to promote sprouting, cells were grown on microcarrier beads in fibrin gels containing peptides. After 48 h, sprouts

were quantified. The ability of NCB2 to promote cell migration was also determined using an *in vitro* scratch assay. Cells were treated and imaged for 5 h. The number of cells invading the scratched area was reported. Results were confirmed in primary mouse brain microvascular endothelial cells (BMEC). NCB2 promotes sprout formation in both BAMEC and BMEC comparable to that of efnB2/CTF2; both enhance sprouting 6-fold larger than untreated cells. Additionally, NCB2 promotes a wound healing phenotype *in vitro* in BAMEC. PDZ-null, scrambled and peptides lacking TAT sequence created neither angiogenic property. NCB2 is a bioactive peptide that possesses the angiogenic properties of efnB2/CTF2. By integrating the TAT sequence, we have created a peptide that can penetrate a variety of cell lines and cause the formation of angiogenic phenotypes. Future studies will explore other angiogenic potential of this peptide such as tube formation and its ability to act *in vivo*.

Disclosures: S.Z. Vance: None. **Y. Yoon:** None. **N. Warren:** None. **N.K. Robakis:** None. **A. Georgakopoulos:** None.

Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 564.13/E32

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: KAKENHI JP (JP17H03558)
discretionary funds of the President of the University of Toyama, in 2018

Title: A new unbeneficial myokine secreted from atrophied skeletal muscle accelerates the onset of Alzheimer's disease

Authors: T. NAGASE, C. TOHDA;
Inst. of Natural Medicine, Univ. of Toyama, Toyama, Japan

Abstract: Several epidemiological and clinical studies show that exercise is positively associated with cognitive function and preventing Alzheimer’s disease (AD). On the contrary, physical inactivity is known as one of risk factors for AD onset. Several myokines are reported to be secreted by exercise, so the positive contribution of those beneficial myokines to cognitive improvement is supposed. In contrast, unbeneficial myokines directly deteriorating cognitive function have not been identified. We hypothesized that unbeneficial myokines exist and accelerate AD onset, and those might be secreted from skeletal muscles at the physically inactivated state. Therefore, this study aimed to investigate the relationship between skeletal muscle atrophy and AD onset, and to identify new myokines involved in the phenomenon. To prepare a disuse muscle atrophy model, bilateral hindlimbs were immobilized by putting into casts for 14 days. Young age of 5XFAD mice (3 months old, male) were used. 5XFAD mice

usually reveal cognitive impairment after 4 - 5 months of age. Object recognition memory and object location memory in casted 5XFAD mice was impaired after the 14-day casting although age matched wild-type mice and non-cast 5XFAD mice showed normal memory function. Numbers of amyloidβ plaques in the brain were not different between casted and non-casted 5XFAD groups. After the memory test, hindlimbs were isolated for organ culture. Conditioned medium of each muscle culture was separated on SDS-PAGE and silver stained. Increased proteins in the conditioned medium of casted 5XFAD were identified by nanoLC-MS/MS analysis. Transferrin was significantly increased in conditioned medium both of gastrocnemius and tibialis anterior muscles of casted 5XFAD mice. Source of increased transferrin was skeletal muscle, but not blood. These results suggest that atrophied skeletal muscles secrete transferrin. Transferrin has never been recognized as a myokine. We suppose that secreted transferrin from skeletal muscles reach to and affect the brain, specific function of transferrin against neurons was investigated. This study found a new myokine, transferrin that might be first identified as unbeneficial myokine for AD onset. Regulating secretion and/or signaling of the transferrin possibly leads to deceleration and inhibition of AD progress.

Disclosures: **T. Nagase:** None. **C. Tohda:** None.

Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 564.14/E33

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant K08DA037465
McLean Sundry Fund

Title: Clathrin nanoparticles efficiently deliver brain-derived neurotrophic factor to the hippocampus, reverse oxidative stress and enhance synaptogenesis and memory in Alzheimer’s mouse model

Authors: *G. VITALIANO[1], C. ADAM[1], G. ZEBALLOS[1], X. CHEN[1], F. DU[1], F. VITALIANO[2];
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Abstract: Background: Advances in treatment of neurodegenerative disorders have been made by administering brain derived neurotrophic factor (BDNF) directly to the brain, or by using drugs that increase BDNF indirectly. BDNF promotes neuroregeneration and restores brain functions but cannot easily cross a blood brain barrier (BBB). Our goal was to develop BDNF-clathrin nanoparticles (CNPs) that can efficiently target brain TrkB receptors and reverse deficits in 3xTg-AD mouse model of Alzheimer’s disease. **Methods:** 3xTg-AD female mice (n=16) were

treated intranasally 2 times weekly from 3-7 months of age with saline (40µl) or CNPs (0.3mg/kg of BDNF with 2.4mg/kg of clathrin). During week 11 of treatment, mice were tested with Barnes maze and Novel Object Recognition tests. During week 12, proton MRS was acquired in the mouse hippocampus (n=8) at a 9.4 T (Varian Inc.) using LASER sequence (Repetition Time/Echo Time, TR/TE = 3000/19 ms). Mice were then sacrificed, and brains were processed using immunohistochemistry. Synaptogenesis and dendritic integrity were determined in the hippocampal regions with Synaptophysin (SYP) and Map2 antibodies respectively. For CNS distribution studies, mice (n=8) received CNP radiolabeled with tritium (4.8 µCi). Brain regions were removed at 4 or 24 hours after CNP administration and concentrations (% injected dose ID/g tissue) were analyzed. **Results:** CNPs delivered BDNF to the mouse hippocampus (0.7 %ID/g) and reversed glial hyperactivity and oxidative/ metabolic stress by significantly decreasing hippocampal levels of myoinositol (mIns/tCr, P=0.0241), glutathione (GSH/H2O, P=0.0231) and lactate (Lac/tCr, P=0.0442) in CNP vs. saline treated 3xTg-AD mice. CNPs significantly improved hippocampal synaptogenesis and dendritic integrity. The SYP immunoreactivity was significantly higher in the CA1 (P=0.0141), CA3 (P=0.0152) and dentate gyrus (DG) (P=0.0073) in CNP vs. saline treated mice. The Map2 immunoreactivity was increased in DG (P=0.0312) of CNP vs. saline treated mice. Hippocampal-based memory acquisition (P=0.029) and novel object recognition (P=0.0073) significantly improved in CNP vs. saline treated 3xTg-AD mice. **Conclusions:** CNPs delivered BDNF to the hippocampus, reversed glial hyperactivity and oxidative stress, enhanced synaptogenesis and dendritic integrity and improved memory in 3xTg-AD mice. Hence, clathrin provides a highly efficient nanoplatform for delivery of BDNF to the brain. This noninvasive nanotechnology may be able to enhance neuronal regeneration and plasticity and restore brain functions better than existing treatments for neurodegenerative disorders.

Disclosures: **G. Vitaliano:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ExQor Technologies. **C. Adam:** None. **G. Zeballos:** None. **X. Chen:** None. **F. Du:** None. **F. Vitaliano:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ExQor Technologies.

Poster

564. Alzheimer's Disease and Other Dementias: Therapeutic Strategies III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 564.15/E34

Topic: C.02. Alzheimer"s Disease and Other Dementias

Support: Ohio Lions Eye Research Foundation
Prevent Blindness Ohio

Title: *In vivo* methods for characterizing visual system pathology in Alzheimer's mouse models

Authors: *G. FRAME[1], E. S. PLYLER[1], C. M. DENGLER-CRISH[2];
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Abstract: Alzheimer's disease (AD) is one of the top ten causes of death in the U.S., yet disease-modifying therapies remain elusive. Given this, early disease detection is a crucial aspect of symptom management and monitoring of disease progression. Of the new techniques being investigated for early detection of AD, retinal imaging and disease-related changes to the visual system remain promising approaches. As such, our lab has data showing that pattern electroretinogram (PERG) and high-resolution ophthalmic imaging can be used *in vivo* to track progression of visual system pathology and functional deficits in 3xtg and APP/PS1 mice. Using a Celeris system (Diagnosys) to measure PERG, we characterized age-related signaling deficits in retina of AD model mice that were contrasted with the same measurements from age-matched healthy control mice. Additionally, we used a Micron-IV Ophthalmoscope (Phoenix Research Labs) to perform *in vivo* imaging of retinal pathology in anesthetized AD-model mice. Following intravitreal injection of fluorescence-tagged amyloid beta antibodies, we were able to visualize retinal amyloid pathology, providing a method for tracking progression of this pathology over time. We also validated these detection methods using post-mortem immunohistochemical approaches. Our results support using these minimally invasive methods to detect early disease pathology in the visual system of experimental AD models and track its progression over time. These techniques provide a means for researchers to investigate the interface between retinal and neural pathology in AD, which will inform our understanding on the utility of clinical retinal imaging in determining disease onset or progression.

Disclosures: G. Frame: None. **E.S. Plyler:** None. **C.M. Dengler-Crish:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.01/E35

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI Foundation

Title: A novel MSD ELISA-based assay for the selective detection and quantitation of rodent HTT protein

Authors: *S. DIJKSTRA[1], A. C. P. CORREIA[1], J. SUIJKER[1], N. A. NGAI[2], P. NAUD[2], M. POIRIER[2], D. F. FISCHER[3], D. MACDONALD[4];

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Abstract: ELISA-type assays are widely used for the detection and quantification of disease related biomarkers, and their robustness and reliability depend mainly on the capture/detection antibody combination used. We previously described a panel of ELISA-based assays for the detection and quantification of various huntingtin (HTT) proteins on the Meso Scale Discovery (MSD) platform, including an assay specific for rodent huntingtin (mouse and rat). This assay employs a rabbit polyclonal antibody directed at the mouse proline-rich domain (PRD)(CHDI-90000147) for capture and a monoclonal anti-HTT antibody (MAB2166) for detection. Long term use of polyclonal antibodies is problematic, therefore we sought to replace CHDI-90000147 with a monoclonal antibody equivalent version to develop a novel rodent HTT assay. The ABfinity platform (Thermo Fisher) was used to generate a set of novel rabbit monoclonal antibodies selective for mouse HTT by targeting the mouse HTT PRD, which is distinct from the human HTT PRD. Antibody characterization was initially performed by Western blot analysis of mouse and human recombinant HTT proteins as well as brain lysates of wild type and homozygous Q175 knock-in mice (which have no endogenous mouse HTT exon 1). Our mAb CHDI-90002133 displayed the most optimal performance in regards to selectivity and specificity, therefore we used it to develop a novel fully monoclonal antibody immunoassay selective for mouse HTT detection on the MSD platform. Here, we describe the use of CHDI-90002133 as capture antibody in combination with either MAB2166 or D7F7 as a detection antibody. Both antibody combinations were able to quantify mouse HTT protein with sensitivity and accuracy. However, only assay CHDI-90002133/D7F7 showed similar or better sensitivity for mouse HTT when compared to the reference original assay CHDI-90000147/MAB2166. Furthermore, we confirmed that this assay is able to detect endogenous rat HTT protein. Assay CHDI-90002133/D7F7 was then validated by demonstrating the expected gene dosage effects in brain lysates from a cohort of Q175 knock-in homozygous, heterozygous and wild type mice. Importantly, this assay is one of a set of HTT quantitation assays transferred from a location in Europe to one in the US for enhanced access. In conclusion, the CHDI-90002133/D7F7 combination of monoclonal antibodies demonstrated to be a promising replacement for our current, polyclonal MSD assay for rodent HTT detection, showing similar performance while mitigating the risk of antibodies being depleted.

Disclosures: **S. Dijkstra:** None. **A.C.P. Correia:** None. **J. Suijker:** None. **N.A. Ngai:** None. **P. Naud:** None. **M. Poirier:** None. **D.F. Fischer:** None. **D. Macdonald:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.02/E36

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CNPq Science Without Borders funding program 403120/2012-8
CNPq Project 480176/2013-2

Title: Hippocampal ultrastructural alterations accompany cognitive and affective deficits in the YAC128 mouse model of Huntington's disease

Authors: *P. S. BROCARDO[1,2], C. DE PAULA NASCIMENTO-CASTRO[2], E. PLÁCIDO[2], E. C. WINKELMANN- DUARTE[1], A. L. S. RODRIGUES[3], J. GIL-MOHAPEL[4];
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Abstract: Introduction: Huntington's disease (HD) is a neurodegenerative disorder characterized by motor, cognitive and psychiatric symptoms. Psychiatric and cognitive disturbances often precede motor symptoms. The main neuropathological characteristic is the selective degeneration of the striatum. However, the involvement of other non-striatal structures such as the hippocampus may contribute to non-motor alterations. Objectives: To characterize behavioral and mitochondrial alterations, as well as to evaluate morphological and ultrastructural changes in the hippocampus of the YAC128 transgenic mouse model of HD. Methods: Experiments to analyze depressive-like behavior (tail suspension test and splash test), and mitochondrial function (respiratory activity) were carried out on 4 and 12-month old YAC128 mice and wild-type (WT) littermate controls. In addition, cognitive deficits (T-maze and rotarod) were evaluated in late symptomatic 12-month old animals. A separate cohort of late symptomatic animals (13 months) was used to evaluate hippocampal morphological alterations. Ultrathin brain sections were obtained stained with 2% lead citrate and 1% uranyl acetate and examined by transmission electron microscopy. Results: YAC128 mice presented depressive-like behaviors at both 4 and 12 months of age, as assessed by the tail suspension test. YAC128 mice also demonstrated a deficit in motor skills acquisition in the rotarod and a deficit in strategy response in the T-maze aquatic test when compared to WT animals. Evaluation of mitochondrial respiration in hippocampal homogenates in the initial (3-4 months) and late (11-14 months) symptomatic phases did not reveal functional deficits. Similarly, YAC128 mice did not present robust alterations in hippocampal mitochondrial ultrastructural morphology. In contrast, the Rough Endoplasmic Reticulum (ER) and Golgi apparatus showed intense dilatation. Analysis of semithin hippocampal sections revealed the presence of degenerate, hyperchromic neurons with irregular morphology as well as nuclear and cytoplasmic condensation in the hippocampal dentate gyrus (DG) of YAC128 mice. Conclusion: Abnormalities in mitochondrial respiratory chain and morphology were not observed in symptomatic YAC128 mice. Therefore, the behavioral alterations present in the early and late stages of HD do not seem to correlate with changes in mitochondrial function. However, a neuronal degenerative process was found in the hippocampal DG granule cells. These results reinforce the progressive nature of HD and the potential role of hippocampal dysfunction in the etiology of the behavioral deficits associated with HD.

Disclosures: **P.S. Brocardo:** None. **C. de Paula Nascimento-Castro:** None. **E. Plácido:** None. **E.C. Winkelmann- Duarte:** None. **A.L.S. Rodrigues:** None. **J. Gil-Mohapel:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.03/E37

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI

Title: Abnormal basal ganglia activity in the Q175 knock-in mouse model of Huntington's disease

Authors: *J. W. CALLAHAN, M. D. BEVAN;
Northwestern Univ., Chicago, IL

Abstract: Huntington's disease (HD) is a neurodegenerative, hereditary, trinucleotide repeat disorder, initially characterized by excessive movement and impulsive behavior. The GABAergic external globus pallidus (GPe) and reciprocally connected glutamatergic subthalamic nucleus (STN) are key components of the indirect and hyperdirect pathways of the basal ganglia that suppress involuntary action. Therefore, abnormal GPe and STN activity could be critical for the symptomatic expression of HD. Using *in vivo* and *ex vivo* cell class-specific recording and optogenetic interrogation approaches, we investigated alterations in the operation of the GPe-STN network in Q175 knock-in (KI) HD mice. We found that in urethane-anesthetized Q175 KI mice 1) GABAergic D2-receptor expressing striatopallidal projection neurons (D2-SPNs) were hypoactive, consistent with their abnormally reduced dendritic excitability; 2) prototypic GPe neuron activity was elevated, consistent with D2-SPN hypoactivity, and the elevation of autonomous GPe neuron activity *ex vivo*; 3) STN neuronal activity was reduced in both anesthetized and awake, behaving Q175 KI mice, consistent with prototypic GPe neuron hyperactivity; 4) STN activity could not be fully restored by optogenetic silencing of prototypic GPe neurons, consistent with the impaired autonomous activity of STN neurons *ex vivo*. Together these data demonstrate that before the loss of neurons, indirect and hyperdirect pathway function is profoundly impaired in HD mice. We are currently investigating whether lowering mutant huntingtin protein in the STN through viral expression of inhibitory zinc finger proteins is sufficient to rescue neuronal activity.

Disclosures: **J.W. Callahan:** None. **M.D. Bevan:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.04/E38

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI Foundation
The Methodist Hospitals Endowed Professorship in Neuroscience

Title: Progressive basal ganglia pathology in male heterozygous q175 knock-in Huntington's disease mice

Authors: Y. DENG, H. WANG, M. JONI, ***A. REINER**;
Anat. & Neurobio., Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: We have characterized the progression of basal ganglia pathology from 2 to 18 months of age in heterozygous male Q175 Huntington's disease (HD) mice compared to age-matched littermate WT mice. We found that striatal projection neurons (SPNs) immunolabeled for DARPP32 were normal in abundance at 2 months but were significantly reduced in abundance by about 20% at 6 months, with reduction of about 40% by 18 months. As the abundance of enkephalinergic (ENK+) indirect pathway SPNs (iSPNs) was similarly decreased, but the abundance of substance P-containing (SP+) direct pathway SPNs (dSPNs) unchanged, the DARPP32 perikaryal reduction appears preferential for ENK iSPNs. Consistent with this, we found reduction in DARPP32 in striatal terminals in globus pallidus externus (GPe) but not in striatal terminals in globus pallidus internus (GPi) or substantia nigra pars reticulata (SNr) by 12 months of age in Q175 mice. Stereological analysis of NeuN+ striatal neurons, however, showed no loss out to 18 months of age, indicating the reductions in DARPP32+ SPNs and ENK+ iSPNs reflect reduced expression rather than neuronal loss. Despite reduced ENK+ iSPNs and unaltered SP+ dSPNs, the abundance of ENK+ terminals in GPe and SP+ terminals in GPi and SNr were increased by 6 months of age, and remained so out to 18 months. Of note, the DARPP32 reductions in SPNs and striato-GPe fibers, and the increased ENK+ and SP+ terminals in striatal target areas were correlated with motor abnormalities such as reduced time on rotarod, and/or shorter distance traveled, slowed speed, and increased turning (a hyperkinetic sign) in open field. Analysis of striatal cholinergic, parvalbuminergic, and NOS+ interneurons revealed they were normal in abundance out to 18 months of age, although cholinergic interneurons showed dendritic attenuation by 6 months. GABAergic neuron abundance was normal in GPe, GPi and SNr out to 18 months, as was nigral dopaminergic neuron abundance, but by 18 months arkypallidal GPe neurons and STN neurons were reduced by about 25%. Our results indicate that progressive SPN neurochemical pathologies have an onset after 2 months of age in heterozygous

male Q175 mice, and arkypallidal GPe and STN neuron loss is seen by 18 months. Heterozygous male Q175 mice may thus model a very early stage of human HD, before there is overt SPN loss.

Disclosures: **Y. Deng:** None. **H. Wang:** None. **M. Joni:** None. **A. Reiner:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.05/E39

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Characterization of Htt-Q130-LEH, a novel heterozygous knock-in rat model of Huntington's disease

Authors: *T. HEIKKINEN[1], T. BRAGGE[1], S. KOPONEN[1], **T. PARKKARI**[1], G. TOMBAUGH[2], S. GELMAN[2], S. ZHONG[2], L. DEVI[2], A. GHAVAMI[2], K. CIRILLO[2], A. BARRE[3], F. GACKIERE[3], D. GUIMOND[3], S. ZAPETTINI[3], B. SAVA[3], P. CHAUSSON[3], E. STEIDL[3], B. BUISSON[3], K. KUHLBRODT[4], A. KAKOULIDOU[4], S. JOBUSCH[4], K. TILLACK[4], A. GAERTNER[4], E. VAN DER KAM[4], R. Z. CHEN[5], D. HOWLAND[5], I. MUNOZ-SANJUAN[5], R. CACHOPE[5], J. ROSINSKI[5], V. BEAUMONT[5];
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Abstract: Using a ZFN-mediated gene editing approach, a knock-in Long-Evans rat model of Huntington's disease (Htt-Q130-LEH) was developed. The model carries a pure ~130 CAG repeat followed by CAACAGCAGCAGCAACAG in Exon 1 of the endogenous rat Htt gene. The mHTT protein is expressed at ~65% of the WT HTT protein throughout the CNS. Heterozygote (HET) and wild type (WT) littermates were subjected to a battery of motor tests every 3 months (m) starting at 3 m of age, including fine motor kinematic analysis, open field, tapered beam balance, grip strength, and weekly bodyweight monitoring. In addition, in vivo tetrode recordings of cortico-striatal and cortico-subthalamic nucleus (STN) transmission were assessed at 12 m for evidence of altered cortico-basal ganglia function. Ex vivo analysis included MesoScaleDiscovery (MSD) quantitation of mHTT, immunohistochemical (IHC) assessment of mHTT aggregation, RNA sequencing, and analysis of striatal medium spiny neuron (MSN) membrane properties and synaptic activity between 3 - 12 m of age.
Until 6 months of age, HET Htt-Q130-LEH rats appear to be largely equivalent to their WT counterparts on all investigated parameters. However, with advancing age, HET rats start to display motor deficits, most notably as altered gait, decreased rearing and velocity in the open field. Bodyweight in male HET and WT rats is similar, whereas female HET rats are slightly heavier from 50 weeks onwards. At 12 m, in vivo electrophysiology showed that both cortico-

striatal and cortico-STN transmission are significantly impaired in HET rats and striatal and cortical aggregates are detectable by MW8/4C9 MSD and S830 IHC analysis. Moreover, RNA sequencing revealed alterations in genes predominantly involved in GPCR / cAMP-mediated and calcium signaling, as well as neuro-inflammation.
In summary, the Htt-Q130-LEH rat exhibits a relatively delayed onset of phenotype that will continue to be monitored at more advanced ages. This model may prove useful for further investigation of mHTT-induced neuropathophysiology.

Disclosures: **T. Heikkinen:** None. **T. Bragge:** None. **S. Koponen:** None. **T. Parkkari:** None. **G. Tombaugh:** None. **S. Gelman:** None. **S. Zhong:** None. **L. Devi:** None. **A. Ghavami:** None. **K. Cirillo:** None. **A. Barre:** None. **F. Gackiere:** None. **D. Guimond:** None. **S. Zapettini:** None. **B. Sava:** None. **P. Chausson:** None. **E. Steidl:** None. **B. Buisson:** None. **K. Kuhlbrodt:** None. **A. Kakoulidou:** None. **S. Jobusch:** None. **K. Tillack:** None. **A. Gaertner:** None. **E. Van Der Kam:** None. **R.Z. Chen:** None. **D. Howland:** None. **I. Munoz-Sanjuan:** None. **R. Cachope:** None. **J. Rosinski:** None. **V. Beaumont:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.06/DP04/E40

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH/NINDS R01 NS099136
NIH/NINDS F32 NS110149
CHDI

Title: Working memory and cortico-basal ganglia circuitry in a novel AAV2.retro-mediated non-human primate (NHP) model of Huntington’s disease (HD)

Authors: *A. R. WEISS[1], Z. LIU[1,2], X. WANG[1,2], J. DOMIRE[1], W. LIGUORE[1], K. BRANDON[1], C. D. KROENKE[1,2,3], J. L. MCBRIDE[1,3];
[1]Div. of Neurosci., Oregon Natl. Primate Res. Ctr., Beaverton, OR; [2]Advanced Imaging Res. Ctr., [3]Dept. of Behavioral Neurosci., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Our laboratory has previously shown that AAV1-mediated expression of mutant HTT (mHTT) in the striatum of rhesus macaques induces motor impairments, disease-related striatal pathology, and reduced working memory capabilities. We recently expanded this NHP model using AAV2.retro, a new capsid with enhanced retrograde transport, to deliver a pathogenic fragment of mHTT with 85 CAG repeats into the striatum, as well as to the cortex, thalamus,

amygdala and other regions in the basal ganglia. Using this approach, we have recently generated a large cohort of NHPs and are querying the disruption of cortico-basal ganglia circuitry for 12-months following intracranial delivery of this mHTT construct (85Q, n=6), a control HTT construct (10Q, n=6), or buffer (n=6). We are collecting repeated MRI scans from these animals to measure volume alterations of cortical and basal ganglia structures (T1-weighted and T2-weighted), to detect changes in white and grey matter microstructure (diffusion tensor imaging, DTI), and to identify areas of decreased cortico-basal ganglia functional connectivity (resting state functional connectivity MRI, RSfcMRI). We are also administering a touchscreen task to assess working memory changes (Delayed Non-match to Sample, DNMS). Here, we will describe our MRI data processing pipelines, and report correlations of behavior and MRI measurements during task acquisition pre-surgery, as well as potential correlations of cognitive and motor decline and imaging as the disease progresses. Using a customized brain atlas, cortico-basal ganglia circuitry was labeled with 22 gray matter regions and 10 white matter tracts. We observed that MRI measures of structural connectivity among these regions correlate with working memory measures collected pre-surgery. Our analyses revealed a significant negative correlation ($p<0.05$) between acquisition of the DNMS task and fractional anisotropy (FA) in dorsolateral prefrontal white matter tracts, indicating that monkeys who made relatively more errors learning the DNMS rule also had lower FA within a subset of prefrontal WM tracts. Serial MRI and DNMS task performance data are currently being collected. We hope that our new model will better replicate the more widespread neuropathology seen throughout the brains of HD patients, enhance our understanding of the mechanisms impacted by mHTT, validate neuroimaging measurements used to stage HD pathology in human subjects, generate new therapeutic biomarkers of disease progression, and provide a second generation viral-vector based monkey model of HD available to the research community for evaluation of promising therapeutics.

Disclosures: **A.R. Weiss:** None. **Z. Liu:** None. **X. Wang:** None. **J. Domire:** None. **W. Liguore:** None. **K. Brandon:** None. **C.D. Kroenke:** None. **J.L. McBride:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.07/E41

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: The difference of mutant Huntingtin expression between HD KI pig and KI mouse tissues

Authors: *X. ZHANG[1], S. YAN[2], X.-J. LI[3];
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Hongkong-Macau Inst. of CNS Regeneration, Jinan Univ., Guangdong, China; [3]Guangdong-Hong Kong-Macau Inst. of CNS Regeneration, Guangzhou, China

Abstract: Huntington's disease (HD) is a typical monogenic neurodegenerative genetic disease that is caused by CAG triplet repeats expansion in the Huntingtin gene (*HTT*). The CAG repeat expansion (>36 CAGs) in the *HTT* gene leads to a polyglutamine (polyQ) expansion that causes HTT to misfold and aggregate in the brain. It is characterized by the accumulation of mutant proteins and neuronal death in the HD patient brains and abnormal behavioral, cognitive, and mental function. HD disease is an ideal model for investigating the pathogenesis of misfolded proteins in neurodegenerative diseases. Recently, we have established HD knock-in (KI) pig model that expresses full-length mutant HTT at the endogenous level. Here we report the expression of mutant HTT in HD KI pig and mouse tissues. We found that mutant HTT expression is not identical between HD KI pig and mouse tissues. Pathological analysis showed that HD KI pig brains display more severe and obvious degeneration than HD KI mouse brains. The differences in HTT expression between HD KI pig and mouse brain tissues may contribute to the differential pathology of HD in different species.

Disclosures: X. Zhang: None. **S. Yan:** None. **X. Li:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.08/E42

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: MRC

Title: Characterision of kynurenine 3-monooxygenase as a therapeutic target for Huntington's disease

Authors: *M. K. BONDULICH[1], A. PAPADOPOULOU[1], G. P. BATES[1], F. GIORGINI[2], Y. SONG[1];
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Abstract: Huntington's disease (HD) is a fatal neurodegenerative disorder characterized by involuntary movements and cognitive decline. HD is caused by a trinucleotide CAG expansion producing an extended polyglutamine stretch in the huntingtin protein (HTT), leading to HTT aggregation and death of vulnerable neurons. The kynurenine pathway (KP) of tryptophan degradation has been closely linked to the pathogenesis of HD, containing several neuroactive metabolites. The enzyme kynurenine 3-monooxygenase (KMO) lies at a pivotal branch of the KP

between the formation of neuro-toxic/protective metabolites. Notably, KMO inhibition ameliorates disease-relevant phenotypes in yeast and fly models of HD. To investigate the role KMO plays in HD pathogenesis, we crossed R6/2 HD model mice to KMO knockout (KO) mice to characterise KP gene expression and metabolite profiles in R6/2 vs R6/2 KMO KO mice, and to test potential therapeutic benefits of ablating KMO.
R6/2 mice were crossed to KMO KO mice to generate six genotypes: wild type (WT), KMO KO heterozygotes (het) and homozygotes (hom), and R6/2 on het and hom KMO KO backgrounds. Body weight was measured from 4-12 weeks of age. Mice were sacrificed at 12 weeks (R6/2 symptomatic stage), with plasma and peripheral/brain tissues analysed. KP gene expression was quantified using QuantiGene Assays. KP metabolites were analysed using HPLC with tandem mass spectrometry. We visualised KP gene expression in cells via RNA in situ hydridization (ISH) using RNAScope Technology. Plasma cytokine levels were measured using the Mesoscale detection system.
R6/2 mice show increase in KMO gene expression at 12 weeks of age in peripheral and brain tissues analysed, as well as alterations in both KP enzyme expression and metabolites as compared to WT controls. The failure to gain weight was less pronounced in R6/2 mice het for KMO KO. Ablation of KMO led to an increase in KYNA and KYN and a decrease in QUIN metabolites in both the periphery and brain tissue in WT and R6/2 mice. Both KP enzyme gene expression and plasma cytokine levels were altered in R6/2 vs WT mice with several significant changes observed upon KMO knockout.
KP metabolites, enzyme gene expression and plasma cytokine levels are dysregulated in R6/2 mice. Knockout of KMO in R6/2 mice restored some of the differences observed. Further analysis is essential to establish a more detailed profile of altered KP function in R6/2 KMO KO mice as well as to evaluate the potential therapeutic effects of KMO knockdown on HD-related phenotypes.

Disclosures: **M.K. Bondulich:** None. **A. Papadopoulou:** None. **G.P. Bates:** None. **F. Giorgini:** None. **Y. Song:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.09/E43

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CONACYT Scholarship 587915

Title: Lack of aryl hydrocarbon receptor in a mice model of Huntington's disease results in a motor and behavioral improvement

Authors: *Q. ANGELES-LÓPEZ[1], L. G. GARCIA-LARA[2], R. CASTANEDA ARELLANO[3], F. PEREZ[4], G. ELIZONDO-AZUELA[5], J. V. SEGOVIA-VILA[6];
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Abstract: Huntington's disease (HD) is an inherited neurodegenerative disorder that is caused by a CAG abnormal repeat expansion in the huntingtin gene coding for a protein with the same name. HD patients present choreiform movements, which are caused by the loss of neurons in the striatum and cerebral cortex. One of the mechanisms proposed to explain neuronal loss is a decrease in brain-derived neurotrophic factor (BDNF). BDNF is involved in different processes in the central nervous system and is regulated by normal huntingtin. Previous works have shown that knocking down the aryl hydrocarbon receptor (Ahr) in cortical neurons results in the increase of BDNF levels. Based on this data, our objective was to evaluate a double transgenic mouse, expressing human mutated huntingtin and knockout for Ahr. Our results show that 30 week-old double transgenic mice have a body weight similar to R6/1 mice, however, feet-clasping, an indicative of neuronal damage in the R6/1 animals, was not observed. In addition, motor coordination and ambulatory behavior did not deteriorate over time unlike the R6/1 mice, but exploratory behavior decreased. Finally, the anxiety behavior of double transgenic mice was similar to wild type mice. This work provides evidence supporting that the absence of Ahr partially prevents the motor and behavioral deterioration observed in a transgenic model of HD.

Disclosures: Q. Angeles-López: None. **L.G. Garcia-Lara:** None. **R. Castaneda Arellano:** None. **F. Perez:** None. **G. Elizondo-Azuela:** None. **J.V. Segovia-Vila:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.10/E44

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: DGAPA-PAPIIT, Grant IN211718

Title: Signaling pathways associated to plasticity recover induced by NT-3 in striatal degeneration

Authors: V. G. GÓMEZ-PINEDA[1], ***E. HERNANDEZ-ECHEAGARAY**[2];
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Abstract: Neurotrophins are associated to development and plasticity of nervous system. Our group has shown that Neurotrophin-3 (NT-3) plays an important role in regulating corticostriatal synaptic transmission and plasticity. Interestingly, NT-3 recovers striatal long term plasticity which is altered in slices from cerebral tissue of mice treated *in vivo* with the mitochondrial toxin 3-nitropropionic acid (3-NP), used to mimic the histopathology of Huntington's disease (HD). In general, high frequency stimulation (HFS) of the corticostriatal pathway in slices recorded *in vitro* produces long term depression (LTD); however, striatal synaptic plasticity is modified by the 3-NP treatment, where HFS produces long term potentiation (LTP) instead of LTD. Also, we know that NT-3 modulates corticostriatal synaptic transmission by stimulating TrkB receptors, while corticostriatal plasticity is modulated by NT-3 through the activation of TrkC receptors. In this study, we evaluated which signaling pathway is triggered by NT-3 to reestablish LTD in brain slices recorded *in vitro* and obtained from male C57/BL6 mice treated *in vivo* to produce striatal damage. Population spikes were recorded at the striatum in the presence of NT-3 and the inhibitors for PLC, MAPK, PI3K or PTPσ. All the evaluated signaling pathways inhibitors prevented the amplitude increase of the synaptic spike induced by NT-3. HFS (100Hz) protocol was used to generate long term plasticity, and it was given in the presence of NT-3 and the signaling pathways inhibitors. The restoration of LTD induced by NT-3 was only impeded by the PLC inhibitor, demonstrating that NT-3 restores LTD in damaged striatum through the stimulation of PLC signaling.

Disclosures: V.G. Gómez-Pineda: None. **E. Hernandez-Echeagaray:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.11/F1

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: K01EB023983
Brigham Research Institute
Sanofi

Title: Targeted delivery of Huntington's disease gene therapeutics

Authors: N. TODD[1], B. ELMER[2], K. B. KEGEL[3], L. S. SHIHABUDDIN[2], L. M. STANEK[2], *J. UPADHYAY[4];
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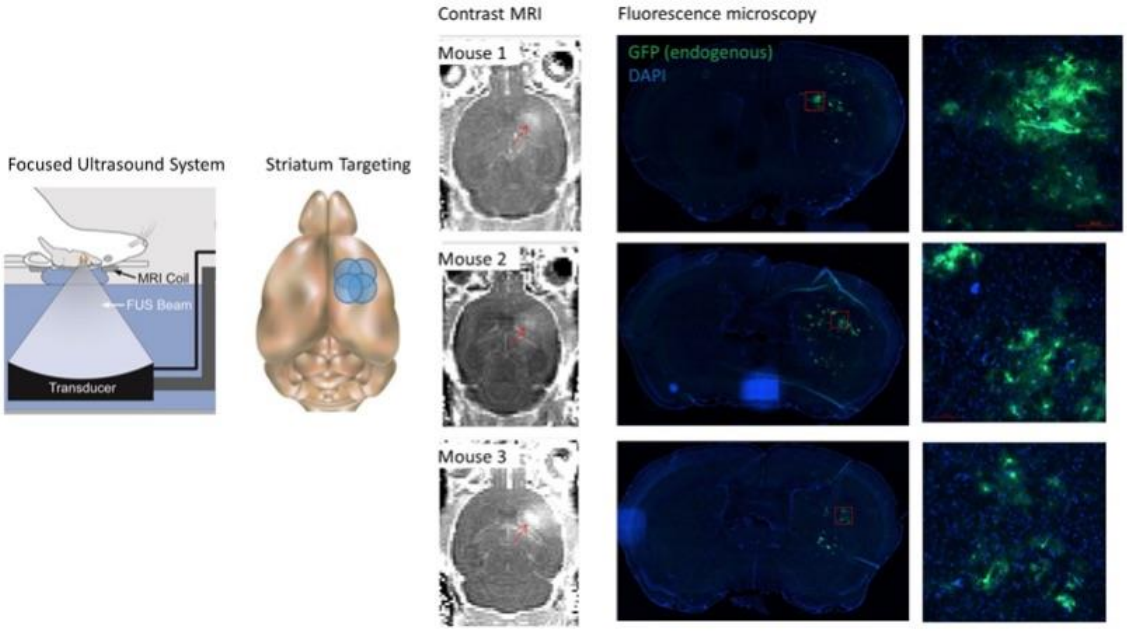
Abstract: The goal of this study is to use the novel technology of focused ultrasound (FUS) to improve the delivery of gene therapies to specific brain structures for the treatment of Huntington's disease. FUS can achieve non-invasive, transient and spatially targeted opening of the blood-brain barrier (BBB) to facilitate delivery of normally non-penetrant agents into the brain at the targeted site. FUS is applied through the intact skull, can be focused to a region of only several millimeters, and can reach both cortical areas and sub-cortical structures.

Gene therapies that knock down expression of the mutant Huntingtin protein are a promising approach to the treatment of Huntington's disease. However, all gene therapies face the interrelated challenges of delivering the therapy across the BBB, targeting a specific brain region, and achieving an adequate therapeutic exposure at the targeted site while minimizing toxicity in healthy brain tissue and other organs. FUS-BBB opening may be an approach to improving the delivery of gene therapies over more invasive existing methods of intrathecal injection or direct neurosurgical injection.

We demonstrated the feasibility of this approach in a pilot study of n=3 wild type mice. FUS-BBB opening was targeted to the right striatum. Microbubbles were given by tail vein injection and FUS sonications were applied at 10 ms bursts and 2 Hz repetition frequency over 120 seconds. An AAV1 capsid label with green fluorescent protein (AAV1-GFP) was given by tail vein injection at a dose of 5.5 vg/mouse. BBB opening was confirmed with contrast MRI. The three mice were sacrificed after three weeks, brains were extracted and prepared for fluorescence microscopy. Figure 1 shows the FUS system, striatum targeting, MRI results, and fluorescence microscopy results.

FUS-BBB opening succeeded in delivering the normally non-penetrant AAV1 capsid into the brain parenchyma in a non-invasive and targeted manner. Future studies will optimize the FUS parameters for improved delivery in wild type mice and YAC128 Huntington's disease model mice.



Disclosures: **N. Todd:** None. **B. Elmer:** A. Employment/Salary (full or part-time):; Sanofi. **K.B. Kegel:** None. **L.S. Shihabuddin:** A. Employment/Salary (full or part-time):; Sanofi. **L.M. Stanek:** A. Employment/Salary (full or part-time):; Sanofi. **J. Upadhyay:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.12/F2

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Conacyt FC1122
ANR-Conacyt 188565

Title: The toll-like receptor 4 in the process of brain damage associated with Huntington's disease

Authors: *P. E. MARTINEZ-GOPAR[1], F. PEREZ-SEVERIANO[2], C. GONZALEZ-ESPINOSA[3];
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Abstract: Toll-like receptors (TLRs) have a broad tissue distribution. TLRs can recognize molecules derived from injured tissues and trigger immune and metabolic responses typical of pathologic states. TLR-4 recognizes molecules of tissue damage, as well as proteins associated with neurodegenerative diseases. Recently, its participation in models of neurodegeneration has been documented. Huntington's disease (HD) is a hereditary neurodegenerative disorder caused by a mutation in the huntingtin protein gene. HD courses with loss of GABAergic neurons in basal ganglia, oxidative damage and neuroinflammatory processes. Intrastriatal (i.s.) administration of quinolinic acid (QA; NMDA agonist) in rodents mimics the neurochemical characteristics of HD (loss of GABAergics neurons and oxidative damage). The objective of this work was to study the participation of TLR-4, in the processes of neurological and oxidant damage observed in a neurochemical model of HD. For this purpose, C57 BL5/J mice (WT) and B6.B10scN-TLR4*lps-del* mice (TLR4-KO) were administered with QA (30 nmol / 1μL, i.s.) and distinct parameters of damage were evaluated, i.e. ipsilateral rotation induced by apomorphine , lipid peroxidation (LP) and the formation of reactive oxygen species (ROS). Results showed that TLR4-KO mice presented a lower number of turns, as well as less oxidative damage (LP and ROS) with respect to the WT animals administered with QA. It is known that the TLR-4 participates in the responses of innate immunity and inflammation caused by molecular patterns associated with pathogens (PAMPs) and tissue damage (DAMPs). Although its influence on the onset of inflammatory reactions that can trigger chronic diseases has been described, its

participation in the damage process observed in HD has not been fully addressed. This work presents, for the first time, evidence that this receptor participates in oxidative damage observed in a neurochemical model of HD. Our work strongly suggests that the TLR-4 receptor could be considered as a therapeutic target for the pharmacological treatment of some deleterious reactions observed in HD.

Disclosures: P.E. Martinez-Gopar: None. **F. Perez-Severiano:** None. **C. Gonzalez-Espinosa:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.13/F3

Topic: C.04. Movement Disorders other than Parkinson"s Disease

Support: CHDI Foundation (A-5552)
William N. & Bernice E. Bumpus Foundation
NIH/NIMH R01 MH060379

Title: Flexible and inflexible T-maze decision-making and neural coding of cost and benefit in wild-type and Huntington’s disease model mice

Authors: *L. G. GIBB, D. HU, A. FRIEDMAN, B. BLOEM, A. GARDNER, K. O'NELL, J. K. XIONG, A. M. GRAYBIEL;
MIT, Cambridge, MA

Abstract: Huntington’s disease (HD) is a devastating, fatal neurodegenerative disease characterized by altered neural function and cell loss in the striatum, cortex and other brain areas, and by emotional, cognitive and motor dysfunction. Reported symptoms include perseveration, aberrant decision-making, abnormal risk evaluation and low motivation. Previous work suggests that HD patients whose early symptoms are predominantly emotional rather than motor tend to show cell loss preferentially in the striosome compartment of the striatum in contrast to the surrounding matrix. Based on this result and on other evidence linking striosomes to evaluation, repetitive behavior and cost-benefit conflict decision-making, we hypothesized that Q175 HD model mice would show altered behavior in T-maze decision-making tasks, including tasks with various combinations of cost and benefit, and that these changes would be related to changes in the patterns of striosomal and matrix activity.
Therefore, we trained 7 Q175 (‘HD’) model and 5 wild-type (WT) mice (11-27 months old) on T-maze tasks similar to ones we have published previously, including benefit-benefit (BB) tasks with equal and unequal rewards, a cost-benefit conflict (CBC) task and, in some mice, a cost-cost (CC) task. Consistent with the perseveration observed in HD patients, we observed a tendency of

HD mice to perseverate in their choice behavior. In the BB task with unequal rewards, HD mice were more likely to choose the high reward again if they had chosen it in the previous trial, whereas WT mice were not.
We made use of the fact that striosomal neurons tend to be born earlier than matrix neurons during embryonic development to express GCaMP6m predominantly in either striosomal or matrix neurons of mice carrying an inducible CreERT2 construct. We implanted GRIN lenses with attached prisms and performed calcium imaging on 5 striosome-labeled and 3 matrix-labeled WT mice performing the BB, CBC, and CC tasks, using the Inscopix nVista 2.0 miniature microscope. Analysis of a subset of our imaging data using linear classifiers suggested that striosomal neurons may be particularly predictive of choice in the cost-cost task. Based on these promising preliminary results, we performed calcium imaging in another group of 2 HD mice and 3 WT mice (7-12 months old). As in our first group of mice with behavioral testing, HD mice tended to perseverate in their choices during the maze imaging sessions. We will discuss the neural underpinnings of this perseverative behavior, a deep understanding of which may contribute to the development of therapies for behavioral changes in HD patients.

Disclosures: **L.G. Gibb:** None. **D. Hu:** None. **A. Friedman:** None. **B. Bloem:** None. **A. Gardner:** None. **K. O'Nell:** None. **J.K. Xiong:** None. **A.M. Graybiel:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.14/F4

Topic: C.04. Movement Disorders other than Parkinson"s Disease

Support: CHDI Foundation A-5552
JSPS KAKENHI Grant #16KK0182
JSPS KAKENHI Grant #17K10899

Title: Mu opioid receptors are strongly upregulated in the Q175 mouse model of Huntington's disease

Authors: *R. MORIGAKI[1,2], J. H. LEE[1,3], T. YOSHIDA[1], C. WÜTHRICH[1], A. M. GRAYBIEL[1];
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Abstract: The mu-opioid receptor (MOR1) is highly expressed in the dorsal striatum and exhibit, in particular, enhanced expression in striosomes. This expression pattern, in fact, has been used as a key marker for the striosomal system (Gerfen, 1984; Graybiel et al, 1981).

However, it is known that the expression of MOR1 is not strong in the lateral caudoputamen of rodents, or in the caudal striatum. This distribution pattern places MOR1-expressing neurons and fibers in a position to modulate associative and limbic-related districts of the striatum. Here we examined the distribution of the MOR1 in the caudoputamen of the Q175 mouse model of Huntington's disease, with the goal of determining whether this important receptor in the striatum was regulated in Q175 mice at successively advanced ages, beginning with mice at post-natal ages of 3 months to 12 months, equivalent to aged mice. We observed striking up-regulation of MOR1 immunostaining (rabbit monoclonal anti-mu opioid receptor antibody ab134054, Abcam, MA) beginning at early ages and becoming more prominent with advancing age. Remarkably, this rendered MOR1 expression, as seen by immunohistochemistry, is highly expressed in the lateral and caudal striatum, where, especially in the caudoputamen, it is scarcely expressed at detectible levels in control littermates of the Q175 mice. It is our hope that these findings could be important in understanding, at the level of rodent models, the distinctions between the motoric and cognitive-emotional symptoms expressed in humans suffering from this debilitating disorder.

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Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.15/F5

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI (A-5552)
JSPS Overseas Research Fellowship
Saks Kavanaugh Foundation

Title: Developmental organization of striosomes and striosome-related circuits

Authors: *A. MATSUSHIMA, A. M. GRAYBIEL;
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Abstract: Striosomal neurons are generated over a protracted time-period during development (from embryonic day (E) 10 until ~E15 in mice), followed by matrix neurons invading the striatal mantle. Within the time window of striosomal neurogenesis, however, there exists a birthdate-dependent difference in ultimate cellular distribution in the mature striatum (Kelly et al., 2017), and in vulnerability to prenatal intervention (Kuo et al., 2017). Here, we aimed to dissect developmental sub-lineages of striosomes by administering fast-kinetic version of tamoxifen to *Dlx1*::CreER/floxed tdTomato or floxed Flp mouse embryos.

First, we found a gradient-pattern of distribution of cell bodies across the striatum, and of axonal projections to the substantia nigra. In combination, only one group of cells, born at a specific developmental timepoint and also located in a specific sector in the striatum, were destined to project to the striosome-dendron bouquets (Crittenden et al., 2016), the highly characteristic feature of the dopamine-containing substantia nigra.
Second, we examined the sub-compartmental distribution of future striosomal cells, and observed stereotypical patterns suggesting rules of development observed by the earliest-born to later-born cells. In addition, the exact birthdates of future striosomal neurons differed across the anterior to posterior striatum, so that they follow the gradient patterns described previously. Thus at least two time-sensitive developmental influences are active in the eventual organization of the striosomal system. Likely there are others.
These results imply that the developmental timepoint of neurogenesis dictates the positions of cells at a sub-compartmental scale, and organizes compartments that form specialized circuits to exert specialized functions. Some of these circuits might be particularly vulnerable to genetic perturbation as in Huntington disease, now under study in the Q175 mouse model of this disorder.

Disclosures: A. Matsushima: None. **A.M. Graybiel:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.16/F6

Topic: C.04. Movement Disorders other than Parkinson"s Disease

Support: CHDI Foundation (A-5552)
Saks Kavanaugh Foundation
William N. & Bernice E. Bumpus Foundation
P. Dana Bartlett

Title: Huntington's disease model Q175 mice exhibit deficits in adaptation of reward licking response in a visual cue-reward learning task

Authors: *M. J. KIM, A. M. GRAYBIEL;
McGovern Inst. for Brain Res. and Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: Animals can acquire responses to sensory stimuli that precede a reward. For example, normal animals typically develop the anticipatory licks to reward-predictive cues as cue-reward association gets strengthened through many repeated trials. The cue-reward association and its correspondent motor (anticipatory licking) adaptation are key features of learning based on the striatum. We hypothesized that Huntington’s disease (HD) model mice would show impairment

in this learning process due to their altered corticostriatal function. To test this hypothesis, Q175 heterozygous (HD) and wild-type (WT) littermate mice (6-8 months old) were trained on a Pavlovian conditioning task using visual cue and reward in a head-fixed apparatus, and their licking responses were monitored throughout training. A drop of sucrose solution was always delivered after an LED light was presented at the left side, but not after the LED illumination on the right side. In WT mice, it was commonly observed that licking responses were gradually shaped over the course of learning. That is, with training, their consummatory licks gradually occurred close to reward delivery, the number of licks increased during the cue period, and the mice exhibited regular lick-bouts initiated by the onset of the reward-predicting cue. At the same time, unnecessary licks (spontaneous licks during unrewarded trials, including unrewarded cue responses) were gradually suppressed. Therefore, the licking response became efficient and occurred selectively in response to the rewarding cue. By contrast, HD mice were not able to adapt their licks to the cue predicting upcoming reward. Rather, they kept relying on their spontaneous licking to check reward availability and obtained the reward. The transition from spontaneous licking to cue-elicited response did not occur even after prolong training. This deficit cannot be accounted for by their motivational drive, as all HD mice failed to develop lick adaptation to the rewarding cue regardless of their total average lick rates. However, when the cue presentation was extended up to their first lick for reward, some of HD mice started to form lick-bouts similar to those commonly observed in WT mice. Therefore, this behavioral phenotype indicates that HD in the early phase disrupts the function of corticostriatal circuitry that might serve important roles in regulating the timing and execution of motoric activity to enable cue-reward association during learning.

Disclosures: **M.J. Kim:** None. **A.M. Graybiel:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.17/F7

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH NS096994
NIH NS111316

Title: Pharmacological reduction of elevated calcium levels in cortical pyramidal neurons for the treatment of Huntington’s disease

Authors: *K. D. OIKONOMOU[1], X. YU[2], B. S. KHAKH[2], M. S. LEVINE[1], C. CEPEDA[1]; [1]IDDRC, Semel Inst. for Neurosci. and Human Behavior, BRI., [2]Dept. of Physiol., UCLA, Los Angeles, CA

Abstract: Huntington's disease (HD) is a hereditary neurodegenerative disorder that predominantly affects striatal medium-sized spiny neurons (MSNs) and cortical pyramidal neurons (CPNs). Functional studies revealed that somatosensory, attention, and cognitive deficits precede motor abnormalities. As such, examining cortical alterations before the onset of striatal dysfunction is of utmost importance. Ca^{2+} dyshomeostasis plays a significant role in the degeneration of MSNs in HD mouse models, as drugs that target the store-operated Ca^{2+} channel (SOC) pathway rescue spine loss and long-term administration of a ryanodine receptor blocker, dantrolene, significantly improves the HD phenotype. Previous studies in our laboratory demonstrated early increases in voltage-gated Ba^{2+} currents in CPNs from symptomatic R6/2 mice. However, there have been no studies assessing modifications of Ca^{2+} signaling in somata and dendrites of CPNs of primary motor cortex throughout HD progression. To test the hypothesis that CPN Ca^{2+} homeostasis is significantly disturbed before the emergence of overt behavioral symptoms, we used the R6/2 mouse model of juvenile HD. Three age groups were studied: postnatal day (P)21-31 before overt symptoms start, P35-42 when overt symptoms begin, and >P60 when the mice are fully symptomatic. We combined whole-cell patch clamp electrophysiology and two-photon microscopy to image layer 2/3 CPNs filled with Oregon Green BAPTA-1. Single or multiple action potentials (APs) were evoked by a series of 50 ms depolarizing current pulses from the resting membrane potential. Accompanying somatic as well as dendritic Ca^{2+} transients were compared between different age groups of mutant mice and their wildtype (WT) age-matched littermates. We found that the amplitude and kinetics of AP-induced Ca^{2+} signals recorded at the somata of CPNs were altered in R6/2 mice from all age groups compared with age-matched WTs. Specifically, in the two older groups, significant differences were observed including increased amplitude and slower kinetics of Ca^{2+} transients associated with either one, two or three APs. In all age groups, Ca^{2+} levels in proximal and distal dendrites of CPNs were greater in R6/2 than WT mice but differences did not reach statistical significance. Importantly, treatment with EVP4593 (3 μM) or dantrolene (20 μM), significantly restored elevated Ca^{2+} responses at the somata of CPNs from symptomatic R6/2 mice. Our findings demonstrate that perturbations of Ca^{2+} homeostasis occur before the onset of overt symptoms, and that they can be rescued by introducing agents that inhibit intracellular Ca^{2+} release.

Disclosures: K.D. Oikonomou: None. **X. Yu:** None. **B.S. Khakh:** None. **M.S. Levine:** None. **C. Cepeda:** None.

Poster

565. Animal Models of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 565.18/F8

Topic: C.04. Movement Disorders other than Parkinson"s Disease

Support: NIH NS096994

Title: Thalamocortical projections are significantly impaired in the R6/2 mouse model of Huntington's disease

Authors: *S. M. HOLLEY, K. OIKONOMOU, G. MKRTCHYAN, C. M. SWIFT, L. MOHAN, C. CEPEDA, M. S. LEVINE;
IDDRC, Semel Inst. for Neurosci. and Human Behavior, BRI, UCLA, Los Angeles, CA

Abstract: Huntington's disease (HD) is a heritable neurodegenerative disorder characterized by impaired motor control in addition to cognitive and psychiatric disturbances. As the disease progresses, there is a massive degeneration of striatal medium-sized spiny neurons (MSNs) and cortical pyramidal neurons (CPNs). Previously, we showed that cells in both motor and sensory thalamic nuclei of R6/2 mice are hyperexcitable and exhibit signs of degeneration. In humans, early reports have observed decreases in the volume of certain thalamic nuclei at later stages of the disease; however, electrophysiological studies designed to assess whether thalamocortical circuits are affected in HD are lacking. Using whole-cell patch clamp electrophysiology in ex vivo brain slices, we recorded membrane properties and synaptic inputs onto cortical pyramidal neurons (CPNs) in the barrel (somatosensory) cortex of ~75 day-old wildtype (WT) and symptomatic R6/2 mice. Similar to previous reports on motor cortex CPNs, we also observed alterations in cell membrane properties in barrel cortex CPNs from R6/2 mice. The CPNs had significantly smaller membrane capacitance, higher input resistance and faster time constant. We also observed the frequencies of both spontaneous inhibitory and excitatory postsynaptic currents (IPSCs and EPSCs, respectively) were reduced in R6/2 CPNs. In order to investigate the contribution of excitatory inputs onto CPNs originating from the thalamus, we expressed channelrhodopsin, driven by the CaMKII promoter, in ventral posteromedial nucleus (VPM) thalamic neurons. Optical activation of VPM terminals elicited large-amplitude IPSCs in both WT and R6/2 CPNs when recorded at a holding potential of +10 mV. This inhibitory response was the result of polysynaptic transmission since optically-evoked IPSCs were completely abolished with the addition of the sodium channel blocker, tetrodotoxin (TTX). Notably, we observed smaller amplitude IPSCs in barrel cortex CPNs from R6/2 mice compared to WTs. The amplitude of optically-evoked EPSCs also was reduced in R6/2 CPNs. Furthermore, we observed a decrease in the frequency of excitatory quantal events in R6/2 CPNs in recordings where extracellular calcium was replaced by strontium. Taken together, these results suggest symptomatic R6/2 mice exhibit reduced connectivity between the thalamus and somatosensory cortex which ultimately may result in faulty integration and processing of somatosensory information.

Disclosures: S.M. Holley: None. **K. Oikonomou:** None. **G. Mkrtchyan:** None. **C.M. Swift:** None. **L. Mohan:** None. **C. Cepeda:** None. **M.S. Levine:** None.

Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.01/F9

Topic: C.06. Neuromuscular Diseases

Support: CAPES 001

Title: Characterization of the equilibrium mutant mice induced by the N-ethyl-N-nitrosourea agent: Behavioral, astrocytes and neurochemical aspects

Authors: *K. E. KIATAQUI, B. C. G. ORLANDO, P. S. RODRIGUES, E. P. SILVA, A. S. SAMPAIO, N. MOREIRA, L. S. MEDEIROS, M. C. GALVAO, T. M. REIS-SILVA, M. M. BERNARDI;
Paulista Univ., São Paulo, Brazil

Abstract: The equilibrium (eqlb) mutant mouse presents a deficiency and motor incoordination induced by a recessive mutation due the exposure of the N-ethyl-N-nitrosourea agent. This mutation causes vestibular defects in the formation of the otoconia, allowing the study of different human pathogenesis. In order to characterize the possible differences of the eqlb mouse, we evaluated 18 eqlb BALB/c mice in the essays of social and aggressive behavior in stable colonies and after isolation, olfactory memory and spatial perception in the hidden cookie protocol and tail suspension test (TST), respectively. Thus, the levels of serotonin and metabolite in the prefrontal cortex (PFC) and astrocytes expression in the superior colliculus were also evaluated. Significant differences were determined by a student t test when pertinent. For the results with more than one variable a two-way ANOVA was conducted. Our results demonstrated lower social interaction of eqlb mice compared to balb/c mice of control group (p=0,002) in stable colonies and an increased social interaction with the intruder (p<0,0001). Regarding the olfactory test, eqlb mice displayed an increased latency to find the cookie [F (1,76) = 18.91, p<0.0001). In the spatial perception test, eqlb presented a decreased immobility compared to control group (p=0,007). Despite the TST has been commonly used for evaluation of depressive-like behavior, it also provides insights of area perception (Manes M., et al 2019). Finally, we observed an increased serotoninergic turnover activity in the PFC (p=0,01) and reduction in the index area of astrocytes in the superior colliculus (p=0,0006). We propose that the lower social interaction in the stable colony and the greater social interaction with the foreign mouse as well as the absence of aggression may be a consequence of deficits in olfactory memory, spatial perception, increased serotonergic activity in the PFC and reduction of the index by astrocyte area of the superior colliculus. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

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Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.02/F10

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant NS085164

Title: The role of mitochondrial complex I dysfunction in synaptic plasticity and maintenance

Authors: *C. FRANK, B. MALLIK;
Univ. of Iowa, Iowa City, IA

Abstract: Neurons are highly polarized cells with immense energy demands. Those energy demands are mainly fulfilled by mitochondria. In response to altered energy states of the neuron, mitochondria can adapt to maintain energy homeostasis and nervous system function. This adaptation, also called mitochondrial plasticity, can be observed as changes in morphology, function or localization of mitochondria at the synapses. Through an RNAi-mediated genetic screen in *Drosophila melanogaster* (about 300 *UAS-RNAi* lines) that covered homologs of genes associated with human neurodegenerative diseases, we have identified mitochondrial complex I subunits as essential for maintaining mitochondrial morphology and synapse function. Mutations affecting mitochondrial complex I subunits have been reported to be involved in severe mitochondrial diseases. The mechanisms by which complex I dysfunction results in disease remain elusive. Here, we report a *Drosophila* model of complex I deficiency caused by a nuclear DNA-encoded *NADH dehydrogenase subunit 20* (*ND-20L*) gene. We show that *ND-20L* RNAi depleted larvae exhibit phenotypes that resemble symptoms of mitochondrial disease, including progressive degeneration of muscle and presynaptic cytoskeleton, enhanced reactive oxygen species (ROS) formation and alteration in mitochondrial morphology. Our genetic and electrophysiological analyses reveal that ND-20L in muscle regulates Dlg-Spectrin scaffold for maintaining Brp-GluR clusters (active zone-receptor apposition) which are crucial for evoked release at the synapses. We also find the ND-20L subunit participates in evoked release at the NMJ terminals. Together, our findings support a model in which diminished complex I activity, and consequent energy deficiency, is responsible for specific synaptic defects. In the context of human complex I dysfunction, similar defects could contribute to pathogenesis.

Disclosures: **C. Frank:** None. **B. Mallik:** None.

Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.03/F11

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant NS102451
MDA Grant 382370

Title: SMN regulates neuromuscular junction integrity through U7 snRNP

Authors: S. TISDALE, M. VAN ALSTYNE, C. M. SIMON, G. Z. MENTIS, ***L. PELLIZZONI**;
Pathology and Cell Biol., Columbia Univ., New York, NY

Abstract: Spinal muscular atrophy (SMA) is an inherited motor neuron disease caused by reduced levels of the ubiquitously expressed SMN protein. SMN is required for the assembly of small nuclear ribonucleoproteins (snRNPs) that carry out pre-mRNA splicing as well as U7 snRNP, which is essential for the 3'-end processing of histone mRNAs. While SMN is well-established to control key aspects of gene expression through its multiple functions in RNP biogenesis, the contribution of individual SMN-dependent RNA pathways to motor circuit pathology in SMA remains poorly defined. We previously demonstrated that SMN deficiency disrupts U7 snRNP biogenesis and histone mRNA 3'-end processing in SMA mice and human patients. Here, we investigated whether impairment of this RNA pathway contributes to SMA pathology in a mouse model of the disease. To do so, we first established a means to selectively enhance U7 snRNP biogenesis and function by overexpression of Lsm10 and Lsm11—two U7 snRNP-specific proteins normally expressed at limiting amounts—leading to increased U7 snRNP levels and histone mRNA 3'-end processing in both normal and SMN-deficient cells. We then applied this approach *in vivo* using AAV9-mediated postnatal delivery of Lsm10 and Lsm11 into the central nervous system of SMA mice. Overexpression of Lsm10 and Lsm11 in SMA mice specifically corrects U7-dependent histone mRNA 3'-end processing defects, but not RNA processing events linked to other functions of SMN (i.e. splicing). Remarkably, comprehensive analysis of morphological and functional parameters of motor circuit connectivity that are affected in SMA revealed strong and specific improvement of neuromuscular junction (NMJ) innervation of vulnerable muscles following restoration of U7 snRNP function in SMA mice. Improved innervation was further associated with enhanced NMJ neurotransmission, reduced skeletal muscle atrophy, and improved motor function. Importantly, we found that SMN deficiency decreases Agrin mRNA expression and the levels of this critical synaptic organizing protein at NMJs of vulnerable but not resistant SMA motor neurons, a defect specifically rescued by LSm10/11 co-expression. Thus, through selective restoration of U7

snRNP biogenesis in SMA mice, our findings demonstrate a key role for U7 snRNP function and histone mRNA 3'-end processing in preserving the functional integrity of the NMJ, uncovering an RNA-mediated mechanism of NMJ loss in SMA. They also highlight an unanticipated functional requirement in post-mitotic motor neurons for an RNA processing pathway that controls histone synthesis and is thought to be biologically relevant only in dividing cells.

Disclosures: S. Tisdale: None. **M. Van Alstyne:** None. **C.M. Simon:** None. **G.Z. Mentis:** None. **L. Pellizzoni:** None.

Poster

566. Neurodegeneration Mechanisms

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Program #/Poster #: 566.04/F12

Topic: C.06. Neuromuscular Diseases

Support: NIH RO1 Grant AA027079
NIH RO1 Grant NS078375

Title: Reduction of serotonergic synapses and its effects in sensory-motor function in spinal muscular atrophy

Authors: *N. DELESTRÉE, E. SEMIZOGLOU, J. G. PAGIAZITIS, A. VUKOJICIC, V. PAUSHKIN, G. Z. MENTIS;
Depts. Pathology and Cell Biol. and Neurol., Columbia University, Ctr. for Motor Neuron Biol. and Dis., New York, NY

Abstract: Spinal muscular atrophy (SMA) is a neurodegenerative disease characterized by motor neuron loss, muscle atrophy and impairment of motor reflexes. One of the earliest hallmark of the disease is the dysfunction and loss of proprioceptive synapses leading to muscle paralysis. Furthermore, gait and posture, which are controlled largely by the neuromodulatory synapses, are dramatically altered in SMA patients. The serotonergic (5-HT) inputs originating in the brainstem Raphe nuclei exert a major neuromodulatory influence on motor neurons. However, whether serotonergic synapses are affected in the course of SMA is not known.
To address this, we utilized the SMN-Δ7 mouse model and investigated the morphological and functional characteristics of 5-HT synapses on motor neurons at different ages. We found that the 5-HT synaptic coverage is reduced by ~40% as early as P4 in vulnerable (L1 and L5-MMC) but not resistant (L5-LMC) motor neurons in SMA mice. Functionally, 5-HT is also known to modulate the monosynaptic sensory-motor arc reflex mediated by proprioceptive synapses on motor neurons. We confirmed that optical stimulation of 5-HT neurons expressing ChannelRhodopsin2 (ChR2) under the Pet1 promoter modulated the spinal reflexes using the *ex vivo* brainstem-spinal cord preparation.

Selective restoration of SMN in serotonergic neurons was investigated using a conditional inversion SMA mouse line, in which Cre is expressed under the selective serotonergic promoter Pet1. We found that this approach rescued 5-HT synapses, indicating the non-cell autonomous effects of SMN deficiency in 5-HT neurons, similar to what we have previously shown in proprioceptive neurons. Surprisingly, SMN restoration in 5-HT neurons also resulted in a partial rescue of proprioceptive synapses on motor neurons, suggesting that 5-HT influences the number and function of proprioceptive synapses during early development and may be involved in the pathological mechanisms of sensory-motor circuit dysfunction in SMA.

Disclosures: **N. Delestrée:** None. **E. Semizoglou:** None. **J.G. Pagiazitis:** None. **A. Vukojicic:** None. **V. Paushkin:** None. **G.Z. Mentis:** None.

Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.05/F13

Topic: C.06. Neuromuscular Diseases

Support: Georgia Tech President's Undergraduate Research Award

Title: Machine learning enhanced dynamic meta-analysis for preclinical ALS combination therapy optimization

Authors: ***A. J. LEE**[1], B. M. LEE[1], E. J. RIDGEWAY[1], C. S. MITCHELL[2];
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Abstract: Attempts to therapeutically target a single Amyotrophic Lateral Sclerosis (ALS) etiological factor have largely failed. Our previous research has showed ALS is a multi-factorial disease with pathophysiology that is dynamically changing and inherently unstable. This project contends carefully timed combination therapy will be ultimately required for therapeutic success. However, predictive medicine is needed to prioritize hundreds of thousands of potential combination therapies and corresponding protocol parameters. This study builds upon and optimizes a relatively new mathematical modeling method called dynamic meta-analysis (DMA), which enables simultaneous examination of interrelationships and regulatory system dynamics not accessible to traditional experimentation or meta-analysis. Both homeostatic wild-type (WT) mouse model and disease-state SOD1 G93A ALS transgenic mouse models are constructed *in silico* and compared to find the best treatment targets as a function of ALS progression. Presently, 2148 data points from 119 peer-reviewed articles (and counting) are included to construct the models. Data is categorized into seven pathophysiological ontologies: apoptosis, bioenergetics, chemistry, excitotoxicity, inflammation, oxidative stress and proteomics based on physiology definition. Each of these factors have two aggregation schemes:

inducing factors and inhibiting factors. The base DMA model is constructed of ordinary differential equation systems that describe each aggregation schemes' dynamics over time. However, this study also applies machine learning global optimization methods to identify and optimize missing parameters due to lack of published data in some categories. Unsupervised learning is used to select the overall pathophysiological solution matrix that best approximates actual mice functional behaviors (rotarod performance, body weight, survival, etc.). The models are validated with external experimental mouse data not included in model construction or training. Results are presented for full, quantitative *in silico* solutions for the "best" WT and ALS mouse models. These models can be applied to better elucidate the dynamic systems etiology of ALS and to prioritize preclinical testing of promising ALS combination therapies. Moreover, this updated technology of employing machine learning to optimize dynamic meta-analysis opens the door to using the same optimized technique for literature mined pathology and therapy assessment models for other multi-factorial neurological diseases.

Disclosures: A.J. Lee: None. **B.M. Lee:** None. **E.J. Ridgeway:** None. **C.S. Mitchell:** None.

Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.06/F14

Topic: C.06. Neuromuscular Diseases

Support: Canada First Research Excellence Fund
Medicine by Design Initiative at University of Toronto

Title: The effects of chemogenetic inhibition of L5-M1 pyramidal neurons in the SOD1-G93A mouse model of amyotrophic lateral sclerosis on the onset and severity of motor symptoms and neurodegeneration

Authors: *S. A. BEDARD[1], K. CHEN[1], J. C. PRESSEY[1], A. LAU[2], J. ROBERTSON[2], M. A. WOODIN[1];
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Abstract: Amyotrophic lateral sclerosis (ALS), also commonly known as Lou Gehrig's disease, is a neurodegenerative disease characterized by loss of neurons responsible for voluntary muscle movement and as there are no effective treatments ~80% of those diagnosed will die within 2-5 years. An early characteristic of ALS is hyperactivity of the primary motor cortex (M1), the region of the brain controlling voluntary movements. Cortical hyperexcitability promotes the degeneration of layer 5 excitatory pyramidal neurons in the primary motor cortex (L5-M1 PN) that connect through the spinal cord to control muscles and are therefore a therapeutic target. We recently discovered that by reversing the hyperactivity in the motor cortex we could delay the

onset of motor symptoms and L5-M1 PN neurodegeneration in the SOD1-G93A mouse model of ALS. We accomplished this reversal of hyperactivity by using Cre-dependant excitatory chemogenetics to specifically increase the activity of inhibitory interneurons in the cortex that synapse onto L5-M1 PNs. While our chemogenetic-mediated functional regeneration holds significant therapeutic potential for ALS patients, the clinical translation of this discovery is limited by the Cre-dependant delivery method of the chemogenetic tools used. In the current work we overcome this limitation by delivering an inhibitory chemogenetic construct directly to L5-M1 PNs using a non-Cre-dependant viral vector strategy. We then assess the effects this intervention on functional and cellular outcomes in the SOD1-G93A mouse model of ALS by subjecting animals to a battery of behavioural motor tasks as well as immunohistochemical, electrophysiological, and biochemical assays in both the pre-symptomatic and symptomatic phases of the disease. This approach holds significant clinical potential because viral vectors are in multiple phase I-III clinical trials, and the chemogenetic activator used in this study (clozapine) is also widely used clinically. To our knowledge this research is the first worldwide to use AAV-directed chemogenetics to promote regeneration in a neurodegenerative disease.

Disclosures: **S.A. Bedard:** None. **K. Chen:** None. **J.C. Pressey:** None. **A. Lau:** None. **J. Robertson:** None. **M.A. Woodin:** None.

Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.07/F15

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant RO1 NS069844

Title: Profiling neuronal stress responses regulated by dual leucine zipper kinase (DLK)

Authors: *E. ASGHARI ADIB[1], J. SHADRACH[2], X. CHEN[4], D. DICKMAN[5], B. A. PIERCHALA[3], C. A. COLLINS[1];
[1]Mol. Cell. and Developmental Biol., [3]Biologic & Materials Sci., [2]Univ. of Michigan, Ann Arbor, MI; [4]Dept. of Neurobio., [5]USC, Los Angeles, CA

Abstract: One of the prominent aspects of neuronal communication is the maintenance of proteins and molecules that are building blocks of functional synapses. Neurons appear to lose this ability in conditions of neurodegenerative diseases (including Alzheimer's disease, Parkinson's Disease and ALS). Recent work has found that the evolutionarily conserved dual leucine zipper kinase DLK mediates pathology in multiple models of ALS and Alzheimer's disease (Le Pichon et al. 2017). DLK is previously known for its role in regulating responses to axonal injury, and recent studies have noted that DLK also becomes activated in scenarios that

disrupt axonal cytoskeleton and axonal transport (reviewed in (Asghari Adib et al. 2018)). Our lab has noted that a consequence of DLK activation in *Drosophila* motoneuron larvae is the down-regulation of multiple synaptic proteins (Li et al. 2017). Collectively these observations raise the hypothesis that DLK may become activated in conditions of stress that impair axonal transport, and that downstream consequences of DLK can lead to synapse loss. This points to DLK as an attractive potential mediator of synapse loss in paradigms of neurodegenerative disease. However, a mechanistic role for DLK in promoting synapse loss is not currently known. With a goal to understand the downstream mechanisms of DLK we are undertaking a RiboTag approach to profile ribosome associated transcripts in motoneurons using both fly and mouse models. In mice we are using ChAT-Cre to conditionally tag ribosomal protein RPL22 in motoneurons that are also conditionally deleted for DLK. In this model we are using sciatic nerve crush as our initial paradigm for activating DLK, however we are interested in additional models including ALS. In flies we are currently determining a deeper phenotypic understanding of the consequences of DLK activation in adult neurons. Using the GeneSwitch system to acutely induce DLK expression in the adult nervous system we observed a rapid decline in locomotor activity and early lethality after shifting 5-day old flies to conditions that induce DLK expression. The brains of these flies show evidence of neuronal remodeling and degeneration: the axon tracts in the mushroom body - a center for learning and memory in the fly - were degenerated and nearly absent 12 days after DLK induction. From these observations we hope to develop a new paradigm for studying the mechanism by which DLK activation in a mature adult nervous system can lead to axon and synapse loss.

Disclosures: E. Asghari Adib: None. **J. Shadrach:** None. **X. Chen:** None. **D. Dickman:** None. **B.A. Pierchala:** None. **C.A. Collins:** None.

Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.08/F16

Topic: C.06. Neuromuscular Diseases

Title: Behavioral and neurochemical abnormalities in a pharmacologically-induced mouse model of Gaucher disease

Authors: *M. MONBUREAU, N. MORISOT, A. MALIK, G. CARROT, J. ROESER, H. JANSSENS, A. RASSOULPOUR;
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Abstract: A growing body of evidence has linked Parkinson's disease (PD) to the neurological form of Gaucher disease (GD). GD is caused by a hereditary deficiency in activity of the lysosomal hydrolase, acid beta-glucosidase (Gba). As a result, the glycosphingolipid

glucosylceramide (GlcCer) accumulates within the lysosomes of cells, including neurons, leading to motor abnormalities. Animal models that exhibit GD hallmarks are needed to help develop new therapies that could benefit GD- and PD-affected patients. Here, we established a pharmacological GD mouse model using subchronic exposure to conduritol-ß-epoxide (CBE). CBE (100 mg/kg, i.p.) was injected daily for 10 days in C57/Bl6 mice starting on post-natal day 15. Immediately after the last CBE administration, mice were tested for hindlimb splay and rotarod performance. We found that CBE-treated mice had a higher hindlimb score compared to control mice, revealing neuromuscular abnormality. In addition, CBE treatment resulted in a shorter latency to fall from the rotarod, indicating motor deficits. Growth in CBE-treated mice was also affected as body weight gain was reduced compared to controls. Following behavioral evaluation, liver, hippocampus, striatum and prefrontal cortex were collected from control and CBE-treated mice. Ongoing experiments are testing the GlcCer levels in the collected tissue. In addition, a future line of research will compare the behavioral and GlcCer profile of the CBE-induced GD model to transgenic mouse models of Gba deficiency. Our data show that CBE-induced GD model recapitulates neuropathologic and behavioral manifestations associated with the disease. The combined use of pharmacological and transgenic mouse models of GD will help evaluate the efficacy of new drug candidates.

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Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.09/F17

Topic: C.06. Neuromuscular Diseases

Title: Hypoxia induced brain injury and cellular recovery in adult zebrafish

Authors: *N. KAYA, J. D. LAUDERDALE, S. T. DOUGAN;
Dept. of Cell. Biol., Univ. of Georgia, Athens, GA

Abstract: There are many effects of hypoxia brain injury in human brain such as memory deficit, motor coordination, and visual impairment. Remarkably, many of these symptoms improve over time, albeit to different extents in different individuals, indicating existence of mechanisms in the human brain to repair and/or compensate for hypoxic/anoxic injuries (HAI); however, the mechanisms involved in hypoxic injury and repair are not well understood. We are developing adult zebrafish as a model for studying hypoxic brain injury. The zebrafish offers several advantages for use in this research, including the ability to visualize and manipulate specific neuronal populations in the brain, use as a drug screening platform to identify compounds for the treatment of HAI, and the potential to identify regenerative mechanism that

could be harnessed in the treatment of people with HAI. In our preliminary experiments, adult zebrafish exposed to hypoxic conditions via an air-proof water chamber exhibited abnormal swimming behavior after hypoxic treatment. Histological analyses revealed a correlation between the extent of hypoxic treatment and damage. Current experiments are focused on determining if there are specific brain regions that are preferentially affected by hypoxic insult and in examining cellular and molecular changes associated with hypoxic insult. Our data suggest that zebrafish can be used as a model to investigate the cellular and molecular events associated with hypoxia-induced brain injury and repair.

Disclosures: **N. Kaya:** A. Employment/Salary (full or part-time):; University of Georgia. **J.D. Lauderdale:** None. **S.T. Dougan:** None.

Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.10/F18

Topic: C.06. Neuromuscular Diseases

Support: NIH (R01NS089586)
Ellison Medical Foundation (AG-NS-1101-13)

Title: Enhanced oligodendrocytes regeneration reduces the early decline in motor coordination and extends the survival of SOD1 (G93A) mice

Authors: *E. GONZALEZ FERNANDEZ, B. PARKER, S. H. KANG;
Ctr. for Neuronal Repair and Rehabil., Shriners Hosp. Pediatric Res. Ctr., Philadelphia, PA

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive motor neuron (MN) degeneration. Non-neuronal cells near the MNs appear to also play critical roles in the progression of ALS. Oligodendrocytes (OLs), the CNS glia forming myelin sheaths, provide metabolic support to neurons, as well as allowing rapid axonal propagation. In a previous study, the genetic deletion of *hSod1 (G37R),* specifically in OLs and OL progenitor cells (OPCs) at a young age, delayed onset of the disease, and prolonged animal survival, implicating OLs in the pathophysiology of MN in ALS. In hSOD1 (G93A) mice, OLs also undergo massive degeneration near MNs, but at the same time, OPCs markedly proliferate and generate new OLs, although it appears that the newly born OLs fail to form compact myelin. However, it is unclear whether OL regeneration in the diseased spinal cord is a natural attempt to mitigate MN dysfunctions, or contributes to disease progression by wasting cellular and nutritional resources in the degenerating spinal cord. To better understand the role oligodendroglia in ALS pathogenesis and the significance of oligodendroglial responses in the disease, we further promoted OL regeneration in *hSOD1 (G93A)* mice. Using *Pdgfra-CreER*

mice, an OPC-specific tamoxifen-inducible Cre driver, we deleted PTEN from OPCs, a negative regulator of OL development, starting at P55. When observed at P100 (P55+45), $CC1^{+}Olig2^{+}$ OLs significantly increased in *Pten* cKO-hSOD1 (G93A) mice compared with littermate mutant SOD1 mice, but the number OPCs did not differ. Whereas there was a sharp decline in rotarod performance in hSOD1 (G93A) mice through an age window (10 - 14 weeks) near disease onset, the *Pten* cKO-hSOD1 (G93A) mice maintained motor skills in this period. The *Pten* cKO also slightly delayed the development of disease-related changes in splay reflex, although the differences in motor performance did not last at later stages. Most strikingly, the *Pten* cKO significantly extended survival of hSOD1 (G93A) mice (median survival: 141 vs. 153 days, n = 19 (control) and 15 (Pten cKO) mice; $P = 0.0051$). Currently, we are further investigating the cellular basis of the positive impacts given by increased oligodendroglial size. Our results reveal that the experimentally enhanced adult-born OL regeneration benefits MN functioning and animal survival in hSOD1 (G93A) mice. Similarly, endogenous OL regeneration may be a natural cellular reaction to compensate for motor deficits caused by MN loss. We conclude that improved survival or facilitated regeneration of OL could be a potential therapeutic strategy for slowing or arresting disease progression in ALS.

Disclosures: E. Gonzalez Fernandez: None. **B. Parker:** None. **S.H. Kang:** None.

Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.11/F19

Topic: C.06. Neuromuscular Diseases

Title: Tdp-43 q331k overexpression leads to adult-onset motor and cognitive impairment in a mouse model

Authors: *E. H. JENSEN, E. MCGUIRK, A. BIALAS, J. YU, L. SHIHABUDDIN, J. DODGE;
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Abstract: TDP-43 protein inclusions are major hallmarks of the neurodegenerative diseases, amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). The familial ALS TDP-43 mutation, Q331K, has been shown to lead to motor deficits in a Prp-TDP-43-Q331K mouse model. However, the effect of this mutation on cognitive and social function has not been fully explored. Starting at 3 months of age, we observed motor dysfunction with significant rotarod impairment, consistent with previous reports. In a sociability assay at 5 months of age, the Q331K TDP-43 mice displayed significantly reduced velocity, fewer movements, but no sociability impairment. Finally, the 6-month old Q331K TDP-43 mice demonstrated mild associative learning and cognitive impairments in fear conditioning and marble burying tests

respectively. Altogether, these results demonstrate that Q331K TDP-43 overexpression leads to adult-onset motor and cognitive deficits that mirror those observed in ALS and FTD disease progression.

Disclosures: **E.H. Jensen:** A. Employment/Salary (full or part-time):; Sanofi Genzyme. **E. McGuirk:** A. Employment/Salary (full or part-time):; Sanofi Genzyme. **A. Bialas:** A. Employment/Salary (full or part-time):; Sanofi Genzyme. **J. Yu:** A. Employment/Salary (full or part-time):; Sanofi Genzyme. **L. Shihabuddin:** A. Employment/Salary (full or part-time):; Sanofi Genzyme. **J. Dodge:** A. Employment/Salary (full or part-time):; Sanofi Genzyme.

Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.12/F20

Topic: C.06. Neuromuscular Diseases

Support: MESTD RS III41005

Title: Changed expression of potassium rectifying channel in glial cells in spinal cord of the ALS rat model

Authors: M. PERIC, D. BATAVELJIC, *P. R. ANDJUS;
Univ. of Belgrade Fac. of Biol., Belgrade, Serbia

Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease. Although it mainly affects lower and upper motor neurons, studies demonstrate that glia has significant role in neuronal death and disease progression. Glial cells maintain equilibrium ion concentration and provide support for neuronal functioning. Important role of glial cells is the potassium uptake and maintenance of ion homeostasis in the extracellular environment. Potassium inwardly rectifying channel 4.1 (Kir4.1) has significant role in keeping potassium ion equilibrium in the central nervous system. Kir4.1 is well studied in astrocytes although its role in other glial cells in ALS is not fully understood. Using markers for oligodendrocytes and microglia, CNPase and Iba1, OX-42, respectively, we examined Kir4.1 expression in cervical and lumbar spinal cord of the end phase $hSOD^{G93A}$ ALS rat model. Colocalization of signal intensity of oligodendroglial and microglial markers and Kir4.1 was quantified by Pearson and Manders coefficients. *In vitro* studies were done on microglia isolated from spinal cords of 2 days old transgenic $hSOD^{G93A}$ rats and their non-transgenic littermates. Presence of Kir4.1 protein was investigated using Western blot while the presence of Kir4.1 mRNA was examined using qPCR. Oligodendrocytes in ALS showed changed organization, morphology and signs of degeneration. In addition, Pearson and Manders colocalization coefficients showed a decrease in Kir4.1 and CNPase signal colocalization in the ventral horn of cervical and lumbar spinal cord of

the end stage ALS animals. Despite global reduction of Kir4.1 in gray matter of spinal cord, islets of Kir4.1 reactivity were observed in ventral gray matter and assigned white matter in ALS model tissue. These islets were also immunopositive for microglial markers showing that microglia forms Kir4.1 positive cell clusters in the end phase of the disease. Further studies on primary microglia demonstrated increased expression of Kir4.1 as well as increase of mRNA for this channel in ALS microglia compared to control. Changes in Kir4.1 in oligodendrocytes and microglia in ALS emphasize the importance of this channel in pathological processes. Reduced Kir4.1 expression in oligodendrocytes and increase of expression in microglia suggest potentially significant role of inwardly rectifiers in physiology of glial cells in neurodegeneration.

Disclosures: **M. Peric:** None. **D. Bataveljic:** None. **P.R. Andjus:** None.

Poster

566. Neurodegeneration Mechanisms

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Topic: C.06. Neuromuscular Diseases

Support: Muscular Dystrophy Association grant MDA382033
NIH/NINDS R01NS062055
Cancer Center Support Grant CA034196
U54 OD020351

Title: CHCHD10 a protein at the intersection of mitochondrial diseases and ALS-FTD

Authors: H. KAWAMATA[1], C. J. ANDERSON[2], K. BREDVIK[3], S. M. MEADOWS[3], C. M. LUTZ[4], *G. MANFREDI[5];
[1]Brain and Mind Res. Inst., [2]Feil Family Brain and Mind Res. Inst., [3]Weill Cornell Med., New York, NY; [4]The Jackson Lab., Bar Harbor, ME; [5]Weill Med. Col. Cornell Univ., New York, NY

Abstract: Mutations in coiled-coil-helix-coiled-coil-helix domain containing 10 (CHCHD10), a mitochondrial protein of unknown function, cause a disease spectrum with clinical features of motor neuron disease, dementia, myopathy and cardiomyopathy. To investigate the pathogenic mechanisms of CHCHD10, we generated mutant knock-in mice harboring the mouse-equivalent of a disease associated human S59L mutation, S55L in the endogenous mouse gene. CHCHD10^{S55L}mice develop progressive motor deficits, myopathy, cardiomyopathy and accelerated mortality. Critically, CHCHD10 accumulates in aggregates with its paralog CHCHD2 specifically in affected tissues of CHCHD10^{S55L}mice, leading to aberrant organelle morphology and function. Aggregates induce a potent mitochondrial integrated stress response (mtISR) through mTORC1 activation, with elevation of stress-induced transcription factors, secretion of myokines, upregulated serine and one-carbon metabolism, and downregulation of

respiratory chain enzymes. Conversely, CHCHD10 ablation does not induce disease pathology or activate the mtISR, indicating that CHCHD10S55L-dependent disease pathology is not caused by loss-of-function. Overall, CHCHD10^{S55L}mice recapitulate crucial aspects of human disease and reveal a novel toxic gain-of-function mechanism through maladaptive mtISR and metabolic dysregulation

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Poster

566. Neurodegeneration Mechanisms

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Program #/Poster #: 566.14/F22

Topic: C.06. Neuromuscular Diseases

Support: T32 GM00736738
F31 NS101966

Title: Retromer complex deficiency in amyotrophic lateral sclerosis

Authors: *E. J. PÉREZ-TORRES[1], V. MISHRA[2], F. LOTTI[1], S. E. PRZEDBORSKI[3]; [2]Motor Neuron Ctr., [3]Neurolog Inst., [1]Columbia Univ., New York, NY

Abstract: Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and fatal neurodegenerative disease that results in the death of motor neurons (MNs) in the spinal cord and brain. The retromer complex's function is to traffic proteins away from the endosome to the trans-Golgi network and to the plasma membrane. Defects in the retromer complex—which traffics proteins away from the endosome to the trans-Golgi network and to the plasma membrane—have been linked to multiple neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease. Here, we study the possible contribution of defects in retromer trafficking to ALS pathology. We started by looking at the expression of retromer complex proteins in post-mortem tissue from ALS patients. We found no significant change in retromer expression in these samples, but noticed high variability among samples and a non-significant average decrease in VPS35 and VPS26A in the spinal cord. Thus, we performed similar experiments in a mouse model of ALS that expresses a G93A mutation in SOD1 (SOD1^{G93A}). In the spinal cord extracts of these models, we saw less variability than we did in the patient extracts and a marked significant decrease in retromer complex proteins. To explore the effects of this deficiency on ALS pathology, we designed two experiments in the SOD1^{G93A}-Tg mouse. We (1) overexpressed Vps35 via an AAV9—which increases the levels of the other retromer components as well—, or (2) knocked out one allele of Vps35—which disrupts the complex—and investigated the effects of these interventions on the ALS-like phenotype of these animals.

Disclosures: **E.J. Pérez-Torres:** None. **V. Mishra:** None. **F. Lotti:** None. **S.E. Przedborski:** None.

Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.15/F23

Topic: C.06. Neuromuscular Diseases

Support: Thierry Latran Foundation (SPIN-ALS project)

Title: Investigating recurrent inhibition in pre-symptomatic adult SOD1-G93A mice

Authors: N. CORNU[1], M. BACZYK[2], D. ZYTNICKI[1], ***M. MANUEL**[1];
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[2]Dept. of Neurobio., Poznań Univ. of Physical Educ., Poznan, Poland

Abstract: Excitotoxicity has long been hypothesized to play a key role in motoneuron degeneration in Amyotrophic Lateral Sclerosis (ALS). This excitotoxicity could arise either from an intrinsic hyperexcitability (which would increase the discharge probability and thereby the calcium inflow), or from alterations in the pre-motor networks leading to excessive glutamatergic excitation of MN and/or decreased inhibition. We have previously provided critical evidence demonstrating that intrinsic hyperexcitability cannot contribute to MN degeneration in ALS (Leroy et al, eLife 2014; Delestrée et al, J Physiol 2014; Martínez-Silva et al, eLife 2018). Furthermore, we have shown that excitatory synapses to motoneurons are depressed in SOD1-G93A mice before degeneration onset (Baczyk et al, SfN 2016). The goal of the present work is to test whether there are alterations in inhibitory circuits that could lead to an excitotoxic stress.
We studied the recurrent inhibition elicited by Renshaw cells. We performed *in vivo* intracellular recordings in adult SOD1-G93A and SOD1-WT transgenic mice at a presymptomatic age (P45-P55). Recurrent inhibition was elicited in Triceps Surae motoneurons by stimulating either the medial gastrocnemius or lateral gastrocnemius nerve after dorsal rhizotomy, to remove any sources of sensory-mediated excitation. The effective synaptic conductance at the soma was measured by injecting small (±0.5 nA) pulses of current immediately before, and during a steady-state IPSP elicited by a 200 Hz stimulation of the nerve, and calculating the difference in the slopes of the I-V plots obtained from each series of pulses.
Our preliminary results from 23 SOD1-G93A MNs (10 mice) and 34 SOD1-WT MNs (7 mice) show that the increase in input conductance elicited by recurrent inhibition was not different between mutant and WT animals (SOD1-G93A: 32 ± 22 nS [0-101 nS]; N=23 vs. SOD1-WT: 29 ± 29 nS [1-146 nS]; N=34). Furthermore, the reversal potential of the synapse, extrapolated from the I-V curves, was also not different between mutant and WT animals (SOD1-G93A: -67 ± 9

mV; [-82--49 mV]; N=23 vs. SOD1-WT: -65 ± 13 mV; [-95--45 mV]; N=34).
Conclusion: MN death in ALS is unlikely to be caused by a decrease in inhibitory inputs to MNs just before the onset of denervation.

Disclosures: **N. Cornu:** None. **M. Baczyk:** None. **D. Zytnicki:** None. **M. Manuel:** None.

Poster

566. Neurodegeneration Mechanisms

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Program #/Poster #: 566.16/F24

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R01 NS038526
NIH Grant P30 NS045758

Title: A Charcot-Marie-tooth disease type 2E point mutation in neurofilament protein L causes protein instability, atrophied axons, and proximal neurofilament accumulations

Authors: *E. J. STONE, A. UCHIDA, P. C. MONSMA, A. BROWN;
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Abstract: Charcot-Marie-Tooth disease type 2E (CMT2E) is a slowly progressive peripheral neuropathy of unknown mechanism caused by mutations in the gene that encodes neurofilament protein L (NFL). NFL is one of five subunits that comprise neurofilaments, which are neuron-specific cytoskeletal polymers that contribute to axon expansion during development. The $NFL^{N98S/+}$ CMT2E mouse model, which is heterozygous for the N98S mutation in the endogenous mouse *Nefl* locus, presents with a disease phenotype and offers an opportunity to study the effects of a CMT2E mutation on neurofilaments *in vivo*. We are using this mouse to ask several questions: 1) Is the mutant protein stably expressed? 2) Does the mutant NFL protein affect the expression levels and assembly of the other neurofilament subunits? 3) Is the mutant protein incorporated into filaments? 4) Does the mutant protein impair neurofilament transport and/or interactions? By Western blotting, we observe a reduction in neurofilament proteins in the mutant sciatic nerve and spinal cord when compared to wild type. Using tandem mass spectrometry of tryptic digests, we find that 41% of the NFL protein in the spinal cord is N98S mutant. To determine the assembly state of the neurofilament subunit proteins, we homogenized spinal cord tissue in Triton X-100 and performed centrifugation to separate soluble (unassembled) and insoluble (assembled) fractions. In the mutant, we observe an elevation of neurofilament triplet proteins in the Triton-soluble fraction and a reduction in the Triton-insoluble fraction. On average, 41% of the NFL protein in the insoluble fraction was mutant compared to 30% in the insoluble fraction. Electron microscopy of spinal cord, dorsal root ganglia, and sciatic nerve confirmed the presence of atrophied axons lacking neurofilaments,

with some axons containing neurofilament accumulations proximally. Strikingly, the neurofilament accumulations exhibited widespread segregation of neurofilaments from their microtubule tracks, which implies an impairment of neurofilament transport. We conclude that the mutant NFL is capable of assembly, but assembles less efficiently than wild type, thereby altering the subunit stoichiometry of the assembled neurofilaments and increasing the soluble pool of all neurofilament subunit proteins. Our data suggest that disease arises from a loss of neurofilaments in axons due to sequestration in cell bodies and proximal axons caused by either (1) alterations in the structure or subunit stoichiometry of the filaments, or (2) toxicity of elevated soluble neurofilament protein. We are currently working to test these hypotheses.

Disclosures: E.J. Stone: None. **A. Uchida:** None. **P.C. Monsma:** None. **A. Brown:** None.

Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.17/F25

Topic: C.06. Neuromuscular Diseases

Title: Electroceutical treatment of dysphagia in a mouse model of ALS

Authors: *B. BALLENGER[1], C. HAXTON[2], K. L. OSMAN[2], J. ARNOLD[1], T. E. LEVER[2]; [1]Sch. of Med., [2]Dept. of Otolaryngology - Head & Neck Surgery, Univ. of Missouri, Columbia, MO

Abstract: Objectives: Dysphagia (swallow impairment) is a debilitating condition that eventually affects every individual diagnosed with ALS, often resulting in malnutrition, dehydration, and fatal aspiration pneumonia. Current treatments are largely palliative and do little to address the underlying neurophysiology. Here, we explore an electroceutical approach targeting the brainstem central pattern generator for swallowing in a mouse model of ALS. **Methods:** We established a surgical protocol for acute delivery of electrical stimulation (ES) to the superior laryngeal nerve (SLN) in the low copy number (LCN) *SOD1-G93A* transgenic mouse model of ALS (i.e., LCN-SOD1). The procedure is performed once as a survival surgery at 6 months of age, corresponding to clinical disease onset in this model. The right SLN is draped over bipolar electrodes for 1 hour of continuous ES using parameters established by our pilot work. Twenty LCN-SOD1 mice (either sex) underwent the surgical protocol, equally divided into 2 groups (SLN stimulation versus sham treatment) for comparison with 2 non-surgical control groups: LCN-SOD1 mice (n=20) and non-transgenic littermates (n=20); age-matched, either sex. To evaluate swallowing function, all mice underwent our established videofluoroscopic swallow study (VFSS) assay that entails monthly testing of awake, freely-behaving animals using low-dose x-ray, starting at 4 months until disease end-stage (20% reduction from maximum body weight).

Results: Preliminary VFSS findings from 3 ES-treated mice demonstrated preserved lick rate during drinking, compared to non-transgenic controls. In contrast, the lick rate of sham-treated and non-surgical LCN-SOD1 controls was significantly slower than ES-treated mice and non-transgenic controls. Analysis of the remaining mice and additional VFSS outcome measures is in progress.
Discussion: Our preliminary results of preserved lick rate in end-stage LCN-SOD1 mice after a single, 1-hour ES treatment to the SLN nerve are quite promising. If additional beneficial outcomes (i.e., preserved swallowing function and extended survival) emerge following completion of data analysis, this pioneering work will provide the scientific premise for exploring electrical stimulation in the treatment of dysphagia in ALS patients.

Disclosures: B. Ballenger: None.

Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.18/F26

Topic: C.06. Neuromuscular Diseases

Support: NIH/NINDS Grant 1R01NS091722
ALSA Grant 1114-471-454
NIH/NINDS Grant 1R21NS105047

Title: Distinct populations of layer 5b pyramidal neurons in the primary motor cortex

Authors: M. V. MOYA[1], M. N. RAO[1], R. KIM[2], C. E. SFERRAZZA[2], N. HEINTZ[1,3], *E. F. SCHMIDT[2];
[1]Lab. of Molec Biol, The Rockefeller Univ., New York, NY; [2]Lab. of Molec Biol, Rockefeller Univ., New York, NY; [3]HHMI, New York, NY

Abstract: Many neurodegenerative diseases lead to the selective degeneration of discrete cell types in the CNS even though many disease-causing mutations occur in genes that are ubiquitously expressed. This is true for amyotrophic lateral sclerosis (ALS), an aggressively fatal disease characterized by the progressive degeneration of the alpha-motoneurons in the spinal cord and the spinal cord projecting “upper” motor neurons in the cerebral cortex. To fully understand the causes of disease onset and to develop more effective therapeutic strategies it is imperative to understand the molecular properties of afflicted cells and identify cellular pathways that may underlie pathological processes. Much of the work over the last three decades has focused on the spinal cord, while relatively little is known about the mechanisms leading to cortical phenotypes. This likely reflects the complexity and heterogenous organization of the cortex and the lack of reliable markers to distinguish the upper motor neurons from other

pyramidal cells. We therefore employed a combination of anatomical and molecular strategies to determine the characteristics that differentiate vulnerable cells from nearby resistant cell types. We show that there are two distinct, but closely related, pyramidal cell subtypes in layer 5b of mouse primary motor cortex with overlapping and distinct axonal projections. Only one of these subtypes is lost in the SOD1-G93A mouse model of familial ALS, establishing vulnerable and an analogous resistant layer 5b populations. Molecular profiling using the translating ribosome affinity purification (TRAP) approach revealed important differences in baseline gene expression in healthy mice, and differential changes in gene expression during disease progression in SOD1-G93A mice. These studies also elucidated novel immunohistological markers to visualize these populations across species. Together, our results provide a foundation to elucidate how molecular properties of distinct cell populations reflect their distinct anatomy and establish selective vulnerability in neurodegenerative disorders.

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Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.19/F27

Topic: C.06. Neuromuscular Diseases

Support: CNPq
CAPES
FAPERJ
INCT

Title: Effects of human Wharton's jelly mesenchymal stem cell therapy in a mouse model of amyotrophic lateral sclerosis

Authors: M. FURTADO, ***L. C. TEIXEIRA PINHEIRO**, J. F. VASQUES, T. PUIG PIJUAN, M. P. PINHEIRO, M. F. SANTIAGO, R. MENDEZ-OTERO, F. GUBERT;
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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal, progressive neurodegenerative disease without effective treatment, characterized by the impairment of the upper and lower motoneurons. Although the pathogenic mechanisms of ALS are not very well understood, it is known that this is a multifactorial disease in which mutations in different genes and/or different pathways are affected leading to neuronal death. In this sense, cell therapy has emerged as a promising alternative and several studies have been carried out to verify its effects and benefits. In the present work, we used different functional tests to evaluate disease progression in

SOD1(G93A) mice and analyzed the effect of cell therapy with human Whaton's jelly mesenchymal stem cells (MSC). Three functional tests were used to evaluate the motor performance of the animals: rotarod, motor score and CatWalk. According to our functional tests, the disease manifests itself between the 12th and 15th weeks. After establishing the functional profile of the mice, we injected MSC intravenously. In this protocol, treated animals showed a delay in disease progression and an increase in lifespan. In addition, preliminary analysis of the anterior horn of the lumbar spinal cord has shown that the number of microglial cells is reduced in the animals receiving MSC. When analyzing the number of motoneurons in the same region of the spinal cord, we did not observe any difference between the groups. Therefore, this work shows that intravenous therapy with MSC is a promising therapy in the treatment of ALS.

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Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.20/F28

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R01NS091749-01A1
NIH Grant F31 NS098764-02

Title: SMA-specific differences in the translatome of spinal motor neurons *in vivo*

Authors: *P. L. PRICE[1], K. ENGEL[2], C.-W. TSAI[3], M. TALIAFERRO[2], C. DIDONATO[4], G. J. BASSELL[1], W. ROSSOLL[3];
[1]Emory Univ., Atlanta, GA; [2]Biochem. and Mol. Genet., Univ. of Colorado Sch. of Med., Aurora, CO; [3]Dept. of Neurosci., Mayo Clin., Jacksonville, FL; [4]Human Mol. Genet., Northwestern Univ., Chicago, IL

Abstract: Spinal Muscular Atrophy (SMA) is a neuromuscular disease characterized by a progressive loss of spinal motor neurons and consequently, a loss of locomotor abilities. SMA is directly caused by insufficient levels of the Survival of Motor Neuron (SMN) protein, yet the molecular mechanisms by which reduced levels of SMN influence motor neuron development and susceptibility remain elusive. Several studies have identified differences in global and compartmentalized mRNA expression *in vitro*, yet evidence for mRNA processing and localization defects *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, or "translatome", in spinal motor neuron cell bodies at pivotal time points in a mouse model of SMA. We observed an early and persistent upregulation of transcripts involved in p53-mediated signaling pathway, as well as a down-regulation of several motor neuron-enriched markers that may contribute to sub-type specification axon growth such as matrix metalloproteinase 9 (MMP9) and chondrolectin (Chodl). Functional studies conducted with novel dysregulated transcripts link SMN-deficiency to cell-type specific changes that directly influence the development of SMA pathology in cell models. Taken together, data from these studies reveal novel targets that contribute to motor neuron pathogenesis in SMA and may serve as valuable candidates for the preservation of motor neurons in neurodegenerative diseases.

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Poster

566. Neurodegeneration Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 566.21/F29

Topic: C.06. Neuromuscular Diseases

Support: ANII I+I - EOLO

Title: Post-paralysis treatment with the electrophilic compound EOLO42016 abrogates neuroinflammation and slows disease progression in inherited ALS

Authors: *S. IBARBURU[1], E. TRÍAS[2], J. RODRIGUEZ-DUARTE[2], G. GALLIUSSI[2], V. LÓPEZ[3], M. KOVACS[2], V. VARELA[2], M. INGOLD[2], C. BATTHYANY[2], L. BARBEITO[2]; [1]Inst. Pasteur De Montevideo, Montevideo, Uruguay; [2]Inst. Pasteur de Montevideo, Montevideo, Uruguay; [3]Facultad de Química, UdelaR, Montevideo, Uruguay

Abstract: Neuroinflammation is a pathological hallmark in Amyotrophic Lateral Sclerosis (ALS), causally associated to the progressive degeneration of upper and lower motor neurons. Drugs targeting neuroinflammation have the potential to slow paralysis progression. We have recently developed new electrophilic drugs capable of inhibiting neuroinflammation by targeting Nrf2/Keap1, NFκB and NLRP3 inflammasome. Here, we have analyzed the protective effects of the compound EOLO42016 on the post-paralysis survival of ALS transgenic rats carrying the $SOD1^{G93A}$ mutation. The drug was orally administered at 100 mg/kg/day starting after paralysis onset. Also, adult microglia isolated from the symptomatic spinal cord of $SOD1^{G93A}$ rats were used to determine the the effect of the drug on inflammatory pathways. We found that EOLO42016 inhibits p65 NF-κB nuclear translocation and the release of interleukin-1β in cultured adult $SOD1^{G93A}$ microglia stimulated with LPS. Furthermore, administration of

EOLO42016 to SOD1^{G93A} rats starting after paralysis onset, significantly prolonged survival by 30% when compared with vehicle. Extend survival was associated to a potent histopathological protective effect denoted by decreased microgliosis and preservation of spinal cord motor neurons and NMJ in the EDL muscle. Therefore, compound EOLO42016 appears unique among other ALS-developmental drugs, being capable of exerting a multi-faceted neuroprotection in both central and peripheral nervous systems via modulation of different mechanisms implicated in ALS pathogenesis.

Disclosures: **S. Ibarburu:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; The research was founded by EOLO Pharma. **E. Trías:** None. **J. Rodriguez-Duarte:** None. **G. Galliussi:** None. **V. López:** None. **M. Kovacs:** None. **V. Varela:** None. **M. Ingold:** None. **C. Batthyany:** None. **L. Barbeito:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.01/F30

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: TSGH-C107-016
TSGH-C108-021

Title: Targeting Nox2 to reduce autoimmune elicited neural damage in the central nervous system

Authors: *C.-F. HU[1], S.-P. WU[4], C.-S. HSU[2], J.-S. HONG[5], S.-J. CHEN[3], C.-C. SHIEH[6]; [2]Ctr. for Precision Med. and Genomics, [3]Pediatrics, [1]Tri-Service Gen. Hosp., Taipei City, Taiwan; [4]Reproductive and Developemental Biol. Lab., Natl. Inst. of Envrn. Hlth. Sci., Durham, NC; [5]NIEHS, Rtp, NC; [6]Lab. of Human Immunological Dis., Natl. Cheng Kung Univ., Tainan city, Taiwan

Abstract: The roles of reactive oxygen species (ROS) contributing to the pathogenesis of experimental autoimmune encephalomyelitis (EAE) is not yet totally understood. Recent strategies of multiple sclerosis treatment centered on T cell-based interventions work successfully on a subset of patients. In this study, we focus roles of innate immunity in the pathogenesis of EAE. We hypothesize that dysregulated ROS production by both macrophage and microglia NADPH oxidase (Nox2) contributes to neural inflammation, damage and demyelination after EAE induction.
We found that Nox2 deficient mice are more resistant to EAE induced neural damage compared

with control mice (C57). Nox2 deficiency results in reduced disease severity scores, less body weight loss, less leukocytes infiltration, lower grades of demyelination, decreased oxidative stress markers 3-nitrotyrosine (3-NT) and Myeloperoxidase (MPO), and lower levels of genes encoded for Nox2, CD11b, proinflammatory cytokines (IL-4, IL-17α, IFNɣ) and chemokine (CCL2, CCL5, CCL6, CCL20, CXCL10) in the spinal cords in comparison with control. Our findings suggest that Nox2-mediated ROS production in macrophage and microglia plays an important role in EAE-induced neuronal damage. Roles of Nox2 in macrophage and microglia in the pathogenesis of EAE are being investigated by using a variety of Nox2 inhibitors. Further studies on the functional assessment of dendritic cells, macrophages and microglia in Nox2 deficient mice after EAE induction.

Disclosures: **C. Hu:** None. **S. Wu:** None. **C. Hsu:** None. **J. Hong:** None. **S. Chen:** None. **C. Shieh:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.02/F31

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NRF 2018R1C1B6005102

Title: Cellular source of hypothalamic macrophage accumulation in diet-induced obesity

Authors: *C. LEE;
Asan Med. Ctr., Seoul, Korea, Republic of

Abstract: Obese mice on a high fat diet (HFD) display signs of inflammation in the hypothalamic arcuate nucleus (ARC), a critical area for controlling systemic energy metabolism. This has been suggested as a key mechanism of obesity-associated hypothalamic dysfunction. We reported earlier that bone marrow-derived macrophages accumulate in the ARC to sustain hypothalamic inflammation upon chronic exposure to an HFD. However, the mechanism of hypothalamic macrophage accumulation remained unclear.We investigated whether circulating monocytes or myeloid precursors contribute to hypothalamic macrophage expansion during chronic HFD feeding. To trace circulating myeloid cells, we generated mice expressing green fluorescent protein (GFP) in the lysozyme M-expressing myeloid cells ($LysM^{GFP}$ mice) and then conducted parabiosis and bone marrow transplantation experiments using these mice. Mice were fed HFD for 12 or 30 weeks before sacrificed to evaluate the presence of $LysM^{GFP}$ cells in the hypothalamus. Hypothalamic vascular permeability in HFD-fed obese mice was also tested by examining extravascular leakage of Evans blue and fluorescence-labelled albumin. Finally, we studied when $LysM^{GFP}$ cells entered the hypothalamus during the development.Our parabiosis

and bone marrow transplantation experiments revealed a significant infiltration of circulating $LysM^{GFP}$ cells in the liver, skeletal muscle, choroid plexus and leptomeninges but not in the hypothalamic ARC during chronic HFD feeding, despite increased hypothalamic vascular permeability. These results suggested that the recruitment of circulating monocytes is not a major mechanism for maintaining and expanding the hypothalamic macrophage population in diet-induced obesity. Instead, we demonstrated that $LysM^{GFP}$ cells infiltrated the hypothalamus during its development. $LysM^{GFP}$ cells appeared in the hypothalamic area from the late embryonic period. This cellular pool suddenly increased immediately after birth, peaked at the postnatal second week, and adopted an adult-pattern of distribution after weaning.These findings suggest that bone marrow-derived macrophages mostly populate the hypothalamus in early postnatal life and may maintain their pool without significant recruitments of circulating monocytes throughout life, even under conditions of chronic HFD-feeding.

Disclosures: C. Lee: None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.03/F32

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: MHRD Fellowship
DBT Grant BT/HRD/35/01/01/2017

Title: Functional interplay between neurons and glia in mice models of familial epilepsy

Authors: *P. SINHA, B. VERMA, S. GANESH;
Biol. Sci. and Bioengineering, Indian Inst. of Technol. Kanpur, Kanpur, India

Abstract: Epilepsy is a chronic neurological condition characterized by recurrent and unprovoked seizures, affecting up to 1% of the global population. The serendipitous discovery of various channel blockers as anti-epileptic drugs (AEDs) substantiated the age-old concept of epilepsy being a channelopathy. Almost all AEDs currently being used are channel blockers. However, a critical look at the genetic basis of epilepsy reveals genetic defects in channel proteins are limited to a few affected families. Genetic defects resulting in epilepsy in a large number of independent families are associated with genes coding for non-channel proteins. For example, genes coding for cysteine protease inhibitors, protein phosphatases, and ubiquitin ligases are mutated in familial forms of epilepsies. The use of channel blocker AEDs is effective in controlling the seizures even in such cases. Their continued usage, however, results in refractive forms (drug-resistant) in over 40 % of the cases, highlighting the need to understand the molecular basis of epileptogenesis better and to develop new drugs.

Far more active than once thought glia plays a significant role in the incidence of epilepsy. We wanted to understand the role of microglia and astrocytes in causing epilepsy in mice models of an autosomal recessive familial epilepsy. Microglia and astrocytes are the major players in regulating neuroinflammation. In our previous studies, we could show that reactive glia causes neuroinflammation with advancing age which in turn renders the aged brain more susceptible to seizure episodes. In our mice models of epilepsy, we see increased gliosis and incidence of seizures. We hypothesized that rescuing neuroinflammation could ameliorate the seizure phenotype in our mice models.
6-month-old mice (C57BL/6J strain) (n=12) were administered with NSAIDs mixed in drinking water ad libitum for two months. Age-matched controls fed with regular water served as control (n=12). We injected pentylenetetrazole (a seizure-inducing drug) intraperitoneally to the NSAIDs administered and control mice to induce seizures and videotaped them for 30 minutes to score seizures. We have looked into the extent of neuroinflammation and oxidative stress by immunohistochemical staining, quantitative RT-PCR, western blotting and enzymatic assays. We found a significant reduction in seizure susceptibility along with downregulated neuroinflammation and decreased oxidative stress markers in treated mice. We conclude that glia plays an important role in maintaining the balance between excitation and inhibition in neurons by regulating inflammation and oxidative stress in the brain.

Disclosures: P. Sinha: None. **B. Verma:** None. **S. Ganesh:** A. Employment/Salary (full or part-time):; Indian Institute of Technology Kanpur. 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.; Department of Biotechnology India.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.04/F33

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Estonian Research Council grant IUT20-64
Estonian Research Council grant IUT20-41
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European Regional Development Fund

Title: GLP1 receptor agonist prevents development of Wolfram syndrome symptoms in the Wfs1 deficient rat

Authors: *K. SEPPA[1], M. TOOTS[1], R. REIMETS[1], T. JAGOMÄE[1], J. R. NYENGAARD[2], E. VASAR[1], A. TERASMAA[1], M. PLAAS[1];

[1]Inst. of Biomedicine and Translational Med., Univ. of Tartu, Tartu, Estonia; [2]Stereology and Electron Microscopy Lab., Aarhus Univ. Hosp., Aarhus, Denmark

Abstract: Background: Wolfram syndrome (WS) is a rare neurodegenerative disorder that is mainly characterized by diabetes mellitus, optic nerve atrophy and progressive brainstem degeneration. Currently, there is no cure for WS and death usually occurs due to brainstem atrophy. Therefore, it is important to find therapies that could protect against the progression of the disease. We have developed and characterized the WS rat model, where exon 5 deletion of the *Wfs1* gene resulted in development of the main symptoms of WS: diabetes mellitus, optic nerve atrophy and medullary degeneration. GLP-1 (glucagon-like peptide-1) receptor agonists (RA) have been accepted as a promising class of anti-diabetic drugs, having the potential to delay or even reverse disease progression. Chronic GLP-1 RA liraglutide treatment reduced ER stress and inflammation in Wfs1 KO rats Langerhans islets and thereby prevented the development of diabetic phenotype. Therefore, potential neuroprotective effects of GLP1 RA were evaluated in Wfs KO rats.
Methods: Wfs1-deficient and wild-type (WT) littermate control rats were used. The rats were 8 months old at the beginning of the experiment and were randomly allocated into the liraglutide or control group (n=6-10) and were treated for 6 months. To evaluate liraglutide therapeutic effect, in vivo MRI was performed and cellular stress markers were measured using histological and stereological methods.
Results: In addition to antidiabetic effect, our recent data suggest that long-term liraglutide treatment has also neuroprotective effects on WS.
Conclusions: Wfs1-KO rat is the only WS animal model with well characterized progression of disease symptoms, including diabetes and neurodegeneration. Therefore, Wfs1-KO rat is valuable pre-clinical tool to evaluate treatment strategies.

Disclosures: K. Seppa: None. **M. Toots:** None. **R. Reimets:** None. **T. Jagomäe:** None. **J.R. Nyengaard:** None. **E. Vasar:** None. **A. Terasmaa:** None. **M. Plaas:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.05/F34

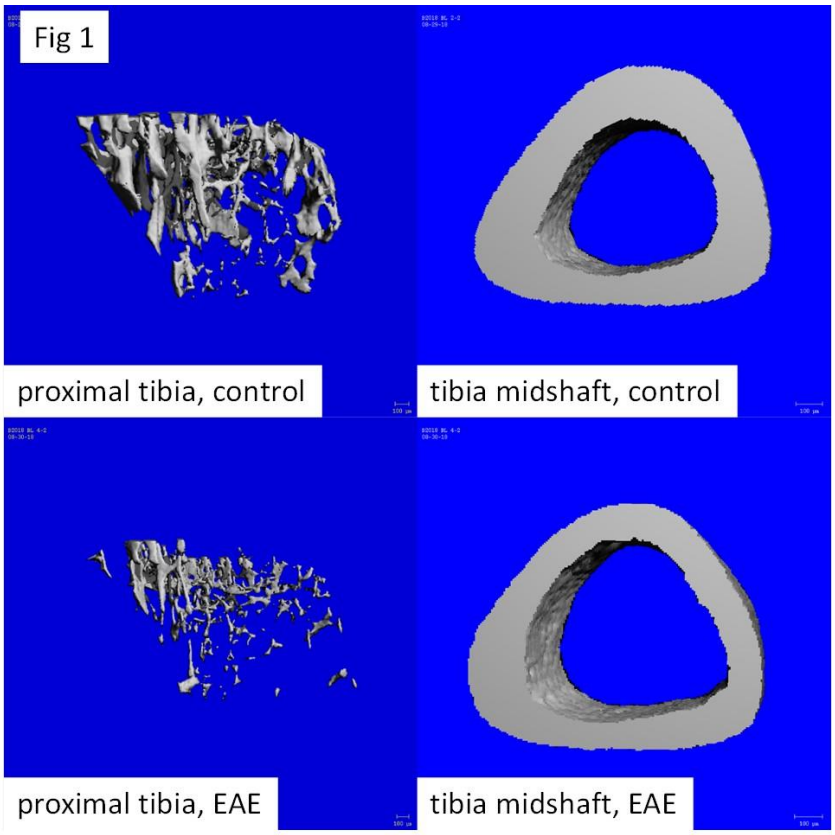
Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

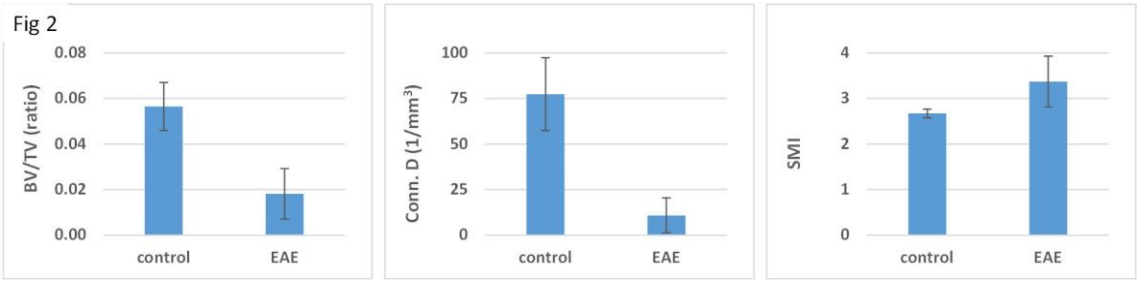
Support: Biomedical Research Innovation Program at the University of Toledo
National Institute of Mental Health (1R01MH113986-01A1)

Title: Osteoporosis in a clinically relevant mouse model of multiple sclerosis

Authors: *B. LIN, D. LAUNDER, **O. A. MILLER**, D. Y. BAILEY, F. K. ASSIFUAH, H. R. CONTI, B. M. KOFFMAN, J. DU;
The Univ. of Toledo, Toledo, OH

Abstract: Multiple sclerosis (MS) is a CNS disease in which the myelin sheath in the brain and spinal cord are damaged, leading to disruption of neural communication. In addition to inciting autoimmunity to neurons, activated T cells causing peripheral inflammation also impacts bone metabolism. The imbalance of bone breakdown and formation is the underlying mechanism of diseases such as osteoporosis. Studies suggest that MS patients are at increased-risk of having osteoporosis. To demonstrate if experimental autoimmune encephalomyelitis (EAE), a widely accepted model of MS, predisposes mice to this bone disorder, C57BL/6 mice were immunized with myelin oligodendrocyte glycoprotein (MOG) to induce EAE, and changes in bone structure/quality were assessed by using μCT. Three-dimensional reconstruction of the mouse tibia showed significant bone loss in EAE mice, compared to healthy mice (control) (Fig 1). Osteoporotic bone in EAE mice was also characterized by decreases in the ratio of bone volume over total volume (BV/TV) and connectivity density (Conn. D) as well as a shift in bone shape from more planar (structure model index (SMI)=0) to more cylindrical (SMI=3) (Fig 2). Activation of osteoclasts, the major cell type mediating bone resorption, was found induced in EAE mouse bone by qRT PCR analysis of osteoclast marker TRAP, Cathepsin K, MMP9 and RANK. Together, our data suggested that EAE can cause osteoporosis in mice, and that this model may be useful to investigate metabolic bone diseases associated with MS.





Disclosures: **B. Lin:** None. **D. Launder:** None. **O.A. Miller:** None. **D.Y. Bailey:** None. **F.K. Assifuah:** None. **H.R. Conti:** None. **B.M. Koffman:** None. **J. Du:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.06/F35

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: JSPS Grant 17K11107

Title: Goshajinkigan, a Japanese traditional herbal medicine, prevents age-related allodynia in senescence-accelerated mice

Authors: ***M. NAKANISHI**[1], N. KOYAMA[2], S. FUKUI[3], H. KITAGAWA[1];
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Abstract: The elderly population is increasing, and they generally exhibit a higher incidence of chronic neuropathic pain and frailty. However, as the incidence of side effects is higher in elderly patients, treatment methods are limited. Goshajinkigan (GJG), a traditional Japanese herbal medicine, is often used to treat symptoms of aging, such as leg pain, low back pain, numbness, itching, and swelling. GJG has few side effects and can be safely administered to elderly. The aim of this study was to investigate the effect of GJG on age-related allodynia using chronic constriction injury(CCI) mice and senescence-accelerated mice (SAMP8). First, C57BL/6J male mice aged 6 weeks were randomly divided into four groups (n = 5): sham, GJG-treated sham, CCI, and GJG-treated CCI groups. CCI mice were prepared using a modification of the procedure of Bennett and Xie. Briefly, three ligatures of 6-0 silk suture were tied loosely around the sciatic nerve at intervals of 1 mm. Sham controls were subjected to the same surgical procedure, except that the sciatic nerve was undisturbed. The mice were fed a normal diet with or without 4% (w/w) GJG. The analgesic effect was evaluated by behavioral tests, the Von Frey test, and cold plate test at 1 day before surgery,and 3, 7, 14, 21, and 28 days after surgery. GJG

significantly reduced allodynia and hyperalgesia from the early phase (von Frey test, $p<0.0001$; cold-plate test, $p<0.0001$; two-way repeated measures ANOVA). Immunohistochemistry and Western blot analysis revealed that GJG decreased the expression of Iba1 and tumor necrosis factor-a(TNF-a) in the spinal cord. Double staining immunohistochemistry showed that most of the tumor necrosis factor-a was co-expressed in Iba1-positive cells at day 3 post-operation. Additionally, senescence-accelerated mice, aged 7 weeks, were randomly divided into four groups ($n = 5$): SAMR1(control), GJG-treated SAMR1, SAMP8, and GJG-treated SAMP8 groups and fed a normal diet with or without GJG. We performed behavioral tests at the age of 12, 24, and 36 weeks. Among senescence-accelerated mice, the SAMP8 group mice showed apparent allodynia compared with SAMR1 (von Frey test, $p<0.05$; cold-plate test, $p<0.05$; two-way repeated measures ANOVA). GJG significantly reduced mechanical and cold allodynia in SAMP8 mice (von Frey test, $p<0.05$; cold-plate test, $p<0.001$; two-way repeated measures ANOVA). GJG ameliorates allodynia in CCI model mice via suppression of TNF-a expression derived from activated microglia. and GJG also prevented allodynia in senescence-accelerated mice. GJG may be a promising drug for the treatment of allodynia induced by neuro-inflammation and aging.

Disclosures: **M. Nakanishi:** None. **N. Koyama:** None. **S. Fukui:** None. **H. Kitagawa:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.07/F36

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NMSS TA-1503-03465
AAN
Race to Erase MS

Title: Ultra-high field MRI to monitor leptomeningeal inflammation in an animal model of multiple sclerosis

Authors: *S. KIM, M. D. SMITH, P. BHARGAVA, P. CALABRESI;
Neurol., Johns Hopkins SOM, Baltimore, MD

Abstract: Leptomeningeal inflammation has been noted to occur in both multiple sclerosis (MS) patients and animal models of MS. Studies have demonstrated that areas of meningeal inflammation consist of B-cells, T-cells, follicular dendritic cells (FDC) and macrophages, with some of these areas demonstrating features of ectopic lymphoid tissue. Meningeal inflammation is associated with increased gray matter demyelination and neuronal damage in adjacent cortical areas in MS patients and a more severe disease course. In recent studies, sites of leptomeningeal

enhancement were detected utilizing contrast-enhanced magnetic resonance imaging (MRI) and these lesions corresponded to areas of meningeal inflammation on autopsy. Thus, meningeal inflammation appears to play an important role in MS disease progression and is detectable at both radiological and pathological level.
Here, we utilized high-field (11.7 Tesla) gadolinium-enhanced FLAIR MRI to identify areas of meningeal inflammation in the relapsing-remitting model of experimental autoimmune encephalomyelitis (rr-EAE) in female SJL/J mice and to test a potential therapy targeting B-cells (anti-CD20). We first identified areas of leptomeningeal enhancement predominantly over the cerebral cortex or in the hippocampal fissure. These areas corresponded to dense inflammatory infiltrates in the meninges, which included B-cells, T-cells, FDC, and macrophages. In longitudinal experiments we noted an increase in the number of these lesions from early (2 weeks) to late stages (> 8 weeks) of EAE and pathologically, we noted increased abundance of B-cells (B220+) within the areas of meningeal inflammation over time. Evaluation of the adjacent cerebral cortex in rr-EAE animals revealed an increase in microglia/ macrophages (Iba-1+ cells) and astrocytes (GFAP+). We also noted increased axonal damage (SMI-32+ spheroids) and demyelination (vacuolar degeneration in luxol fast blue staining), suggesting meningeal inflammation could lead to axonal damage and demyelination in the underlying cortex.
We then used this model to evaluate the effect of anti-CD20, a treatment used to deplete peripheral B-cells, on meningeal inflammation. Despite a reduction in the proportion of B- and T-cells within lesions, there was no significant difference in number of leptomeningeal enhancing lesions between anti-CD20 and isotype control groups suggesting that targeting of B-cells alone may be insufficient to eliminate meningeal inflammation in MS. This model will help evaluate putative treatment strategies that may impact meningeal inflammation and may help identify those that hold promise in human trials.

Disclosures: S. Kim: None. **M.D. Smith:** None. **P. Bhargava:** None. **P. Calabresi:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.08/F37

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Characterization of cytokine levels in LPS-treated mice: Multiplex assay of key inflammatory mediators in neurodegenerative disorders

Authors: *K. M. PALDANIUS, L. RAUHALA, T.-K. STENIUS, F. KHAN, T. BOLKVADZE, R. O. PUSSINEN, T. HUHTALA, D. MISZCZUK;
Charles River Discovery, Kuopio, Finland

Abstract: Inflammation is a key feature in several neurodegenerative disorders. Multiplex assays, such as Luminex platform, offer a possibility to simultaneous detection of multiple inflammatory mediators from single sample for better evaluation of complexity of immune response. However, detecting minute concentrations of secreted cytokines particularly in solid tissues can be challenging. The objective of this study is to optimize a multiplex assay platform for assessment of a time course of inflammatory response in the brain, peripheral tissues and body fluids in C57BL/6J mice after systemic lipopolysaccharide (LPS) challenge.
A single intraperitoneal LPS injection (5-20 mg/kg of serotype 055:B5) was used to activate the immune system of the test animals, and to induce measurable local and systemic levels of inflammation regulating cytokines and chemokines. At 6h, 24h, and 7d after LPS administration CSF, plasma, hypothalamus, hippocampus, striatum, and cortical pieces were collected. Liver and spleen were used as systemic control tissues. All samples were fresh-frozen for the measurement of IFN-γ, IL-10, IL-1β, IL-6, MCP-1/CCL2, and TNF-α using Luminex platform. The results of this work will help to characterize the effect of systemic LPS in mice, as well as give valuable insight into the relationship between brain and peripheral tissue and body fluids in levels of key mediators of inflammation using validated measurement protocols. Overall, the data helps in validating biomarkers, which are relevant to neuroinflammatory models.

Disclosures: K.M. Paldanius: None. **L. Rauhala:** None. **T. Stenius:** None. **F. Khan:** None. **T. Bolkvadze:** None. **R.O. Pussinen:** None. **T. Huhtala:** None. **D. Miszczuk:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.09/F38

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: ABINEP M1/P2

Title: Early detection of experimental cerebral malaria associated brain pathology

Authors: R. BHATTACHARJEE[1,2], K. HARIT[1], S. ARNIM[1], *E. BUDINGER[2], J. GOLDSCHMIDT[2], K. MATUSCHEWSKI[3,4], D. SCHLÜTER[1,5,6], G. NISHANTH[1,5];
[1]Inst. of Med. Microbiology, Otto-von-Guericke Univ. Magdeburg, Magdeburg, Germany; [2]Systems Physiol. of Learning, Leibniz Inst. for Neurobio., Magdeburg, Germany; [3]Parasitology Unit, Max Planck Inst. for Infection Biol., Berlin, Germany; [4]Dept. of Mol. Parasitology, Humboldt Univ., Berlin, Germany; [5]Hannover Med. Sch., Inst. of Med. Microbiology and Hosp. Epidemiology, Hannover, Germany; [6]Helmholtz Ctr. for Infection Res., Braunschweig, Germany

Abstract: *Introduction:* Cerebral malaria (CM) is a complex neurological syndrome of human malaria caused by the parasite *Plasmodium falciparum*. Experimental cerebral malaria (ECM),

induced by *Plasmodium berghei* ANKA (*Pb*A), is the widely used rodent disease model to study CM. Early detection of the disease before the rapid onset of clinical symptoms would aid in development of better anti-malarial treatment regimes.
Objective: To detect the disease before the onset of clinical symptoms and to study the brain pathology associated with the disease progression.
Materials and methods: C57BL/6 mice were injected with *Pb*A-infected red blood cells. One group of mice was treated with pyrimethamine (anti-malarial drug) starting at day 5 post infection (p.i.) (asymptomatic stage) while the control group received PBS. Single-photon emission computed tomography (SPECT) was performed to visualize the changes in regional blood flow. Blood brain barrier (BBB) integrity was monitored by Evans blue staining. Cerebral chemokine and cytokine expression were measured by qRT-PCR. Brain pathology was studied by immunohistochemistry.
Results: Parasite DNA was detectable in the brain at day 5 p.i. suggesting an early accumulation of infected RBCs in the brain. SPECT imaging of untreated mice showed heterogeneous and diffused hypo-perfusion in the cortical region beginning at day 5 p.i, before the onset of clinical symptoms and progressed until day 7 where the mice succumb to the infection. The disturbance of the rostral migratory stream (RMS) could also be detected at day 5 p.i which progressed until day 7 where the RMS was completely disrupted. Further immunohistochemistry analysis showed widespread brain pathology particularly in the olfactory bulb and the brain stem regions. Concomitantly, the chemokine and cytokine responses in these areas were also enhanced. The above mentioned changes were detectable at day 5 p.i, when the BBB was still intact and progressed till day 7 when the integrity of the BBB was disrupted and the mice succumbed to ECM. Treatment of the mice with pyrimethamine from day 5p.i prevented the progression of the brain pathology and protected mice from ECM.
Conclusion: Brain pathology begins in the asymptomatic stage of the disease. Disruption of the RMS and consequently, neurogenesis could explain the loss of neurocognitive functions in human cerebral malaria. Olfactory bulb and brain stem are the worst effected regions of the brain during disease progression. Early detection and treatment would prevent the progression of brain pathology and protect from ECM.

Disclosures: R. Bhattacharjee: None. **K. Harit:** None. **S. Arnim:** None. **E. Budinger:** None. **J. Goldschmidt:** None. **K. Matuschewski:** None. **D. Schlüter:** None. **G. Nishanth:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.10/F39

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Hippocampal inflammation in a mouse model of perioperative neurocognitive disorders

Authors: *X. XIANG[1], G. YANG[2], S. ZHU[1];
[1]Zhejiang Univ., Hangzhou, China; [2]Anesthesiol., Columbia Univ., New York, NY

Abstract: Perioperative neurocognitive disorders include acute delirium and longer-lasting postoperative cognitive dysfunction. Despite the prevalence of these conditions in older adults, the pathophysiology of perioperative neurocognitive disorders remains unknown. Many lines of evidence indicate that systemic inflammation has a profound impact on neurocognitive function. Using ELISA, we found that peripheral surgery caused a transient elevation of proinflammatory cytokine IL-6 in both plasma and the central nervous system, which peaked 6 hours after surgery and returned to baseline thereafter. We then performed transcriptome analysis to further investigate surgery-induced neuroinflammatory responses. Mouse hippocampus was collected 6 hours post-surgery and processed for RNA-Seq. We found a total of 268 genes that showed altered expression levels following surgery, among which 170 genes were up-regulated and 98 were down-regulated. Subsequent functional enrichment analysis identified several KEGG pathways involved in inflammatory mediator regulation of TRP channels, neuroactive ligand-receptor interaction and cholinergic synapses. Quantitative real-time PCR confirmed 15 genes of interest associated with dysregulation of the immune responses. The results of this ongoing study suggest a potential role of hippocampal inflammation in the development of perioperative neurocognitive disorders.

Disclosures: **X. Xiang:** None. **G. Yang:** None. **S. Zhu:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.11/F40

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Holothuria scabra extract reduces cytosolic phospholipase A2 expression induced by Plasmodium yoelii infection

Authors: *S. CHOMPOOPONG[1], L. KWATHAI[1], P. SANGUANWONG[1], P. UAWITHYA[1], I.-C. LIU[2];
[1]Dept. of Anatomy, Fac. of Med. Siriraj, Bangkoknoi, Thailand; [2]Inst. of Med. Sci., Tzu Chi Univ., Hualien, Taiwan

Abstract: Cytosolic phospholipase A2 (cPLA2), the lipolytic enzyme, plays a key role in mediating agonist-induced arachidonic acid (AA) release from membrane phospholipids for eicosanoid production in various cell types. AA is further converted to prostaglandin (PG) by

constitutive cyclooxygenases (COX)-1 or inducible COX-2 during inflammation triggered by tumor necrosis factor-alpha (TNF- α). To confirm the anti-inflammatory effect, whether the ethanol extract of sea cucumber, *Holothuria scabra (*HsE) can reduce cPLA2 in *Plasmodium yoelii* infected mice (Py). At day 5 after infection, Py mice were daily treated for 3 days with HsE,10 mg/kg. Artesunate (As), 32 mg/kg was used as standard anti-malarial drug. HsE has not directly suppressed the parasitic infection of red blood cells. However, co-treatment with anti-malarial drug, HsE+As showed the increase in survival rate of Py mice. The rapid murine coma and behavior score (RMCBS) demonstrated the more improved neurological score in HsE+As group. Western blot analysis resulted on the decrease in cPLA2 at day 8, together with the significant decreased TNF-α and COX-2 expression of brains in Py-HsE mice that showed prolong survival rate ($P<0.05$). In acute plasmodium infection, parasites can bind to Toll-like receptors (TLR) on macrophages and triggering the production of cytokines, reactive oxygen species, and lipid mediators. Therefore, high systemic levels of TNF-α that is both protective (by restricting parasitemia) and pathogenic (by promoting anemia) can promote acute inflammatory responses such as increased vascular permeability, by recruiting leukocytes to the site of infection. The bioactive components of HsE, saponins or triterpene glycosides have also shown the anti-inflammatory effects by regulating the enzymatic activity of cPLA2 and COX-2 in metabolism of AA to PG.

Disclosures: S. Chompoopong: None. **L. Kwathai:** None. **P. Sanguanwong:** None. **P. Uawithya:** None. **I. Liu:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.12/F41

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Narellan Rotary Club

Title: Behavioural and histological changes in cuprizone-fed mice

Authors: *P. J. SHORTLAND[1], M. K. SEN[1], M. S. ALMUSLEHI[1], J. R. COORSSEN[2], D. A. MAHNS[1];
[1]Western Sydney Univ., Penrith, Australia; [2]Brock Univ., St. Catharines, ON, Canada

Abstract: Feeding cuprizone (CPZ) to rodents causes demyelination and reactive gliosis in the CNS; these are hallmarks of some neurodegenerative diseases like multiple sclerosis. Clinically, these conditions cause changes in sensory and motor symptoms, such as pain and loss of motor function. However, relatively little is known regarding the behavioural deficits associated with CPZ treatment and much of what is known is contradictory. This study investigated whether 5

weeks oral feeding of 0.2% CPZ to young adult mice triggers sensorimotor behavioural changes. Behavioural tests included measurement of nociceptive withdrawal reflex responses (Hargreaves and dynamic plantar aesthesiometer) and exploratory behaviour (cylinder) and locomotion (ladder crossing and walking beam) tests and this was compared to histological analysis of the relevant CNS regions by analysis of neuronal and glial cell components. Within 2-3 weeks of CPZ feeding, mice showed hyperactivity using the grooming and rearing tests and crossed ladder more quickly compared to control mice. On both the ladder and beam tests, CPZ mice exhibited more foot slips compared to controls. In contrast, no changes in nociceptive thresholds to thermal or mechanical stimuli were seen between groups. Histological analysis showed demyelination throughout the CNS, which was most prominent in white matter tracts in the cerebrum but also elevated in areas such as the hippocampus and diencephalon. Profound demyelination and gliosis was seen in the cerebellar peduncles, deep cerebellar nuclei and brainstem regions associated with the vestibular system. However, in the spinal cord changes were minimal. No loss of neurons (assessed by neuronal nuclei protein, NeuN) or motoneurons (assessed by choline acetyl transferase, ChAT) staining was found but a significant increase in astrocyte staining (seen with glial fibrillary acid protein, GFAP) was seen throughout the white matter tracts of all levels of the spinal cord. The results suggest that CPZ induces subtle motor changes such as ataxia and that this is associated with deficits in CNS regions associated with motor and balance functions such as the cerebellum and brainstem. This study also provides the first comprehensive histological analysis of demyelination and gliosis in the CNS of CPZ-treated mice.

Disclosures: P.J. Shortland: None. **M.K. Sen:** None. **M.S. Almuslehi:** None. **J.R. Coorssen:** None. **D.A. Mahns:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.13/F42

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Space Biology NASA Postdoctoral Fellowship Award
NASA Space Biology Grant to RKG (NNH14ZTT001N

Title: Overexpression of catalase in mitochondria mitigates changes in inflammatory cytokine levels in the mouse hippocampus due to simulated microgravity and social isolation

Authors: *L. RUBINSTEIN[1], A.-S. SCHREURS[2], C. TAHIMIC[2], S. STEZINA[2], S. THORES[2], M. LOWE[2], A. RONCA[2], R. GLOBUS[2];
[1]NASA Ames Res. Ctr., Mountain View, CA; [2]NASA, Mountain View, CA

Abstract: Spaceflight missions are becoming longer and the physiological toll these missions have on human health is high. Aging, sedentary lifestyle, and spaceflight have degenerative effects on multiple systems, including CNS deficits, and immune dysfunction. We hypothesize that prolonged exposure to the spaceflight environment leads to accumulation of oxidative damage which may lead to neurodegeneration. We used the hindlimb unloading (HU) model to simulate weightlessness in wildtype or transgenic mCAT mice, overexpression human catalase in the mitochondria. HU model is typically conducted in single housing conditions. Since mice are social animals, a social HU model was developed in our lab, enabling us to determine the effects of both social isolation and simulated microgravity. Responses to 30 day of HU were assessed: abundance of 4-Hydroxynonenal (4HNE),Park7,cytokine Luminex array in the hippocampus and in plasma and behavioral data was collected. The analysis of behavior patterns showed that mCAT HU mice were more active and conducted more exploratory activities compared to normally loaded mice. Simulated microgravity and/or social isolation both caused changes in patterns of cytokine protein expression in the hippocampus and in plasma. Two-way ANOVA revealed significant interaction effects of HU and genotype in expression levels of five cytokines (out of 35) amongst socially-housed animals in the hippocampus. Interestingly, elevation of these generally pro-inflammatory cytokines by HU in WT mice was mitigated in MCAT mice, suggesting a role for mitochondrial ROS signaling in inflammatory CNS responses to microgravity. Socially housed mice had lower level of 4HNE in the hippocampus compared to singly housed animals. Substantive cytokine hippocampal changes were observed in the socially isolated mice; protein abundance of 15 cytokines, was significantly higher in single vs social housed animals. This effect was mitigated in MCAT mice, implicating the importance of mitochondrial ROS in social isolation. The cytokine responses to social isolation were more extensive in brain vs plasma. Interestingly, there was no overlap in cytokine responses to microgravity and isolation suggesting two separate mechanisms were involved in response to these stressors. Taken together, our results showed that both simulated microgravity and social isolation affected cytokine levels in the hippocampus and plasma and MCAT mice were at least partially protected from these changes. These findings implicate a potentially important role for mitochondrial ROS in CNS responses to the challenges posed both by prolonged missions in space and bedrest on Earth.

Disclosures: L. Rubinstein: None. **A. Schreurs:** None. **C. Tahimic:** None. **S. Stezina:** None. **S. Thores:** None. **M. Lowe:** None. **A. Ronca:** None. **R. Globus:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.14/F43

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: TNF-alpha, IL-1 beta and myeloperoxidase inhibition contribute to the analgesic and anti-inflammatory curative effects of the aqueous and methanol extracts of paullinia pinnata (sapindaceae) in septic mono-arthritis in rats

Authors: *P. T. TSEUGUEM PUM[1], A. NGANGOUM MOUGA[1], M. KENFACK TSAGUE[1], B. KOLBER[2], K. TIDGEWELL[2], T. NGUELEFACK[1];
[1]Univ. of Dschang, Dschang, Cameroon; [2]Duquesne Univ., Pittsburgh, PA

Abstract: Our previous study showed that the aqueous (AEPP) and methanol (MEPP) extracts from the leaves of *Paullinia pinnata* possess preventive anti-arthritic effects but whether it could treat well established arthritis was still unknown. This work was undertaken to evaluate the curative effect of AEPP and MEPP on Complete Freud's Adjuvant (CFA) induced septic mono-arthritis (SM-A).
SM-A was induced by injecting 50 µl of CFA in the left hind ankle of each rats and *P. pinnata* extracts were administered orally at the doses of 100 and 200 mg/kg for 16th days, starting on the 7th day after CFA injection. Methotrexate (250 µg/kg) was used as reference drug. Hyperalgesia and inflammation were monitored for 24 hours after the first treatment (acute) or for 16 days from the beginning of the treatment (chronic). At the end of the experiment, plasma samples were collected for TNF-α and IL-1β assays. The synovial liquid was collected for MPO quantification and the histo-morphology of the injected ankle was also assessed.
Treatment with the AEPP and MEPP significantly ($p<0.001$) and dose-dependently reduced CFA-induced hyperalgesia by up to 65.6%. *P. pinnata* extracts significantly reduced the ankle/paw oedema with a maximal effect observed at the 4th hour after administration. In the chronic treatment, both extracts induced significant and time-dependent antihyperalgesic and anti-inflammatory effect with up to 97.8% inhibition of pain and complete resorption of inflammation. AEPP and MPP significantly ($p<0.01$) inhibited plasma TNF-α by 51.5%. At all the doses used, both extracts significantly ($p<0.001$) reduced IL-1β by up to 88% and MPO by 90%. *P. pinnata* extracts improved tissue reorganization in treated SM-A rats.
These results shows that *P. pinnata's* leaves extracts possess curative effects against CFA-induced SM-A. The inhibition of TNF-α, IL-1β and the reduction of inflammatory cells infiltration may contribute to these activities.

Disclosures: P.T. Tseuguem pum: None. **A. Ngangoum Mouga:** None. **M. Kenfack tsague:** None. **B. Kolber:** None. **K. Tidgewell:** None. **T. Nguelefack:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.15/F44

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Italian Foundation for Multiple Sclerosis 2014/R/6
Regione Toscana Rare Disease Projects-Heath Projects 2007 and 2009

Title: Neuroimmunological characterization of a mouse model of primary progressive multiple sclerosis and effects of immunosuppressive or neuroprotective strategies on disease evolution

Authors: *G. RANIERI, D. BUONVICINO, S. PRATESI, D. GUASTI, A. CHIARUGI; Univ. of Florence, Florence, Italy

Abstract: Progressive multiple sclerosis (PMS) is a devastating disorder sustained by unknown neuroimmune interactions. Recently, immune-independent, neural bioenergetic derangements have been hypothesized as causative of neurodegeneration in PMS patients. To gather information on the immune and neurodegenerative components during PMS, in the present study we investigated the molecular and cellular events occurring in the NOD mouse model of experimental autoimmune encephalomyelitis (EAE). In these mice, we also evaluated the effects of clinically-relevant immunosuppressive (dexamethasone) or bioenergetic (bezafibrate and biotin) drugs on functional, immune and neuropathological parameters. We found that disease evolution in NOD mice is similar to that of the clinical form of primary PMS, and is characterized by severe neurodegeneration in the spinal cord. Unexpectedly, although CD4 and CD8 lymphocytes but not B or NK cells infiltrate the spinal cord linearly with time, their suppression by different dexamethasone treatment schedules does not affect disease progression. Even the spreading of the autoimmune response towards new immunogenic myelin antigens occurs neither in the periphery nor in the CNS of EAE mice. Conversely, we found that mitochondrial dysfunctions evidenced by altered morphology, reduced contents of mtDNA and decreased transcript levels for respiratory complex subunits occur at early disease stages and precede axonal degeneration within spinal cord columns. However, the mitochondria boosting drugs bezafibrate and biotin are unable to reduce disability progression. Overall, for the first time we show that EAE in NOD mice is featured by early CNS mitochondrial dysfunctions and neuroimmune infiltrates at least in part secondary to neurodegeneration. Data suggest that the EAE NOD mouse model recapitulates primary PMS, and can be harnessed to identify innovative therapies to counteract disease progression.

Disclosures: G. Ranieri: None. **D. Buonvicino:** None. **S. Pratesi:** None. **D. Guasti:** None. **A. Chiarugi:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.16/F45

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Dimethylfumarate plays a protective role against migraine in nitroglycerin-treated mice

Authors: *E. ESPOSITO, G. CASILI, M. LANZA, A. FILIPPONE, I. PATERNITI, M. CAMPOLO, S. CUZZOCREA;
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Abstract: Migraine is a primary headache disorder characterized by recurring, episodic, and unilateral throbbing pain in the head. Cutaneous hyperalgesia occurs during migraine attacks, and is a risk factor for the recurrent attack and chronification of migraine. Exploring the potential mechanisms of this feature may warrant preventive treatment strategies. Systemic administration of NTG causes a delayed spontaneous headache attack. It has been found that the nuclear factor E2-related factor 2/antioxidant response element (Nrf2/ARE) pathway is the most important endogenous antioxidant defense system. However, the role of Nrf2/ARE pathway in hyperalgesia in migraine remains unclear. Thus, the aim of this study was to investigate the involvement of Nrf2/ARE pathway in NTG-induced hyperalgesia.Mice were orally administered dimethylfumarate (DMF) at the doses of 10-100 mg/kg, 5 minutes after NTG intraperitoneal injections. The expression levels of NF-B p65, IκBα, iNOS, COX-2, Nrf-2, Mn-SOD, HO-1 HO, and NQO1 in the trigeminal nucleus caudalis (TNC), were detected by Western blot. Tail flick, hot plate, formalin and photophobia tests were used to evaluate neuropathic pain and migraine-related light sensitivity.DMF upregulated downstream HO1 and NQO1, suppressed TGVS activation, and ameliorated the decrease of tactile thresholds in NTG-induced mice. Our findings indicated that DMF was involved in anti-hyperalgesia through Nrf2/ARE pathway. In addition, the anti-inflammatory effect of DMF, reducing the production of proinflammatory cytokines and microglia activation, may contribute to its role in migraine treatment.Our data provides a novel insight into the potential application of antioxidants as novel candidates in drug development for migraine.

Disclosures: E. Esposito: None. **G. Casili:** None. **M. Lanza:** None. **A. Filippone:** None. **I. Paterniti:** None. **M. Campolo:** None. **S. Cuzzocrea:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.17/F46

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant HD092941

Title: miRNA regulation in early inflammatory signals induced by hypoxic ischemia encephalopathy in neonates

Authors: *T. C. HILLMAN, L. SIEBOLD, J. A. ABDALA, C. G. WILSON;
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Abstract: Hypoxic ischemic encephalopathy (HIE) is a devastating perinatal injury which claims the lives of millions and leaves thousands more with long-term morbidities. Post-HIE insult, an inflammatory response occurs resulting in a cascade of additional damage to the neural circuits surrounding the primary location of insult. Three stages characterize this response: latent (0 to ~12 hours), secondary (12 hours to 3 days) and tertiary (3 days to months). While current therapies work to slow down inflammation (i.e., hypothermia), little is known about the expression and regulation of cytokines during the early inflammatory response (0 - 12 hours). Understanding the early inflammatory response provides a target for treatment of high-risk neonates. Using *Cytoscape* and *Targetscan*, we found that four miRNA targets (miR-155, 146a, 124 and 210) play a key role in neuroinflammation in stroke. We hypothesize that the decreased levels of miR-155, 146a and 124 in HIE increase early pro-inflammatory signaling and promote inflammation immediately following HIE insult. To test this hypothesis, we will analyze cytokine profiles using Western blot and *LEGENDplex* at 1, 2, 6, 9 and 12 hours in Rice-Vannucci (RV) and intrauterine occlusion hypoxia (IUO-H) models. Total tissue samples, isolated from cerebral cortex and hippocampus will be processed using *Qiagen* kits for both miRNA and protein isolation. Expression profiles of both pro-inflammatory and anti-inflammatory cytokines will show a peak in early inflammatory cytokines and allow us to identify key cytokines involved in the early inflammatory response. Additionally, we will determine the role of maternal factors in IUO-H surgery on the expression of cytokine profiles post-HIE insult. Cytokine profiles will provide key expression peaks for pro-inflammatory and anti-inflammatory cytokines post insult. These studies hold the promise of interventional therapy to alleviate the impact of HIE in neonates.

Disclosures: T.C. Hillman: None. **L. Siebold:** None. **J.A. Abdala:** None. **C.G. Wilson:** None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.18/G1

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: The use of curcumin encapsulated dendrimer nanoparticles as anti-inflammatory agents for glioblastoma therapy in C57BL/6J mice

Authors: *N. MUNRO;
Central Michigan Univ., Mount Pleasant, MI

Abstract: Glioblastoma (GB) is an aggressive form of brain tumor. Currently there are no viable treatment options outside of radiation and chemotherapy for this disease. Less than 30% of patients with GB live two years post-diagnosis. GB is known to cause significant inflammation leading to increase in tumor size and metastasis. Therefore, reducing inflammation in GB could be a potential therapy for the cancer. We are utilizing dendrimer nanoparticles (D) with curcumin (a known phytochemical having anti-inflammatory property) encapsulated within the dendrimers. Dendrimers are multi-branched, star-shaped macromolecules with nanometer-scale dimensions. Dendrimers can be defined by three components. The first being a central core, the second being an interior dendritic structure (the branches), and finally an exterior surface with functional surface groups. What makes dendrimers potentially very useful for the treatment of many diseases is that fact that the shielded interior cores can carry cargo within them. For this study, we used Cystamine core (S=S) dendrimer, which has the ability to split in two to dendrons (halves) in the presence of glutathione, which is present at high concentrations in the GB cells. This will enable the curcumin cargo to be delivered within the GB cells thereby rendering their anti-inflammatory properties. WIn addition to Curcumin, when the dendrimer splits, it is converted into its reduced form and forms thiol groups (-SH), having the anti-inflammatory effect. Our *in vitro* study showed that curcumin causes GB cell death while specifically sparing other types of cell such as stem cells and neurons at certain concentrations. In addition, we have showed that Curcumin as well as the cystamine dendrimers show anti-inflammatory effects in cells. OFollowing this, our *in vivo* study involved use of mice having tumor induced by Gl261 cells. Following treatment with dendrimers and dendrimer encapsulated curcumin showed a decrease in astrocytes within the brain suggesting a decrease in inflammation around the tumor site; a decrease in the amount of activated microglia within the brain, also suggesting a decrease in inflammation; and a significant increase in lifespan of mice with GB. Overall our study shows that the use of curcumin encapsulated dendrimer nanoparticles is a viable treatment for GB due to the anti-inflammatory effect and longer lifespan that has been observed.

Disclosures: N. Munro: None.

Poster

567. Neuroinflammation and Animal Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 567.19/G2

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: partialy VIEP-2019

Title: Study of a new analogue of paroxetine 3HPSS in a model of depression induced by lipopolysaccharide

Authors: P. HERNÁNDEZ-ARRAMBIDE, D. CHAMORRO-ARENAS, I. PARRA, I. MARTÍNEZ, F. LUNA, I. D. LIMÓN, V. ALATRISTE, L. QUINTERO, S. CRUZ-GREGORIO, R. MEZA-LEÓN, F. SARTILLO-PISCIL, *L. MARTINEZ MENDIETA; Benemérita Univ. Autónoma de Puebla, Puebla, Mexico

Abstract: Depression is a common psychiatric disorder with a complex and multifactorial etiology, according to WHO, 2018 around 300 million people around the world suffer from it. The study of diseases such as depression in animal models is of great interest to clarify the processes that underlie it, in the same way, the use of drugs in these models helps the development of new therapeutic targets. As a treatment in depression, paroxetine, a selective inhibitor of serotonin reuptake, has shown better results in comparison with other antidepressants. Due to the importance of the development of new drugs, we designed and synthesized a new analog of paroxetine, which is named 3HPSS. Our objective was to evaluate the possible antidepressant and neuroprotective effects of the paroxetine analog in an animal model of depressive behavior. Adult male Wistar rats 280-330g received an injection of LPS [32µg / 2µl] into the dorsolateral striatum by stereotaxic surgery. Animals with LPS received saline, paroxetine or 3HPSS (10 mg/kg i.p. x14 days) the depressive behaviors were evaluated in sucrose preference test, cylinder model, open field and forced swimming, as well as the expression of TH and Caspase-3 in the nigrostriatal pathway. Rats injured with LPS and treated with the paroxetine analog, showed a decrease in depressive behaviors, as well as motor asymmetry. Also, animals treated with LPS had a lower TH-ir and major expression of Caspase-3 in nigrostriatal pathway. The treatment with 3HPSS reduces depressive behavior and motor asymmetry. Moreover, the immunoreactivity to TH and Nurr-1 was improved by 3HPSS treatment. In summary, the new analog of paroxetine, 3HPSS has a high-potential as anti-depressive in the LPS - model.

Disclosures: P. Hernández-Arrambide: None. **D. Chamorro-Arenas:** None. **I. Parra:** None. **I. Martínez:** None. **F. Luna:** None. **I.D. Limón:** None. **V. Alatriste:** None. **L. Quintero:** None. **S. Cruz-Gregorio:** None. **R. Meza-León:** None. **F. Sartillo-Piscil:** None. **L. Martinez Mendieta:** None.

Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.01/G3

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Dr. Miriam and Sheldon G. Adelson Medical Research Foundation
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NIH Training Grant T32 NS007222-36

Title: Characterization of the immune response to sciatic nerve injury: Implications for sensory axon growth and regeneration

Authors: *A. L. KALINSKI[1], C. YOON[2], P. DUNCKER[2], L. HUFFMAN[2], J. ATKINSON[2], B. SEGAL[2], R. GIGER[2];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Univ. of Michigan Med. Sch., Ann Arbor, MI

Abstract: To investigate the immune response to sciatic nerve injury (SNI), adult C57BL/6 mice were subjected to a mid-thigh crush injury. To assess the presence, abundance and phenotypes of immune cells that respond to SNI, we used immunofluorescence staining of tissue sections combined with flow cytometry of *(i)* lumbar DRGs, *(ii)* the proximal nerve stump, *(iii)* the distal nerve stump, and *(iv)* the spinal cord. Changes in SNI-induced gene expression were assessed by RNA-sequencing of DRGs and NanoString analysis of FACS isolated immune cells from injured nerve tissue. As an orthogonal method we measured cytokine and chemokine levels in the nerve and DRGs by luminex. The principal findings are as follows: Neutrophils are the first responders to SNI, they rapidly swarm into the injury site and distal nerve stump, peak around 24 hours, and disappear by 3 days following SNI. Monocytes/macrophages arrive later, peak around day 3 and show a significant decline 7 days post-SNI. Dendritic cells and lymphocytes responded more slowly and gradually increase in the distal nerve. Inflammation in the proximal nerve and DRGs is comparatively mild; with a modest increase in monocytes/macrophages. Experiments with wildtype/TdTomato parabiotic mice revealed that blood-derived immune cells infiltrate the crush site and distal nerve stump, but are largely absent from the proximal nerve, DRGs and lumbar spinal cord. Consistent with flow cytometry, RNA-seq revealed a modest increase in immune cell specific transcripts in de-afferented DRGs. In a similar vein, few cytokines and chemokines show a significant increase in de-afferented DRGs, but they are strongly upregulated in the injured nerve. The monocyte/macrophage population in the injured nerve is highly heterogeneous: cells show a pro-inflammatory $Ly6C^{high}$ phenotype on day 1 that gradually changes to a $Ly6C^{low}$ phenotype on day 3 and day 7 post injury. Ingenuity pathway analysis of RNA-seq data identified GM-CSF (Csf2) as a top regulator of SNI triggered inflammation. In Csf2 knock-out mice, maturation of $Ly6C^{high}$ to $Ly6C^{low}$ monocytes/macrophages is attenuated and conditioning injury induced regeneration of ascending sensory axons in the dorsal columns is significantly compromised when compared to wildtype mice. Collectively, our studies show that SNI triggers a sterile immune response reminiscent of the immune response to injured non-neural tissues, and when perturbed, as in Csf2 KO mice, leads to defects in axon regeneration. Our studies underscore the importance of a carefully orchestrated immune response to successful nervous tissue regeneration.

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Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.02/G4

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Neuroprotective effect of dimethylfumarate on oxaliplatin-induced neuropathic pain

Authors: *M. CAMPOLO[1], G. CASILI[1], I. PATERNITI[1], A. FILIPPONE[1], M. LANZA[1], S. CUZZOCREA[1], E. ESPOSITO[2];
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Abstract: Introduction: Chemotherapy-induced neuropathy is a common, dose-dependent adverse effect of several antineoplastics, like oxaliplatin. It can lead to detrimental dose reductions and discontinuation of treatment, and severely affects the quality of life of cancer survivors.Fumaric acid esters (FAEs) showed beneficial effects in pre-clinical models of neuroinflammation and toxic oxidative stress, so the aim of the present work was to evaluate the potential beneficial effects of dimethyl fumarate (DMF), the most pharmacologically effective molecules among the FAEs,in a model of oxaliplatin-induced peripheral neuropathy.**Materials and methods:**Chemotherapic pain was induced by an intraperitoneally injection of oxaliplatin (oxa) in rats on 5 consecutive days (D0-4) at an injection volume of 0.2 ml for a final cumulative dose of 10 mg/kg. In prophylactic paradigms, DMF was given orally 15-20 min prior oxa. Sacrifice was made on day 25.**Results:**Our results demonstrated that oxaliplatin developed mechano-hypersensitivity (allodynia and hyperalgesia) in rats; this was associated with the hyperactivation of astrocytes and an increased production of pro-inflammatory cytokines (IL-1β and TNF) in the dorsal horn of the spinal cord. Moreover, we showed that oxaliplatin activated NFkB pathway and modulated Nrf-2 ones. The oral injection of DMF attenuated inflammatory and oxidative process, decreasing neuropathic pain.**Discussion and conclusion:**Our findings identify DMF as a therapeutic target in chemotherapy-induced painful neuropathy, throughout the biomolecular signaling NF-κB/Nrf-2 axis. Therefore, we can consider DMF as a promising adjunct to chemoterapy to reduce chronic pain in patients.

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Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.03/G5

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NSF GRFP 1144467
NSF REU DBI 1560389
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Title: Aluminum exposure linked to neurodegeneration in honey bees (Apis mellifera spp.)

Authors: *A. CHICAS-MOSIER[1], T. E. BLACK[2], K. P. HESTER[3], L. BELZUNCES[4], J. L. AGOSTO-RIVERA[5], C. I. ABRAMSON[2];
[1]Integrative Biol., [2]Psychology, [3]Physiol., Oklahoma State Univ., Stillwater, OK; [4]Envrn. Toxicology, Inst. Natl. de la Recherche Agronomique, Avignon, France; [5]Biol., Univ. of Puerto Rico-Rio Piedras, San Juan, PR

Abstract: Poor mining practices and soil acidification increase bioavailability and uptake of aluminum by flora. Contaminated plant tissues are then ingested by other organisms and can cause neurodegeneration by degrading acetylcholinesterase. Aluminum exposure has been implicated in the development of human brain disorders such as Alzheimer's and Parkinson's Diseases. The cholinergic system is conserved across taxa and therefore model species can be used to understand toxicant induced change. This presentation discusses captive survival, individual motility, acetylcholinesterase (AChE) enzyme activity, and brain accumulation experiments in honey bees exposed to aluminum. Captive experiments in *Apis mellifera mellifera* have shown that exposure destabilizes circadian rhythmicity, causes hyperactivity, and decreases lifespan ($p<0.0001$). These data have been corroborated by bee-head AChE enzyme activity and suggest a hormetic response in *Apis mellifera mellifera* ($p<0.0001$). However the AChE response is dependent on subspecies and some tolerance is demonstrated in *Apis mellifera ligustica*. Brain accumulation studies are not yet complete but literature suggests that bioaccumulation of aluminum occurs in bumble bee larvae. The aim of the accumulation studies is to determine if and where aluminum is stored in the bodies of honey bees. The severity of the response to aluminum exposure in completed datasets has been tied to subspecies but effects of aluminum exposure have occurred across *Apis mellifera spp.* We conclude that neurodegeneration from ingesting aluminum is likely a limiting factor to pollinator health and may contribute to population decline in insects, however further understanding of subspecies tolerance is needed. Additionally, given the cholinergic conservation across taxa; these results

indicate that neurodegeneration could occur in other species but subpopulation tolerance requires further study.

Disclosures: A. Chicas-Mosier: None. **T.E. Black:** None. **K.P. Hester:** None. **L. Belzunces:** None. **J.L. Agosto-Rivera:** None. **C.I. Abramson:** None.

Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.04/G6

Topic: C.01. Brain Wellness and Aging

Support: R43 NIH AG16551
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NIH AG05131
Cognitive Clarity Inc.
ProteoTech Inc.

Title: A specific extract from the amazon rain forest plant uncaria tomentosa (cat's claw) is a potent inhibitor and reducer of brain plaques, tangles and inflammation

Authors: *A. D. SNOW[1], G. M. CASTILLO[2], B. P. NGUYEN[2], P. Y. CHOI[2], J. A. CUMMINGS[1], J. CAM[2], Q. HU[2], T. LAKE[1], W. PAN[3], A. J. KASTIN[3], D. A. KIRSCHNER[4], S. G. WOOD[5], E. M. ROCKENSTEIN[6], E. MASLIAH[7], S. LORIMER[8], R. E. TANZI[9], L. LARSEN[8];
[1]Cognitive Clarity Inc, Edmonds, WA; [2]ProteoTech Inc., Kirkland, WA; [3]Blood-Brain Barrier Lab., Louisiana State Univ., Baton Rouge, LA; [4]Boston Col., Boston, MA; [5]Chem. and Biochem., Brigham Young Univ., Provo, UT; [6]Neurosciences, [7]Neurosciences and Pathology, UCSD, San Diego, CA; [8]Chem., Univ. of Otago, Dunedin, New Zealand; [9]Neurol., Massachusetts Gen. Hosp. and Harvard Univ., Charlestown, MA

Abstract: Brain aging and Alzheimer's disease demonstrate the accumulation of beta-amyloid protein plaques, tau protein tangles, and neuroinflammation. Plaques, Tangles and Inflammation (“PTI") is the trilogy that contributes directly to accelerated memory loss and cognitive decline. Over 10 years of research studies are presented that identified a specific plant extract and its constituents as a potential alternative natural solution for preventing and reducing brain plaques, tangles and inflammation. PTI-00703 cat's claw (*Uncaria tomentosa* from a specific source) is a natural plant extract from the Amazon rain forest woody vine identified as a potent inhibitor and reducer of beta-amyloid plaque fibrils, tau protein filaments/fibrils, and neuroinflammation. *In vitro* testing (Thioflavin T fluorometry, Congo red and Thioflavin S staining, electron

microscopy) showed remarkable inhibition of beta-amyloid fibril formation and tau protein filament formation, and near-instant dissolution of pre-formed plaque fibrils and tau tangles. Circular dichroism spectroscopy demonstrated a marked reduction in beta-sheet secondary folding of both beta-amyloid fibrils and tau protein paired helical filaments. Sophisticated structural elucidation studies identified the main constituents in PTI-00703 cat's claw responsible for the observed effects to be specific proanthocyanidins (i.e. epicatechin dimers and variants thereof) as newly identified polyphenolic components within *Uncaria tomentosa* that possess both plaque and tangle reducing and inhibitory activity. One major identified specific polyphenol within PTI-00703 cat's claw was epicatechin-4β-epicatechin (proanthocyanidin B2) that markedly reduced brain plaque load and improved short-term memory in younger and older APP plaque-producing TASD-41 transgenic mice (over 55% in a 3-month period). Proanthocyanidin B2 was also a potent inhibitor of brain inflammation as shown by a marked reduction in astrocytosis and microgliosis in TASD-41 transgenic mice. Cat's claw is previously known to be a potent reducer of both interleukin-1 and TNF-alpha. Blood-brain-barrier studies in Sprague-Dawley rats and CD-1 mice indicated that the major components of PTI-00703 cat's claw crossed the blood-brain-barrier and entered the brain parenchyma and cortex within 2 minutes of being in the blood (following capillary depletion methods). The discovery of a plant extract from the Amazon rain forest as a natural potent inhibitor and reducer of plaques, tangles and inflammation is postulated to represent a potential breakthrough for the non-pharmaceutical approach for brain aging and Alzheimer's disease.

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Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.05/G7

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Michael J Fox Foundation
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Harold and Ronna Cooper Post-Doctoral Fellowship for Parkinson's Disease Research
The Orchard Foundation
The Consolidated Anti-Aging Foundation

Title: C1q knockout mice have elevated sensitivity to glycolipid elevations and show aberrant forms of lipidated alpha-synuclein

Authors: *O. R. BREKK, J. KORECKA, A. MOSKITES, O. ISACSON, P. J. HALLETT; McLean Hosp., Belmont, MA

Abstract: Aging is the most significant risk factor for developing genetic and sporadic neurodegenerative disorders, including Parkinson's disease (PD) and Alzheimer's disease (AD). At the level of genetics, mutations in *gba1* - encoding the lysosomal hydrolase glucocerebrosidase (GCase) - is the strongest predictor of PD risk. We have previously observed age-dependent reductions in GCase activity in PD, and normal aging of both human (Rocha et al., 2015, Ann. Clin. Trans. Neurol.) and mouse brain (Hallett & Huebecker et al., 2018, Neurobiol. Aging), with concurrent accumulation of a variety of glycosphingolipid species (GSLs), including glucosylceramide and glucosylsphingosine. Pharmacological inhibition of GCase by systemic conduritol-b-epoxide (CBE) application as a mouse model of complete GBA loss (Gaucher's-like) induces aggregation of the PD-associated protein alpha-synuclein (aSYN) with concurrent neuroinflammation and induction of the classical complement (CC) innate immunity pathway, as evident by C1q accumulation in the brain (Rocha et al., 2015, Antioxid. Redox Signal.). To assess whether lipid perturbations induced by systemic CBE application could be attenuated by inhibition of canonical CC initiation, we challenged C1q-deficient transgenic mice (C1qKO) with a 28-day chronic CBE paradigm. C1q-deficient mice showed much greater sensitization to CBE compared to WT. Western blot analysis revealed a ~4 times elevation in cleaved C5a compared to WT brains at baseline with further induction upon CBE treatment. Remarkably, at baseline and after CBE treatment, the typical monomeric, soluble aSYN was absent in both C1qKO mouse brain and red blood cells (RBCs). Instead, the C1qKO mice had the insoluble aSYN lipidated species of ~24kDa, which we have previously identified to coincide with normal aging of the mouse brain (Brekk et al., 2019). We interpret the C5a elevation as a compensation in the C1qKO mice to initiate and accelerate the complement cascade. Furthermore, the C1qKO mice have evidence at baseline for lipidation changes of aSYN that is consistent with greater sensitivity to glycosphingolipid challenges.

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Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.06/G8

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Conacyt FC1122
ANR-Conacyt 188565

Title: Huntingtin mediates internalization of the TLR-4 and intracellular signaling in mast cells

Authors: *M. J. PEREZ-RODRIGUEZ[1,2], A. IBARRA-SANCHEZ[1], C. GONZALEZ-ESPINOSA[1], F. PEREZ-SEVERIANO[2];
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Abstract: Mast cells (MCs) are tissue-resident immune cells that modulate local inflammatory reactions related to allergies and tissue damage. MCs are also important on immune responses against Gram-negative bacteria since, after activation of Toll-like receptor 4 (TLR-4) with bacterial lipopolysaccharide (LPS), produce Tumor Necrosis Factor (TNF) and a number of pro-inflammatory and regulatory cytokines. Despite the existing information on the molecular events that lead to the production of pro-inflammatory mediators in MCs, a detailed description of all the molecular elements involved in the phenomenon is far from being complete. Recent evidence in patients with Huntington's disease (HD) suggests that the mutated huntingtin (mHtt) modifies vesicular transport, protein trafficking, and gene expression on distinct cell types that could contribute to the pathology. However, the role of Htt in the process of cytokine secretion in MCs has not been elucidated. In this work, characterization of bone marrow-derived mast cells (BMMCs) from transgenic mice expressing mHtt (line R6/1) was performed by transmission and scanning electron microscopy. Expression of the high affinity IgE receptor (FcεRI) and TLR-4 was evaluated by flow cytometry. Secretion of inflammatory mediators by anaphylactic degranulation or the constitutive pathway was evaluated measuring the release of β-hexosaminidase after FcεRI triggering, or TNFα, IL-6 and CCL-2 production after TLR-4 activation using LPS. The results show that similar shape, size and receptor expression were found in both types of BMMCs, mHtt did not modify the anaphylactic secretion pathway but mHtt-expressing BMMCs secreted significantly less *de novo* synthesized cytokines after TLR-4 triggering. The defect on TNF production was related to the lack of intracellular trafficking of TLR4, absence of ERK1/2 phosphorylation, and TNF mRNA accumulation. The defect was proven to be relevant *in vivo*, in a MCs-dependent model of endotoxemia. Our data show, for the first time, that Huntingtin has a differential participation in the secretion of inflammatory mediators in MCs, which can be potentially relevant for inflammatory reactions in humans.

Disclosures: **M.J. Perez-Rodriguez:** None. **A. Ibarra-Sanchez:** None. **C. Gonzalez-Espinosa:** None. **F. Perez-Severiano:** None.

Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.07/G9

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: The effects of a non-steroidal anti-inflammatory agent on cyclophosphamide induced changes in behavior, hippocampal neurogenesis, and neuroinflammation

Authors: *S. M. PAVLOCK[1], A. KESARWANI[1], D. M. MC CARTHY[2], P. JEAN-PIERRE[3], P. G. BHIDE[1];
[1]Biomed. Sci., [3]Behavioral Sci. and Social Med., [2]Florida State Univ. Col. of Med., Tallahassee, FL

Abstract: Breast cancer is one of the most commonly diagnosed cancers among U.S. women. Breast cancer patients undergoing chemotherapy report behavioral deficits including depression, anxiety, and memory loss, collectively referred to as “chemo brain.” In addition, inflammatory biomarkers are upregulated in breast cancer patients undergoing chemotherapy suggesting that neuroinflammation contributes to “chemo brain”. We hypothesized that anti-inflammatory drugs alleviate chemotherapy-induced behavioral deficits by mitigating neuroinflammation. Intact and ovariectomized female C57Bl/6 mice were placed on a diet containing naproxen (375 ppm), a non-steroidal anti-inflammatory drug, or on a control diet. One-week later cyclophosphamide (CP), a chemotherapy drug that crosses the blood brain barrier was administered (100 mg/kg; i.p.) every 3 days for 2 weeks. Mice were tested in the elevated zero maze (anxiety-like behavior), the Y-maze (spatial working memory), tail suspension test (depression), and a photobeam home-cage activity monitoring system (exploratory behavior and locomotor activity). Following the behavioral testing, the mice were administered bromodeoxyuridine (BrdU; 50 mg/kg, i.p) every 12 hours for 2.5 days. Upon sacrifice, trunk blood and hippocampi were collected to analyze cytokines and hippocampal neurogenesis. All groups of mice displayed significant anxiety-like phenotype. CP decreased exploratory behavior and spontaneous locomotor activity, and naproxen restored both these behaviors to baseline. CP, ovariectomy or naproxen did not produce significant effects on any other behavioral phenotypes. There was a significant CP x ovariectomy interaction on depression-like behavior, with CP producing opposite effects on intact versus ovariectomized mice. Ovariectomy reduced multiple cytokines in the hippocampus and the effect was independent of CP. Hippocampal IL-10 level was significantly influenced by CP. There was a significant CP X naproxen interaction for IL-1α, IL-12p70, IL-2, IL-3 and IL-10. CP decreased BrdU+ cells in the dentate gyrus and decreased

hippocampal volume. Unexpectedly, cytokine levels were increased by naproxen in CP-exposed mice suggesting that neuroinflammation induced by CP was heightened by naproxen. Thus, our data show that CP contributes to chemo brain by producing significant changes in behavior, neuroinflammation and hippocampal neurogenesis. These changes occur in the absence of cancer, and they may be influenced by hormonal factors.

Disclosures: S.M. Pavlock: None. **A. Kesarwani:** None. **D.M. Mc Carthy:** None. **P. Jean-Pierre:** None. **P.G. Bhide:** None.

Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.08/G10

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Studying the role of toxoplasma effector protein GRA15 in the CNS

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Abstract: *Toxoplasma gondii* is an intracellular parasite that causes a chronic, asymptomatic infection of the central nervous system (CNS) in up to 1/3 of the human population. In the immunocompromised, this CNS infection can be fatal. Like most intracellular pathogens, *T. gondii* highly manipulates host cells through the secretion of effector proteins that target host signaling pathways. Some of these effector proteins are polymorphic between different *T. gondii* strains leading to *T. gondii* strain-specific manipulations of host cells. For example, dense granule protein 15 from a type II *T. gondii* strain ($GRA15_{II}$), but not from a type I or type III strain, activates the NFκB pathway in macrophages, leading to strain-specific differences in macrophage polarization. Though the impact of GRA15 has been studied *in vivo* in acute infection, no studies have addressed how $GRA15_{II}$ might affect CNS host cells or the CNS immune microenvironment.
To determine the role of GRA15 in persistent infection, we used CRISPR/Cas9 to generate a type II GRA15 knockout (IIΔ*gra15*) that also secretes Cre recombinase fusion protein (IIΔ*gra15:TCre*) into host cells early in invasion. The IIΔ*gra15:TCre* strain was validated to no longer activate NFκB and be capable of causing Cre-mediated recombination. We then used this strain and a wild-type type II:*TCre* strain to infect mice that express a green fluorescent protein (GFP) only after Cre-mediated recombination, allowing us to track CNS cells injected with the *T. gondii* protein *in vivo*. At three weeks post infection, the brains were harvested and analyzed for several parameters including: the number of GFP^+ neurons, the number of infiltrating T cells and macrophages, and the brain parasite burden. To date, our preliminary data has revealed that compared to the infection with the II:*TCre* strain, the IIΔ*gra15:TCre* strain: i) fails to activate

NFκB, ii) has less dissemination to the CNS, and iii) has a lower CNS parasite burden. Current studies we will perform include a cyst count that will quantify the number of live parasites as the qPCR for B1 picks up all, whether the parasite is alive or dead. We are also generating the complement strain to determine if the original effects of the *gra15* locus are shown. Lastly, we will infect neurons with the II:*TCre* strain and stain for NFκB to determine if the same effects occur in this cell type. Performing these studies will continue to allow us to determine the role of GRA15 on *T. gondii's* ability to disseminate to the brain, establish a chronic infection in the brain, and provoke a CNS immune response.

Disclosures: S. Kumar: None. **A.A. Koshy:** None. **J.A. Kochanowsky:** None.

Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.09/G11

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant AG058109
OSUCOM

Title: Aging modulates inflammatory and behavioral responses to a tumor

Authors: *L. D. STREHLE, A. A. LAHOUD, J. KAUR, J. J. KRUEPKE, J. M. JOHNSON, R. M. BARRIENTOS, L. M. PYTER;
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Abstract: Breast cancer is the most common cancer among women, with the median age of diagnosis being 62. These patients report persistent behavioral issues (mood disorders, cognitive decline), as well as elevations in circulating inflammatory markers. Despite the clinical population consisting primarily of women who have already gone through menopause, few rodent cancer models by which to study underlying mechanisms incorporate aging into their models. Aging and tumors independently increase inflammation and induce anxiety-like behavior and cognitive deficits in rodent models; therefore, we predicted that aging would further exacerbate tumor effects on these endpoints. Aged female balb/c mice (16-17 months old) were ovariectomized (to simulate hormonal menopause); young adult female mice (3-4 months old) with intact ovaries served as controls. Half of the aged mice and half of the young adult mice were orthotopically inoculated with non-metastatic mammary tumor cells; controls underwent a sham surgery. Mice were tested 2.5 weeks following surgery, using a battery of standardized behavioral tests to assess cognitive performance and affective-like behavior (tail suspension test). Blood, tumors, and brain tissue were then collected. Tumors in young mice grow more quickly than in aged mice. Using PCR arrays of hippocampal tissue, tumors in aged

mice increased inflammatory gene expression (*Il-1B, Il-6*), whereas protein concentrations of the same markers decreased. In parallel, tumors decreased immobility in the aged mice only during the tail suspension test. Regardless of age, tumors increased circulating levels of cytokines and chemokines in the blood (Il-2, Il-10, Cxcl1). These results suggest that cancer modulates inflammatory pathways and hippocampal translational mechanisms in an age-dependent manner, indicating the importance of utilizing aged models in understanding breast cancer and its effects.

Disclosures: **L.D. Strehle:** None. **A.A. Lahoud:** None. **J. Kaur:** None. **J.J. Kruepke:** None. **J.M. Johnson:** None. **R.M. Barrientos:** None. **L.M. Pyter:** None.

Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.10/G12

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant R03 NS094071
NIH Grant R01 NS097195
NIH Grant 2P30MH062261

Title: Small molecule ONC201 inhibits HIV-1 replication in brain macrophages via FOXO3a and TRAIL

Authors: *Y. HUANG[1], R. ZHAO[1], Y. LI[1,2], J. ZHENG[2];
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Abstract: Despite the success of antiretroviral therapy (ART), eradication of HIV-1 from brain reservoirs remains elusive. HIV-1 brain reservoirs include perivascular macrophages that are behind the blood-brain barrier and difficult to access by ART. Macrophages express transcription factor FOXO3a and the TNF superfamily cytokine TRAIL, which are known to target HIV-1-infected macrophages for viral suppression. ONC201 is a novel and potent FOXO3a activator capable of inducing TRAIL. It can cross the blood-brain barrier, and has shown an antitumor effect in clinical trials. We hypothesized that activation of FOXO3a/TRAIL by ONC201 will reduce the size of HIV-1 brain reservoirs. Using primary human monocyte-derived macrophages, we demonstrated that ONC201 dose-dependently decreased HIV-1 replication levels as determined by HIV-1 reverse transcriptase activity assay and Western blots for p24. Consistent with data on HIV-1 replication, ONC201 also reduced integrated HIV-1 DNA in infected macrophages in two-step Alu-based nested PCR. Blocking TRAIL or knockdown of FOXO3a with siRNA reversed ONC201-mediated HIV-1 suppression, suggesting that ONC201 inhibits

HIV-1 through FOXO3a and TRAIL. The anti-HIV-1 effect of ONC201 was further validated *in vivo* in NOD/scid-IL-2Rgcnull mice. After intracranial injection of HIV-1-infected macrophages into the basal ganglia, we treated the mice daily with ONC201 through intraperitoneal injection for 6 days. ONC201 significantly decreased p24 levels in both the macrophages and the brain tissues, suggesting that ONC201 suppresses HIV-1 *in vivo*. Therefore, ONC201 can be a promising drug candidate to combat persistent HIV-1 infection in the brain reservoirs.

Disclosures: **Y. Huang:** None. **R. Zhao:** None. **Y. Li:** None. **J. Zheng:** None.

Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.11/G13

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: UW SMPH Dept. of Anesthesiology R&D fund

Title: Differential effects of piroxicam versus minocycline on acute lipopolysaccharide-induced sickness behavior and slow wave EEG activity in young c57bl6 mice

Authors: *Z. W. SULTAN, B. M. KRAUSE, S. M. GRADY, C. A. MURPHY, R. D. SANDERS, M. I. BANKS;
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Abstract: Targeting inflammatory pathways may underlie successful therapies for postoperative delirium. Previously, we have shown bacterial lipopolysaccharide (LPS) given intraperitoneally increases cortical slow wave activity (SWA) during wakefulness in normal C57BL/6 mice, recapitulating electrophysiological signs of delirium. Here we demonstrate that piroxicam, a COX inhibitor, attenuates this LPS response in mice while minocycline, a tetracycline, does not. We evaluated the effects of piroxicam (10 mg/kg) or minocycline (50 mg/kg) treatment on the response to LPS (25 μg/kg) in 4-month old adult C57BL/6 mice. All experiments lasted 6 hours, with IP injections of treatment or vehicle administered after hour 1 and LPS after hour 2. Minocycline/vehicle or piroxicam/vehicle pre-treatment began 2 days and 1 day prior to LPS administration, respectively. Behavioral effects of LPS +/- treatment were assayed by monitoring activity levels, derived from luminance changes in the video signal. Two sets of experiments were performed: 1) behavior-only (n = 16) and 2) simultaneous EEG and behavior (n = 7). In behavioral experiments, mice received minocycline/vehicle or piroxicam/vehicle (n=4 each). In EEG experiments, animals were chronically implanted with skull screws to record cortical activity during behavior (n=3 minocycline, n=4 piroxicam). We compared changes in animal activity and slope of the least-squares fit between 4-second windows of movement and 1-4 Hz power spectral density over hours 4 & 5 relative to hour 1 (baseline).

Animal movement decreased in hours 2 & 3 after LPS injection (95, 96, and 81% decreases from baseline for vehicle, minocycline, and piroxicam, respectively). Piroxicam rescued activity in hour 4 after LPS (7% decrease from baseline compared to 93 and 94% for vehicle and minocycline). Following LPS treatment, the piroxicam group showed smaller increases in slope [mean (SD) frontal channels: 0.26 (0.12); parietal: -0.02 (0.11)] compared to minocycline [0.98 (0.33); 0.53 (0.22)].
These results suggest piroxicam, but not minocycline, attenuates the LPS-driven decrease in activity and increase in SWA during movement in mice. In the future we will seek to understand the neural mediators underlying the relationship between wakeful SWA and systemic inflammation.

Disclosures: Z.W. Sultan: None. **B.M. Krause:** None. **S.M. Grady:** None. **C.A. Murphy:** None. **R.D. Sanders:** None. **M.I. Banks:** None.

Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.12/G14

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Impact of prenatal ZIKV infection on the development of hippocampal and cortical structures

Authors: *R. T. PATEL[1], M. L. SHERER[2], N. A. HAAS[1], M. PARCELLS[3], J. M. SCHWARZ[4];
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Abstract: The widespread epidemic of Zika infection (ZIKV) first reported in the Americas, has uncovered the devastating impact of ZIKV infection especially in pregnant women. ZIKV has emerged as a major challenge for global health agencies due to its ability to cause congenital Zika syndrome which is characterized by brain abnormalities and microcephaly in neonates as well as cognitive developmental challenges in young children. Although, the causal link between ZIKV prenatal infection and serious brain abnormalities seems unquestionable, present findings only offer a limited scope of ZIKV pathogenicity. Pediatricians are now reporting an increased risk of seizures, irritability, and cognitive developmental delays in ZIKV affected children, some of whom appeared asymptomatic at birth Currently, our lab has developed a rat model of prenatal ZIKV infection which results in vertical transmission of the virus to the fetus, produces a significant febrile response in the dams, and a significant increase in cell death in the cortex and hippocampus of surviving affected offspring. Using our model in conjunction with functional magnetic resonance imaging, a non-invasive technique of MRI, we hope to identify

early on which offspring are at later risk for developmental delays in learning so that we can target these individuals for therapeutic interventions. In this study, we find that fMRI shows subtle but significant maturational changes in specific brain regions. This model will allow us to better understand 1) how structural changes in the brain correlate with active infection, 2) when these changes begin to emerge during development, and 3) how they may correlate with or predict the onset of deficits in learning and memory. We demonstrate that prenatal ZIKV infection significantly affects neurodevelopment, suggesting that long-term clinical monitoring of pediatric cases is warranted.

Disclosures: R.T. Patel: None. **M.L. Sherer:** None. **N.A. Haas:** None. **J.M. Schwarz:** None. **M. Parcells:** None.

Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.13/G15

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: IBRO-SfN Travel Grant Award
General Electric Company - GE
The São Paulo Research Foundation, FAPESP

Title: [^{11}C]PIB PET imaging can detect white and grey matter demyelination in a non-human primate model of progressive multiple sclerosis

Authors: *C. C. REAL[1], R. H. CARVALHO[1], S. CININI[2], A. T. GARCEZ[1], F. L. S. DURAN[1], F. L. N. MARQUES[1], L. E. MELLO[2], G. BUSATTO FILHO[1], E. F. J. DE VRIES[3], L. R. G. BRITTO[4], C. A. BUCHPIGUEL[1], D. DE PAULA FARIA[1];
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Abstract: Multiple sclerosis (MS) is a demyelinating and inflammatory disease of the central nervous system. Its diagnosis is clinical, and confirmed by magnetic resonance imaging that is not ideal for discrimination of white or grey demyelination from inflammatory lesions. Positron Emission Tomography (PET), using specific radiopharmaceuticals, can be a tool to differentiate between these processes. [^{11}C]PIB PET is widely used for detection of β-amyloid plaques, but has also been suggested for the analysis of myelin content due to white matter uptake. The aim of this study was to evaluate [^{11}C]PIB PET imaging as a tool for detecting demyelinated regions in white and grey matter of non-human primate model of progressive MS. Experimental autoimmune encephalomyelitis (EAE) was induced in marmosets by injection of recombinant

human myelin oligodendrocyte glycoprotein (rhMOG) emulsified in either Incomplete Freund's Adjuvant (IFA) or Complete Freund's Adjuvant (CFA). The animals were evaluated for neurological signs. [^{11}C]PIB PET images were acquired prior to immunization (baseline) and after the appearance of signs of the disease (end of experiment). Brain tissue was isolated for histological analysis by luxol fast blue and *in vitro* autoradiography with [^{11}C]PIB. PET image analysis was performed with PMOD© 3.4 software. The scans were manually co-registered to a T2 weighted magnetic resonance imaging (MRI) template for marmoset. Volumes of interest for 39 brain regions were drawn on the MRI based on the marmoset brain atlas. All experiments were approved by the Ethical Committee (FMUSP 056/15). All rhMOG/IFA-treated and rhMOG/CFA-treated animals showed clinical signs of EAE, with different aggressiveness. In general, immunization with rhMOG/IFA resulted in a less aggressive EAE model. The body weight loss was significantly higher after immunization with rhMOG/CFA (8.2%, P=0.03). The rhMOG/CFA group presented a significant [^{11}C]PIB uptake reduction only in the left motor cortex (-9.5 %, P=0.008). For the rhMOG/IFA group, significant regional unilateral decreases in [^{11}C]PIB uptake in the right hemisphere of the brain were observed in the splenium of corpus callosum (-38.4 %, P = 0.04), globus pallidus (-22.9%, P=0.04) and tail of the caudate nucleus (-28.9 %, P=0.03). [^{11}C]PIB uptake significantly correlated with luxol fast blue histology (myelin marker), both in the rhMOG/IFA (r^2= 0.32, P < 0.0001) and the rhMOG/CFA group (r^2= 0.46, P < 0.0001). In addition, *in vitro* autoradiography corroborated PET image analyses. [^{11}C]PIB PET imaging is an efficient tool for detecting demyelination in grey and white matter, in a non-human primate model of progressive MS.

Disclosures: C.C. Real: None. **R.H. Carvalho:** None. **S. Cinini:** None. **A.T. Garcez:** None. **F.L.S. Duran:** None. **F.L.N. Marques:** None. **L.E. Mello:** None. **G. Busatto Filho:** None. **E.F.J. de Vries:** None. **L.R.G. Britto:** None. **C.A. Buchpiguel:** None. **D. de Paula Faria:** None.

Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.14/G16

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: DHS #EMW-2013-FP-0766

Title: Transcriptional changes in mouse amygdala and hippocampus after exposure to firefighting overhaul environment

Authors: *S. A. KRAUKLIS[1], S. J. GAINEY[2], J. DRNEVICH[3], A. E. TOWERS[4], S. KERBER[6], D. L. SMITH[7], K. W. FENT[8], G. P. HORN[5], G. G. FREUND[4];
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Pathology, [5]Illinois Fire Service Inst., Univ. of Illinois At Urbana-Champaign, Urbana, IL; [6]Firefighter Safety Res. Inst., Univ. of Loyola-Maryland, Colombia, MD; [7]Dept. of Hlth. and Human Physiological Sci., Skidmore Col., Saratoga Springs, NY; [8]CDC/NIOSH/DSHEFS, Cincinnati, OH

Abstract: In addition to increased respiratory health risks, fire service workers also display an increased incidence of mental illnesses including anxiety, depression, and post-traumatic stress symptoms. Self-contained breathing apparatuses (SCBA) are used by fire service workers to diminish exposure to products of combustion. The use of personal protective equipment, including SCBA is often absent in the overhaul environment, where the building is inspected following the extinction of the active blaze. In examining the effect of exposure to the overhaul environment in lung tissue, we found evidence of overrepresentation of gene expression changes in pathways involved with cancer and immune regulation. The overhaul group (OH) was compared to the fireground group (FG), which was transported to the site of the exercise and placed in the portion of the structure where fire and overhaul did not occur. Due to the implications of neuroimmune pathways on mental illness, we examine the effects of unprotected exposure to overhaul on transcript expression in the amygdala and hippocampus. Amygdalae and hippocampi were harvested 2 hours after removal from the overhaul environment. Total RNA was extracted and submitted for sequencing with 100nt single-end reads. Surrogate variable analysis identified 5 surrogate variables to remove sources of variation, such as day effect. Compared to FG, OH amygdala displayed transcription changes in 1269 genes (FDR $p<0.05$) and the hippocampus showed changes in 1412 genes (FDR $p<0.05$). In the amygdala, 20 of the affected genes are annotated by Gene Ontology for involvement in inflammatory response and 14 of the affected genes are implicated in the activation of the MAPK cascade, which is associated with neuroinflammation, depressive behavior, and cognitive impairment in mice. The apoptotic process is annotated in 43 of the impacted amygdala transcripts and in 53 in the hippocampus. Of the affected hippocampus genes, 15 are identified as playing a role in potassium ion transport by Gene Ontology annotation. Potassium ion flux plays a key role in neuronal hyperpolarization and brain-based inflammasome activation. Thus, our findings suggest unprotected overhaul exposure may impact mental health through the modulation of pathways tied to neuroinflammation and excitotoxicity.

Disclosures: S.A. Krauklis: None. **S.J. Gainey:** None. **A.E. Towers:** None. **J. Drnevich:** None. **G.P. Horn:** None. **G.G. Freund:** None. **K.W. Fent:** None. **D.L. Smith:** None. **S. Kerber:** None.

Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.15/G17

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Sundry Funding, MGH

Title: Immunohistochemical characterization of ACTA2 knockout mice reveals significant vascular, white matter and glial cell abnormalities

Authors: *S. MCCARTHY[1], F. E. HERISSON[2], J. WRIGHT[3], D. MILEWICZ[4], P. L. MUSOLINO[5];
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Abstract: The ACTA2 gene encodes for alpha smooth muscle actin isotope 2 (SMA), a critical component of vascular smooth muscle cells and pericytes. Mutations in this gene can cause smooth muscle cell dysfunction and a severe form of cerebrovascular disease that leads to white matter injury and stroke in childhood. Mechanisms by which the mutant protein causes the disease are still unknown; however, preliminary data indicates mice with mutant heterozygous ACTA2 share aspects of the systemic vascular phenotype with ACTA2 knockout (KO) mice. In this study, our goal is to characterize differences in cellular characteristics of vasculature, white matter, cortical and subcoritical structures in ACTA2 KO mice. We hypothesize that loss of SMA causes abnormalities in the vessels and leads to white matter disease by increased astrocyte and microglial activation. To characterize brain elements, wild type (N=4), ACTA2 KO (N=6), and heterozygous (N=2) mouse strains were sacrificed at 3 months and brains were sectioned for immunohistological analysis. 10x, 20x, and 40x (where necessary) imaging comprehensively visualized the entire brain and provided high resolution images of smaller molecules. ImageJ and Prism Graph Pad were used to quantify differences between strains. Immunohistochemistry of calponin staining in wild type and KO mice revealed large and medium vessel dilation and increased tortuosity of perforating arterioles in KO mouse models throughout cortex and white matter regions. Immunofluorescence of MBP revealed less compacted myelin in the body and forceps of the corpus callosum with decreased thickness in the KO mouse compared to wild type ($p=0.0165$). IBA-1 staining showed depletion of overall microglial count and globular morphology consistent with activated microglia/monocyte phenotype in the cortex and white matter of the KO mice ($p=0.029$). Increased intensity and more prominent arborization of astrocytes was observed by GFAP stain in the KO mice. Endothelial staining with CD31 showed thinner capillaries with increased cells per vessel (quantified by DAPI nuclear stain) and branching patterns ($p<0.001$) distributed in the cortex of both heterozygote and KO mice. In summary, ACTA2 KO mice demonstrate significant diffuse micro and macro vascular abnormalities. White matter injury was observed, as is seen in patients with ACTA2 mutations. Decreased microglial cells, and activation of astrocytes and microglia suggests SMA loss impacts the brain's innate inflammatory system. Further research is necessary to determine functional consequences of these observation as well as developmental and longitudinal aspects of the ACTA2 cerebrovascular phenotype.

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Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.16/G18

Topic: B.11. Glial Mechanisms

Support: RF1 AG057409
R01 AG056259
DP1 DA041722
NRF-2017M3C7A1028945

Title: S-nitrosylation of cathepsin B inhibits autophagic flux, contributing to neurodegenerative disease

Authors: *K. KIM[1], T. NAKAMURA[2], J.-Y. KOH[3], C.-K. OH[4], S. A. LIPTON[5], Y.-H. KIM[1]; [1]Sejong Univ., Seoul, Korea, Republic of; [2]Mol. Med., The Scripps Res. Inst., La Jolla, CA; [3]Univ. Ulsan Col. Med., Seoul-City, Korea, Republic of; [4]Scintillon Inst., San Diego, CA; [5]Ctr. for Translational Neurosci., Scripps Res. Inst. and UC San Diego, La Jolla, CA

Abstract: It is well known that inhibition of autophagic flux or the ubiquitin-proteasome system (UPS) is critical in neurodegenerative diseases because these diseases manifest protein aggregates, including amyloid β, tau, α-synuclein, and mutant huntingtin in brains. In addition, nitric oxide (NO) is known to contribute to neurodegenerative diseases. Therefore, in the present study we examined the possible relationship between NO and autophagic flux. First, we found that addition of exogenous NO donors blocked autophagic flux at both the initiation and final degradation stages. Demonstrating inhibition of initiation of autophagy by NO, we found GFP-LC3 puncta and LC3 II conversion were significantly decreased 2 hr after addition of the NO donor S-nitrosocysteine (SNOC) to GFP-LC3-expressing H4 glioma cells (GL-H4). In contrast, at later time points up to 8 hr after NO addition, we observed accumulation of GFP-LC3 puncta, LC3 II, and p62 protein levels. In addition, using mCherry-GFP-LC3 for monitoring autophagy flux, we found that mCherry red fluorescence was increased by NO, consistent with the notion that autophagic flux was blocked at a step after fusion of autophagosomes and lysosomes. As further evidence, we also observed that protein aggregates of mutant Huntingtin and α-synuclein were increased after exposure to NO. Next, since autophagic flux appeared to be blocked after fusion of autophagosomes and lysosomes, we focused on lysosomal dysfunction and examined whether protease activity of the major cathepsins, cathepsin B (CTSB), cathepsin L or cathepsin D, was inhibited by protein S-nitrosylation. We found that only CTSB was S-nitrosylated, resulting in inhibition of its enzymatic activity. Additionally, the specific CTSB chemical

inhibitor, CA074, also blocked autophagic flux, mimicking exposure to NO. To identify the cysteine residue(s) that is S-nitrosylated in CTSB, we mutated each cysteine residue to alanine; Cys43 in the pro-form of CTSB as well as Cys29 and Cys240 in mature CTSB appeared to be sites of S-nitrosylation because S-nitrosylation was completely abrogated only in the triple mutant. Finally, we also found increases in S-nitrosylation of CTSB and reduction of CTSB activity *in vivo* in the 5XFAD transgenic mouse model of Alzheimer's disease (AD). Our results suggest that S-nitrosylation of CTSB may affect autophagic flux, contribute to the pathogenesis of AD, and represent a novel target for therapeutic intervention.

Disclosures: K. Kim: None. **T. Nakamura:** None. **J. Koh:** None. **C. Oh:** None. **S.A. Lipton:** None. **Y. Kim:** None.

Poster

568. Neuroinflammation and Animal Models II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 568.17/G19

Topic: B.11. Glial Mechanisms

Support: NRF-2017R1D1A1B05028221

Title: Zinc protects against A2E-induced toxicity in ARPE19 cells

Authors: *J. CHOI[1], B.-R. SEO[1], J.-Y. KOH[2], Y. YOON[3];
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Abstract: Accumulation of extracellular aggregates called drusen and degeneration of photoreceptor and retinal pigment epithelial (RPE) cells are hallmark features of dry age-related macular degeneration (AMD). A growing body of evidence indicates that lysosomal dysfunction in RPE cells may contribute to dry AMD pathology. We have previously shown that raising intracellular zinc levels can restore lysosomal acidity and its degradative function (Yoon et al. IOVS, 2010; Seo et al Neurobiol Aging, 2015). In the present study, we examined the effects of raising intracellular zinc on lysosomal alkalization/dysfunction and cell death induced by retinal lipofuscin, A2E.
To induce lysosomal dysfunction in a human RPE cell line (ARPE19), we used A2E. To examine the effect of raising intracellular zinc against A2E-induced changes, we used zinc ionophores (clioquinol and 1H10). A2E accumulation in ARPE19 cells was evaluated by measuring its autofluorescence. Lysosomal pH was measured by using pHrodo™ Red-AM. A2E-induced cell death was quantitatively assessed by measuring lactate dehydrogenase (LDH) activity released into the culture medium.
Twenty-four hours after A2E treatment, ARPE19 cells exhibited A2E accumulation and

decreases in pHrodo™ Red fluorescence (i.e. increases in lysosomal pH), and subsequently underwent cell death. Zinc ionophores reduced A2E accumulation and restored lysosomal pH back to the acidic range. In addition, zinc ionophores substantially reduced cell death induced by A2E. All the effects of zinc ionophores on A2E-induced changes were blocked by the addition of TPEN, a membrane-permeant zinc chelator.
Our results support the possibility that adequate levels of zinc, especially in lysosomes, may help overcome A2E-induced cytotoxic changes in ARPE19 cells, which may contribute to the pathogenesis of AMD.

Disclosures: **J. Choi:** None. **B. Seo:** None. **J. Koh:** None. **Y. Yoon:** None.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.01/G20

Topic: C.09.Stroke

Support: SERB PDF/2017/000137

Title: Improved biopharmaceutic properties of asparagus racemosus root ethanolic extract to confer neuroprotection in cerebral stroke via phytosomal delivery

Authors: *H. AHMAD[1], D. MISHRA[2], R. SAXENA[2], D. MISHRA[2], C. V. RAO[1], A. K. DWIVEDI[2];
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Abstract: *Asparagus racemosus* (AR; also known as Shatavari) roots have been extensively used in traditional systems of medicine. It has been found to possess several neuropharmacological effects like nootropic, antiamnesic, antidepressant and antiepileptic properties. However; like most botanicals its efficient oral use is limited due to issues in solubility and bioavailability. Phytosomes are amphiphilic moieties where the bioactive is anchored through the chemical bond to the polar head of phospholipids. These lipid compatible molecular complexes have been known to be effective carriers of plant based polar bioactives and other botanicals. The authors here have reported preparation of AR loaded phytosomal systems (ARP) aimed at improved biopharmaceutic properties based on assessment of aqueous solubility, surface morphology, zeta potential, physical stability, FT-IR, in vitro dissolution, pharmacokinetic parameters. The neuro-protective effects of ARP were investigated in an experimental ischemia model in rats 1 hour prior to ischemia and 3 hours post reperfusion at 50 mg/kg per oral equivalent dose. It was found that ARP could successfully reduce neurological deficit scoring as well as the infarct size. Findings revealed that 1 hour pre treatment with ARP significantly reduced infarction to about 17.56% compared to a reduction of 41.58% brought

about by AR and likewise a at 3 hours post treatment ARP reduced infarct volume by about 27.22% compared to a 40.28% reduction afforded by AR alone. This study demonstrates that AR can elicit improvement in biopharmaceutic and neuro-protective properties when administered as phytosomes (ARP) and shows promise for carrying on further investigations in its role in alleviating I/R injury in stroke.
Keywords: *Asparagus racemosus*, Shatavari, phytosome, neuroprotection, stroke, ischemia

Disclosures: H. Ahmad: None. **D. Mishra:** None. **R. Saxena:** None. **D. Mishra:** None. **C.V. Rao:** None. **A.K. Dwivedi:** None.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.02/G21

Topic: C.09.Stroke

Title: DNA methylation in neuronal cell death at the early stage of ischemic status

Authors: *M. ASADA[1], H. HAYASHI[1], K. KIKUIRI[1], K. MURAKAMI[1], B. YUAN[2], N. TAKAGI[1];
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Abstract: DNA methylation observed in mammals occurs in cytosine of CpG dinucleotide. Cytosine methylation is mediated by DNA methyltransferases (DNMTs) that transfer methyl groups to carbon C-5 of cytosine and then produce 5-methylcytosine (5mC). Especially, DNA methylation of promoter region is thought to be one of the gene repression mechanisms. Thus, it is an essential epigenetic mark for the gene expression in mammals. It has been reported that DNA methylation is involved in pathogenesis of a number of diseases. In cerebral ischemia, infarct volume is decreased by inhibition of DNMTs. However, it is not fully elucidated about changes in DNA methylation and expressions of DNMTs at the early stage after cerebral ischemia. In this study, we first used a rat middle cerebral artery occlusion / reperfusion (MCAO/R) model for *in vivo* study. Immunohistological staining revealed that 5mC-positive neurons were increased in the ipsilateral cortex. Based on this result, we thought DNA methylation might be occurred in ischemic neuron. Then, *N*-methyl-D-aspartate (NMDA) - induced neuronal cell death was examined using primary cultured rat cortical neurons. We found that 5mC positive neurons were increased until 1 h after NMDA treatment and then decreased to the same level as NMDA untreated group. DNMT3a, one of the *de novo* DNA methylation enzymes, protein expression was not changed until 1 h after NMDA treatment and significantly decreased thereafter compared with untreated group. These results indicated that DNA methylation was promoted in damaged neurons at the early stage after NMDA treatment. We

furthermore determined effects of DNMTs inhibitor RG108 on NMDA-induced neuronal cell death. We demonstrated that the inhibitor protected neurons markedly from NMDA-induced cell death. Consequently, DNA methylation at the early stage of ischemic status may contribute to neuronal cell death.

Disclosures: **M. Asada:** None. **H. Hayashi:** None. **K. Kikuiri:** None. **K. Murakami:** None. **B. Yuan:** None. **N. Takagi:** None.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.03/G22

Topic: C.09.Stroke

Title: Deficiency of the Fn14 receptor enhances synaptic plasticity after acute ischemic stroke and promotes functional recovery without affecting infarct volume

Authors: K. ENNIS[1], D. NAGY[2], S. SU[1], A. THOMAS[1], J. MAHONEY[1], A. NELSON[1], D. MURPHY[3], G. MARSH[2], T. REYNOLDS[2], S. HAMANN[2], C. EHRENFELS[3], R. MASSOL[3], M. ARNOLD[3], M. HAJOS[2], ***L. C. BURKLY**[1];
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Abstract: Synaptic remodeling is thought to underlie functional recovery following acute ischemic stroke (AIS). We postulated that signaling by the microglia-enriched cytokine, TWEAK, through its neuronally-expressed receptor, Fn14, may play a role in synaptic remodeling after AIS based on the identification of Fn14 as a key molecular regulator of synaptic refinement in sensory-dependent visual development in the mouse dorsal lateral geniculate nucleus[1]. It has also been shown that TWEAK and Fn14 mRNA and protein levels are elevated in mouse models of AIS. Here we used a distal middle cerebral artery occlusion + hypoxia (DH-MCAO) mouse model of ischemic stroke that produces somatosensory cortical infarcts and impairments in sensorimotor function, assessed by Erasmus ladder, and hippocampal (HC) basal neurotransmission and long-term potentiation (LTP). Using genetic Fn14 knockout (Fn14KO) mice as a tool to inhibit Fn14 signaling, we assessed the effect of Fn14 deficiency on acute neuronal death and functional recovery in 16-week old male Fn14KO and wildtype (WT) littermate mice after stroke or sham-injury. We first established that naïve Fn14KO mice do not exhibit differences in brain anatomy, histology, cortical and HC dendritic spine density, basal synaptic neurotransmission or synaptic plasticity in HC LTP compared to WT mice. After AIS, Fn14 deletion did not affect infarct size at 24 hours post-stroke, suggesting Fn14 did not mediate acute neuroprotection in this model. However, Fn14KO mice were completely protected against the stroke-induced HC deficits in basal neurotransmission and LTP observed in WT littermates at 12 weeks post-stroke. Notably, the deficits observed in HC slices from WT stroke mice were

normalized by ex vivo addition of an antibody that blocks TWEAK signaling through the Fn14 receptor, consistent with a post-stroke benefit of Fn14 deficiency in vivo. Fn14KO mice were also protected against stroke-induced functional impairment, as shown by a reduced frequency of missteps with the contralateral paws, compared to WT mice as early as 2 weeks following stroke. There was no differential performance between Fn14KO and WT sham-injured animals. We conclude that the Fn14 receptor plays an essential role in synaptic plasticity in both physiological and pathophysiological contexts. Inhibition of the Fn14 receptor following AIS may enhance synaptic plasticity and thereby provide therapeutic benefit to augment functional recovery.

[1] Cheadle, L., Tzeng, C., Kalish, B., Harmin, D., Rivera, S., & Ling, E. et al. (2018). Visual Experience-Dependent Expression of Fn14 Is Required for Retinogeniculate Refinement. *Neuron*, *99*(3), 525-539.e10.

Disclosures: **K. Ennis:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen. **D. Nagy:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen. **S. Su:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen. **A. Thomas:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen. **J. Mahoney:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen. **A. Nelson:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen. **D. Murphy:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen. **G. Marsh:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen. **T. Reynolds:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen. **S. Hamann:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen. **C. Ehrenfels:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen. **R. Massol:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen. **M. Arnold:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen. **M. Hajos:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property

rights/patent holder, excluding diversified mutual funds); Biogen. **L.C. Burkly:** A. Employment/Salary (full or part-time):; Biogen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biogen.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.04/G23

Topic: C.09.Stroke

Title: Therapeutic angiogenesis: Nogo-A targeted therapy promotes vascular and functional recovery following stroke

Authors: *R. RUST[1], L. GRÖNNERT[2], R. Z. WEBER[2], G. MULDERS[2], A. M. SARTORI[1], A.-S. HOFER[1], M. E. SCHWAB[3];
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Abstract: Therapeutic angiogenesis is a promising regenerative strategy to promote functional recovery following stroke. Despite clinical evidence that an increase of angiogenesis in the peri-infarct region is beneficial, no therapeutics promoting vascular growth are currently available. So far, pre-clinical studies almost exclusively focused on supplementation of vascular growth factors, which have been shown to be not safe due to the large hemorrhagic risk. We pursued a different strategy by targeting Nogo-A, a potent inhibitor of neurite outgrowth. More recently, Nogo-A has been shown to be a negative regulator of developmental CNS angiogenesis; its respective function in the ischemic CNS is unknown. We demonstrate that genetic deletion of Nogo-A or one of its corresponding receptors, S1PR2, improves vascular sprouting and repair and reduces neurological deficits after focal cerebral ischemia. These findings were reproduced in a therapeutic approach using intrathecal anti-Nogo-A antibodies; such a therapy is currently in clinical testing for spinal cord injury. These results provide a basis for a therapeutic blockage of inhibitory molecules to improve vascular repair and thus may represent a novel therapeutic option for cerebral ischemia.

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Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.05/G24

Topic: C.09.Stroke

Support: NIH/NINDS 1R01NS096225
American Heart Association 17GRNT33660336
American Heart Association 19PRE34390909
American Heart Association 13SDG1395001413

Title: Neuroprotective role of protein arginine methyltransferases in cerebral ischemia

Authors: *A. COUTO E SILVA[1], C. Y.-C. WU[2], H. POSSOIT[2], G. A. CLEMONS[1], R. H.-C. LEE[2], H. W. LIN[2];
[1]Cell. Biol. and Anat., [2]Neurol., LSU Hlth. Sci. Ctr. Shreveport, Shreveport, LA

Abstract: Cardiopulmonary arrest (CA) is a leading cause of mortality in the USA. CA-induced hypoperfusion contributes to neuronal cell death leading to cognitive impairment. We aim to identify novel neuroprotective therapies which can modulate CBF and provide neuroprotection. We discovered that palmitic acid methyl ester (PAME) is a vasodilator/neuroprotective agent that is released in the presence of arginine derivatives (i.e. L-arginine, N^{ω}-Nitro-L-Arginine). Arginine derivatives are a substrate for protein arginine methyltransferases (PRMTs) that can methylate various biological targets causing pre/post-transcriptional/translational modifications. Because PAME's release is enhanced in the presence of arginine derivatives, our hypothesis is that methylation of palmitic acid (PA) to form PAME via PRMTs is essential to enable PAME's beneficial actions against ischemia, to provide enhancements in CBF, neuroprotection, and functional recovery. We measured CBF via laser speckle flowmetry before and 24 hours after asphyxial CA (ACA, 6 min), a global model of cerebral ischemia. Post-treatment of PAME, but not PA, increased cortical CBF *in vivo* (21.0%±1.0%) to alleviate ACA-induced hypoperfusion. We assessed cell morphology and neurodegenerative stress in the CA1 region of the hippocampus via hematoxylin and eosin, and Fluoro-Jade C (FJC) staining. Our results suggest that the number of normal neurons in ACA rats (492.3±95.6) was significantly reduced as compared to control (909.6±20.1) and ACA+PAME post-treated rats (804.7±27.2). ACA caused an increase in FJC-positive neurons (564.1±75.3), while ACA+PAME alleviated neurodegeneration (170.7±10.2). Moreover, PAME treatment improved working memory function after ACA [alternation ratio ACA (0.26±0.05), ACA+PAME (0.48±0.03)]. We measured mRNA/protein expression of PRMT enzymes to investigate their role in the methylation of PA. Our results suggest that PRMT8 expression is enhanced in the presence of arginine derivatives. PRMT8 is present solely in the central nervous system with no known

function. PRMT8KO mice presented with reduced endogenous regional CBF as compared to wild-type, to suggest a possible role in the methylation of PA. We also measured mitochondrial oxygen consumption rate of hippocampal slices from wild-type and PRMT8KO mice. PRMT8KO hippocampal slices presented with reduced reserve capacity, to suggest that the knockout of PRMT8 results in mitochondrial dysfunction. Overall, our results suggest that PRMT8 plays an important role to maintain CBF and mitochondrial function, and could methylate PA to form PAME, to enhance CBF, neuroprotection, and functional outcomes after CA.

Disclosures: A. Couto E Silva: None. **C.Y. Wu:** None. **H. Possoit:** None. **G.A. Clemons:** None. **R.H. Lee:** None. **H.W. Lin:** None.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.06/G25

Topic: C.09.Stroke

Support: NIH RF1AG042189

Title: MicroRNA (mir)20a-3p preserves astrocyte mitochondrial function in ischemic conditions

Authors: *T. BRANYAN[1,2], R. SRINIVASAN[2,1], F. SOHRABJI[2,1];
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Abstract: Previous work from our lab has shown that astrocytes from middle-aged reproductively senescent (acyclic) rats, who typically sustain larger infarct volumes after stroke, have a reduced functional capacity for glutamate clearance and production of trophic factors as compared to astrocytes from adult (normally-cycling) rats, who typically have smaller infarct volumes. Epigenetic analysis revealed greater H3K4 trimethylation of the promoter region of the mir17-92 cluster in adult astrocytes, and qRT-PCR analysis confirmed increased expression of all members of this cluster including a 240-fold elevation of mir20a-3p. Intravenous injection of mir20a-3p mimics, delivered 4h after induction of ischemia, improved stroke outcomes in middle-aged female rats. *In silico* analysis indicates that mir20a-3p modulates mitochondrial genes. The present study tested the effect of mir20-3p on mitochondrial function in astrocytes under normoxic and ischemic conditions. Cultures of male and female human astrocytes were grown until confluent and assigned to normoxic (21% O_2, 25 mM glucose) or ischemic (1% O_2, 0 mM glucose) conditions for 6 hours. Cells were treated with 50 nM mir20a-3p, 50 nM scrambled control miR or vehicle. Additionally, astrocyte cultures were treated with FAM-labeled mir20a-3p oligos, and imaging of these cells indicates that the miRNA is readily taken up

by astrocytes. We assessed mitochondrial function through Fluorescent Recovery After Photobleaching (FRAP) using Mitotracker deep red as a stain for living mitochondria. Astrocytes subject to OGD or normoxia achieved maximal recovery after photobleaching by ~30 seconds and displayed stable fluorescent signal thereafter. Pretreatment with mir20a-3p significantly accelerated recovery after photobleaching compared to cells pre-treated with scrambled miR or vehicle in normoxia and OGD for both sexes. A significant sex difference was observed in recovery after photobleaching, with the male cells experiencing a dampened effect on recovery in response to mir20a-3p or scrambled treatments. Since the rate of fluorescent recovery measures the continuity of the mitochondrial membranes, these data suggest that mir20a-3p likely promotes mitochondrial fusion or inhibits mitochondrial fission. If greater continuity of the mitochondrial membrane compensates for the greater energy demand required after ischemic injury, these data may also explain why stroke recovery is better in young females as compared to males.

Disclosures: **T. Branyan:** None. **R. Srinivasan:** None. **F. Sohrabji:** None.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.07/G26

Topic: C.09.Stroke

Support: NIH Grant NS100294

Title: Kv1.3 as a pharmacological target for reducing neuroinflammation in the wake of ischemic stroke in both sexes

Authors: Y.-J. CHEN, H. M. NGUYEN, Y. CUI, ***H. WULFF**;
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Abstract: The voltage-gated potassium channel Kv1.3 was first discovered in human T cells in 1984 and has since then been pursued as a target for T-cell mediated autoimmune diseases. Kv1.3 is further expressed on pro-inflammatory M1-like microglia and our laboratory therefore more recently evaluated the small molecule Kv1.3 blocker PAP-1 in models of ischemic stroke and Alzheimer's disease. In both male C57BL/6J mice and male Wistar rats, treatment with PAP-1 started 12 hours after reperfusion reduced infarction and inflammatory brain cytokine levels and improved neurological deficit on day-8 after reperfusion MCAO (Y.-J. Chen et al. 2018). We are now testing the therapeutic hypothesis that Kv1.3 inhibition is equally effective in both sexes. As a first step we established 60-min MCAO with reperfusion in female C57BL/6J mice and found that females have smaller infarcts, but that 16-week old animals of both sexes have qualitatively similar pathologies with similar IBA^{+}-microglia/macrophage and T cell

densities in the infarct and a $GFAP^+$ glial scar surrounding the infarct. Based on patch-clamp recordings performed on acutely isolated $CD11^+$ cells $Cx3cr1^{GFP/+}$ male and female mice exhibit similar Kv1.3 current amplitudes and densities on microglia/macrophages from the infarcted area. Immunofluorescent staining revealed that in both male and female $Cx3cr1^{GFP/+}$ mice Kv1.3 expression increases with time after MCAO, peaks between day-7 and day-15 and is localized to GFP^+ microglia/macrophages and $CD3^+$ T cells in the infarcted area. Since these findings suggest that both males and females would equally benefit from Kv1.3 inhibition following ischemic stroke, we compared 16-week old male and female WT C57BL/6J and $Kv1.3^{-/-}$ mice following 60 min-MCAO with reperfusion. T2-weigthed MRI revealed that Kv1.3-deletion produces a similar improvement in neurological deficit and a reduction in infarct volume in both males (WT: 20.5 ± 1.3%, n = 10; $Kv1.3^{-/-}$: 13.3 ± 1.3%, n = 14; $p < 0.01$) and females (WT: 11.4 ± 1.4%, n = 11; $Kv1.3^{-/-}$: 7.4 ± 1.3%; n = 14, p = 0.03). While we of course still need to test the effect of pharmacological Kv1.3 inhibition in aged animals of both sexes, we believe that our results allow us to hypothesize that Kv1.3 inhibition will be equally beneficial in both males and females by reducing microglia/macrophage and T-cell mediated neuroinflammation.

Disclosures: H. Wulff: None. **Y. Chen:** None. **H.M. Nguyen:** None. **Y. Cui:** None.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.08/G27

Topic: C.09.Stroke

Support: CIHR Grant 390986

Title: Elevation of extracellular glycine levels attenuates deficits following ischemic stroke *in vivo*

Authors: *J. D. CAPPELLI[1], P. KHACHO[2], A. SOKOLOVSKI[3], B. WANG[1], S. RAYMOND[1], P. CHUDALAYANDI[1], A. Y. WONG[4], R. BERGERON[1];
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Abstract: Background: *Ischemic strokes* are the 2nd leading cause of death worldwide and the 1st leading cause of disability, yet there are limited viable treatment options for the at-risk population. Triggered by an arterial obstruction, ischemics strokes cut off the vital supply of oxygen and glucose in the brain. This induces a breakdown of basic neuronal and glial functions, resulting in an increase in the extracellular level of the excitatory amino acid glutamate and overactivation of calcium-permeable *N*-methyl-d-aspartate receptors (NMDARs), inducing cell death. While molecular pathways of stroke have been known for some time, promising NMDAR

antagonists have failed to improve stroke outcome in clinical trials. Thus, alternatives to the direct antagonism of NMDARs are needed. **Rationale:** NMDARs are tetrameric ion channels activated by the simultaneous binding of glutamate and glycine to the GluN2 and GluN1 subunits, respectively. Preliminary *in vitro* data suggests that increasing extracellular glycine levels (>1mM) reduces the NMDAR current amplitude through a process termed glycine-induced NMDAR internalization (GINI). **Objective**: To characterize how elevating glycine levels modulates NMDAR behaviour *in vitro,* and how it can be neuroprotective *in vivo*, following ischemic stroke paradigms. To examine the mechanism through which the pharmacological elevation of brain glycine levels is neuroprotective *in vivo*.**Results:** Our data show that pharmacologically increasing endogenous glycine with the glycine transporter (GlyT1) blocker, *N[3-(4'-fluorophenyl)-3-(4'-phenylphenoxy) propyl] sarcosine* (NFPS), results in a reduction in stroke volumes and cell death in two models of focal ischemia: photothrombosis (PT) and endothelin-1 (ET-1). In addition, animals treated with NFPS had a significant attenuation in behavioural deficits post stroke compared to saline treated animals, in the adhesive removal task and the horizontal ladder task. In order to show that this effect was the result of GINI during stroke, we stereotaxically injected animals with a non-internalizing GluN1 (A714L) Adeno Associated Virus (AAV). The injection of mutant GluN1 did indeed abolish the therapeutic effect of NFPS. Interestingly, our preliminary data suggest that NFPS also attenuates reduction in blood-flow during PT stroke through the COX1/EP4 mediated pathway, using Laser Doppler Flow (LDF) recordings.**Conclusion:** Taken together, our data demonstrate that blockade of GlyT1's is neuroprotective following ischemic stroke. Therefore, this may be a novel means of pharmacologically attenuating stroke symptoms.

Disclosures: J.D. Cappelli: None. **P. Khacho:** None. **A. Sokolovski:** None. **B. Wang:** None. **S. Raymond:** None. **P. Chudalayandi:** None. **A.Y. Wong:** None. **R. Bergeron:** None.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.09/G28

Topic: C.09.Stroke

Title: Post-treatment of sumanirole provide neuroprotection against ischemic stroke injury in rat model

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Abstract: Background and Purpose: Regardless of the rapid increase of the global burden of ischemic stroke, currently, there are few therapeutic option available to lessen tissue death

following a stroke. Recent studies have shown that mitochondria have a decisive role in response to cerebral ischemia and are an effective target for stroke therapy in rodent models. We investigated whether mitochondrial dysfunction and neurocognition is regulated by dopamine D2 agonist, Sumanirole (SUM). **Materials and Methods**: Male Wistar rats (220-250g) were divided into four groups (n=6), and pre-trained for neurobehavioural assessment. After training, Group 2, Group 3 and Group 4 rats underwent transient middle cerebral artery occlusion (tMCAO) for 1 h followed by reperfusion for 23 h. Group 2 rats were received normal saline while Group 3 rats received SUM with the dose of 1 mg/k.g b.wt (s.c.) and Group 4 rats received SUM with the dose of 3 mg/k.g b.wt (s.c.) after 1, 6, 12, and 18 h of occlusion, respectively. The neurobehavioral assessment was done after 24 h to evaluate behavioural deficits. Subsequently, all animals were sacrificed and brain tissue was collected for analysis of oxidative stress parameters and mitochondrial ROS. **Results:** Behavioural deficits like motor in-coordination and loss of grip strength as well as mitochondrial ROS were enhanced in the ischemic injury. However, treatment with SUM significantly attenuated these impairments, depicts reduction in infarct volume, oxidative stress and improvement in mitochondrial oxidative stress. **Conclusion:** The results of our study revealed that SUM ameliorates neurobehavioral deficits, oxidative imbalance and mitochondrial impairments. **Keywords:** Ischemic stroke, Sumanirole, Mitochondria, oxidative stress and Neuroprotection

Disclosures: P. Kaushik: None. **H. Tabassum:** None. **S. Parvez:** None.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.10/G29

Topic: C.09.Stroke

Support: NIH Grant 5R01NS103822-02

Title: N-formyl peptide receptor 2 activation via annexin A1 up-regulates hematoma resolution after germinal matrix hemorrhage

Authors: *J. FLORES[1], Y. DING[2], D. MCBRIDE[3], J. TANG[2], J. ZHANG[2];
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Abstract: Germinal matrix hemorrhage (GMH) is one of the leading causes of morbidity and mortality in preterm infants in the United States with little progress made in its clinical management. Survivors are often afflicted with long-term neurological sequelae, which include cerebral palsy, mental retardation, and post-hemorrhagic hydrocephalus. Blood clots disrupting normal cerebrospinal fluid circulation and absorption after germinal matrix hemorrhage are key

contributors towards post-hemorrhagic hydrocephalus development. n-formyl peptide receptor 2 (FPR2), a G-protein-coupled receptor, has been associated with the activation of scavenger receptor CD36. CD36, a transmembrane glycoprotein, plays an essential role in microglia phagocytic blood clot clearance after GMH and its upregulation has been shown to enhance hematoma resolution and attenuate post-hemorrhagic hydrocephalus. Currently, FPR2's role in blood clot clearance after hemorrhagic stroke is unknown. We hypothesize that FPR2 activation by Annexin A1 will enhance hematoma resolution via upregulation of the CD36 signaling pathway, thereby improving short- and long-term neurological outcomes. Bacterial collagenase (0.3 U) was infused intraparenchymally into the right hemispheric ganglionic eminence in male and female P7 rat pups to induce GMH. Annexin A1 and FPR2 Inhibitor (Boc2) were given at 1-hour post-GMH via intranasal administration. Short-term neurobehavior were assessed using negative geotaxis test. Hematoma volume was assessed using hemoglobin assay. Protein expression was assessed using western blots. Long-term neurocognitive deficits and motor coordination were assessed using Morris water maze, rotarod, and foot fault tests. Nissl staining was conducted on long-term samples to calculate ventricular dilation. We randomly assigned each rat pup to groups and time points without bias 24 hours prior to GMH induction. All investigators responsible for neurobehavior, western blots, hemoglobin assay, ventricular dilation, and data analysis were blinded to experimental groups. Sample size was determined by using a minimum detectable difference in means of 10, a standard deviation of 4, a power of 0.80, and an alpha of 0.05 to determine that 6 animals per experimental group were necessary to gain statistical significance. We have demonstrated that Annexin A1 treatment decreased hemoglobin content and improved neurobehavior at 72 hours post-ictus. Annexin A1 attenuated post-hemorrhagic hydrocephalus and neurological deficits 4 weeks post-ictus. Lastly, treatment increased FPR2 and CD36 expression, FPR2's role in hematoma resolution after GMH.

Disclosures: **J. Flores:** None. **Y. Ding:** None. **D. McBride:** None. **J. Tang:** None. **J. Zhang:** None.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.11/G30

Topic: C.09.Stroke

Support: This study supported by Scientific and Technological Research Council of Turkey (TÜBİTAK) (Project number: 118S131).

Title: The role of 12/15 lipoxygenase inhibition on stroke induced neuroinflammation

Authors: C. CAKIR-AKTAS[1], M. YEMISCI[1], E. EREN-KOCAK[1], T. DALKARA[2], E. BODUR[3], K. VAN LEYEN[4], *H. KARATAS-KURSUN[1];

[1]Hacettepe University, Inst. Neurolog. Sciences&Psychiatry, Ankara, Turkey; [2]Hacettepe Univ. Fac. of Med., Ankara, Turkey; [3]Dept. of Biochem., Hacettepe Univ., Ankara, Turkey; [4]Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Lipoxygenases (LOX) have important roles in stroke, atherosclerosis, diabetes and hypertension. 12/15-LOX inhibition reduces infarct size and brain edema in the acute phase of experimental stroke (1,2). Neuroinflammation has an essential role in the pathophysiology of stroke, however the effect of 12/15-LOX on this process has not been clarified yet. The aim of this study was to investigate the role of 12/15-LOX inhibition by a novel potent 12/15-LOX inhibitor on the neuroinflammation of acute and subacute phases of stroke.

In this study, ischemia/recanalization was performed by Middle Cerebral Artery occlusion (MCAo) with intraluminal filament model in male Swiss albino mice. Either ML351 (50 mg/kg), newly synthesized 12/15-LOX inhibitor (3) or its solvent, DMSO, was injected intraperitoneally at recanalization after 1 hr of occlusion. Mice were sacrificed at 6, 24 and 72 hrs after ischemia induction. Ischemic regions of brain tissue were isolated. Inflammatory cytokines (IL-6, IL-10 and TGF-beta) were quantified by ELISA. We compared the level of cytokines in treatment, control and naïve brain samples (n=3/group). For the detection of microglial activation, mice were sacrificed by cardiac perfusion at each time point. Immunohistochemical staining protocols were performed for a microglia marker, Iba-1.

IL-6, a proinflammatory cytokine, level was increased in the control ischemic brains compared to naïve and significantly reduced (closed to naïve level) by ML351 for each time point of MCAo ($p<0.001$). The anti-inflammatory cytokine IL-10 was decreased in control and significantly increased in the treatment groups ($p<0.001$). However, TGF-beta another anti-inflammatory cytokine was decreased in controls and induced only in subacute phase of ischemia, 72 hrs in the treatment group ($p<0.001$). 12/15-LOX inhibition also diminished microglial activation in the acute phase, in contrast microglia were activated in the sub-acute phase of ischemia. While the proinflammatory cytokine levels were decreased, anti-inflammatory cytokines were increased after ischemia with ML351 treatment. In accordance with this data, the microglial phenotype was switched from M1 to M2 phase at 72 hrs of ischemia according to immunohistochemical Iba-1 signal.

These results suggest that one of the possible mechanisms of 12/15-LOX inhibition involves the suppression of neuroinflammation in both the acute and the subacute phase of cerebral ischemia by decreasing the pro-inflammatory cytokine and increasing the anti-inflammatory cytokine levels. These findings support the earlier studies recommending 12/15-LOX inhibitors as a treatment option for stroke therapy.

Disclosures: C. Cakir-Aktas: None. **M. Yemisci:** None. **E. Eren-Kocak:** None. **T. Dalkara:** None. **E. Bodur:** None. **K. van Leyen:** None. **H. Karatas-Kursun:** None.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.12/G31

Topic: C.09.Stroke

Support: NIH R01 NS099595
AARGD 16-440893
NIH P20 GM109040
NIH R25 GM072643

Title: Intranasal insulin treatment improves functional stroke outcomes in mice

Authors: C. J. SMITH, S. NGUYEN, L. S. WATSON, *C. S. ROBINSON;
Med. Univ. of South Carolina, Charleston, SC

Abstract: Strokes pose both a physical and financial burden on patients, it has been estimated by the CDC that strokes cost the United States $34 billion dollars due to treatment and inability to work. The road to rehabilitation after stroke can be a long strenuous process many recovering stroke patients require physical and cognitive rehabilitation. Often times rehabilitation focus is placed on trying to restore physical abilities while the cognitive deficits are not addressed with the same urgency. Many stroke patients not only require rehabilitation but are also diagnosed with hyperinsulinemia; characterized as elevated levels of insulin circulating in the blood resulting from reduced insulin transport from the periphery to the brain, causing an insulin deficiency. Brian insulin promotes neuroplasticity, synaptogenesis, has anti-inflammatory, anti-thrombotic, vasodilatory, anti-apoptotic properties, and is involved in cognition. The benefits of brain insulin give way to numerous research avenues that promote stroke recovery. We hypothesize that intranasal insulin treatment will improve functional recovery following an ischemic stroke in a mouse model of hyperinsulinemia. To explore our current hypothesis ischemic stroke is induced using a 30-minute middle cerebral artery occlusion (MCAO) in a high-fat diet induced and standard diet induced male mouse model (n>11). The animals are assessed on the following criteria; survival, weight, neurological severity score, motor and cognitive function after receiving either intranasal saline (0.9%) or intranasal insulin (1.75U). Preliminary results indicate high-fat diet-induced hyperinsulinemia leads increased adverse neurological deficits and functional recovery following ischemic stroke. Furthermore, our preliminary studies indicate that intranasal insulin may have advantageous benefits improving functional recovery from stroke in the high-fat mice.

Disclosures: C.J. Smith: None. **S. Nguyen:** None. **L.S. Watson:** None. **C.S. Robinson:** None.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.13/G32

Topic: C.09.Stroke

Support: NIH Grant 5R01NS091146-05
NIH Diversity Supplement 3R01NS091146-05S1

Title: Activation of Jak2/Stat1 pathway by IFN gamma induces CXCR3 signaling and inflammatory response by mouse cerebral endothelial cells and astrocytes

Authors: *E. D. WINFORD[1], S. M. DAVIS[2], K. R. PENNYPACKER[2];
[1]Neurosci., [2]Neurol., Univ. of Kentucky, Lexington, KY

Abstract: Emergent large vessel occlusion (ELVO) is the deadliest form of stroke and is caused by a blockage within a major a cerebral artery, usually the middle cerebral artery. This condition triggers edema, which occurs due to the movement of water into the brain. Cerebral edema can produce massive brain damage which can result in disability and death. Leukemia inhibitory factor (LIF), a neuroprotective and anti-inflammatory cytokine, decreases neurodegeneration and increases survival after intraluminal middle cerebral artery occlusion (MCAO) model, a rat model of ELVO. Previously we have reported that IFNγ is the primary inflammatory mediator in the MCAO model. Treatment with LIF decreases its expression and prevents the upregulation of CXCL10, an IFNγ-inducible chemokine. This study examined the presence of IFNγ on mouse endothelial cells and astrocytes by measuring the expression of CXCL9, another IFNγ-inducible chemokine, and determined the ability of LIF to block IFNγ signaling. Exposing cerebral microvascular endothelial cells to 1 ng/ml IFNγ significantly induced expression of CXCL9 under both normoxic conditions and oxygen-glucose deprivation (OGD). Cells exposed to normoxic conditions were plated and allowed to mature for 7 days, then stimulated with 1 ng/ml IFNγ. At 6, 24, 48 and 72 hours after stimulation, supernatants were collected, and ELISA was used to measure the amount of CXCL9 released. Cells subjected to OGD were allowed to mature for 7 days. On day 7, glucose-free DMEM was added to cells, and they were placed in an oxygen-free chamber for 6 h. After 6 h, the glucose-free DMEM was replaced with glucose-containing DMEM containing 1 ng/ml IFNγ. Supernatants were collected at the previously mentioned time points d, and the concentration of CXCL9 was determined via ELISA. To determine whether IFNγ upregulates CXCL9 via the JAK2/STAT1 pathway, cells were treated with 1 ng/ml IFNγ, 50uM fludarabine (STAT1i) and 100uM AG490 (JAK2i). Treatment with JAK2 and STAT1 inhibitors significantly blocked the induction of CXCL9. Also, these cells were treated with LIF (200 ng/ml) and IFNγ under normoxic conditions and OGD. Surprisingly, LIF + IFNγ significantly increased the release of CXCL9 by endothelial cells exposed to OGD.

One potential explanation for these results is that LIF induces CXCL9 expression to open the BBB. LIF is known to promote an anti-inflammatory phenotype in $CD4^+$ T cells and macrophages. Thus, the opening of the BBB could be to allow anti-inflammatory leukocytes to enter the ischemic brain and promote repair after stroke

Disclosures: E.D. Winford: None. **S.M. Davis:** None. **K.R. Pennypacker:** None.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.14/G33

Topic: C.09.Stroke

Title: Temporal evaluation of heme oxygenase-1 expression in peri-infarct neurons and astrocytes after ischemic reperfusion injury

Authors: *D. SINGH[1], H. WASAN[2], U. SHARMA[3], A. DINDA[4], R. KH[5];
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Abstract: Heme oxygenase-1 (HO1) is a redox-sensitive, inducible and rate limiting enzyme of heme metabolism. HO1 catalyzes heme to Fe^{2+}, carbon monoxide and biliverdin. After ischemia reperfusion, HO1 has demonstrated neuro-protective effects via its anti-inflammatory, anti-apoptotic and anti-oxidant properties. Here, we evaluate the expression pattern of HO1 in peri-infarct neurons and astrocytes at various time points after ischemia reperfusion injury in rats. Middle cerebral artery occlusion model was established in male Wistar rats (260-290 g) after ethical approval. After 60 min of ischemia, doccol suture was removed to produce reperfusion injury. In sham, all procedures were performed except insertion of suture. Rats were sacrificed after 2 h, 8 h, 24 h, 72 h and 7 days of reperfusion. At each time point, MRI was done. HO-1 expression was studied by western blot. For cell specific expression, HO1 was co-localized with neurons and astrocytes using dual immunofluorescence. MR images showed infarct damage after ischemia reperfusion injury at all-time points. Western blot data revealed HO1 expression in peri-infarct region to be significantly increased at all-time points with maximum expression at 24 h ($p<0.01$) of reperfusion when compared with sham. Dual immunofluorescence revealed that HO1 expression in peri-infarct area starts in few neurons and astrocytes at 2 h with slight increase at 8 h of reperfusion. At 24 h after reperfusion, HO1 was expressed significantly high, more in astrocytes than neurons. Though the expression of HO1 was less at 72 h and 7 days as compared to 24 h, it was expressed in astrocytes predominantly. The results showed that HO1 expression was significantly increased mainly in atrocytes as early as 2 h after MCAo with

maximum at 24 h followed by a gradual decrease. Since, increasing HO1 has been neuro-protective; stimulating HO1 at later time points may be a good therapeutic strategy.

Disclosures: D. Singh: None. **H. Wasan:** None. **U. Sharma:** None. **A. Dinda:** None. **R. Kh:** None.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.15/G34

Topic: C.09.Stroke

Support: NIH Grant R21NS095192
NIH Grant R01NS099531
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NIH Grant RO1NS109459

Title: Ascorbate protects against secondary brain damage after focal ischemia via modulation of TET3

Authors: *K. MORRIS-BLANCO[1], M. J. BERTOGLIAT[2], B. CHELLUBOINA[1], R. VEMUGANTI[3];
[1]Univ. of Wisconsin-Madison, Madison, WI; [2]Univ. of Wisconsin - Madison, Madison, WI; [3]Neurolog. Surgery, Univ. of Wisconsin, Madison, WI

Abstract: Ascorbate is an antioxidant and an enzyme cofactor known for its importance in the maintenance of brain function as well as a neuroprotective agent in response to oxidative stress. Recently ascorbate has been identified as a modulator of the ten-eleven translocase (TET) enzymes that produce 5-hydroxymethylcytosine (5-hmC), a CNS-enriched epigenetic modification that is associated with transcriptional activation and neuroprotection. In the current study, we evaluated the role of ascorbate on 5-hmC and its therapeutic potential against ischemic brain injury. Adult mice were subjected to transient middle cerebral artery occlusion (MCAO) and ascorbate was injected intraperitoneally (i.p.) at 5 min, 30 min or 2h of reperfusion. Ascorbate led to robust induction of TET3 activity and 5hmC in the peri-infarct region of the cortex and reduced infarct size at both early and delayed treatment. Knockdown of TET3 by intracerebral injection using siRNA blocked the ascorbate-induced increases in 5hmC and led to increased brain degeneration and mortality. Ascorbate treatment also significantly reduced infarct size and enhanced the expression of several genes involved in neuroprotection in a TET3-dependent manner. We further showed that delayed treatment of ascorbate was also effective at reducing infarct and promoted functional recovery in aged male and female mice and diabetic

male mice. Collectively, these results indicate that ascorbate regulates the 5hmC epigenetic modification in a therapeutic manner.

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Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.16/G35

Topic: A.01. Neurogenesis and Gliogenesis

Support: National Research Foundation of Korea (NRF) grant NRF-2017R1A2B4002704

Title: Changes in the expression of gene associated with retinoid-interferon induced mortality-19 in the dentate gyrus of Camk2α-hetero knockout mice

Authors: *S.-N. HWANG, J.-C. KIM, S. KIM;
The Catholic Univ. of Korea, Seoul, Korea, Republic of

Abstract: Gene associated with retinoid-interferon-induced mortality-19 (GRIM-19) is a subunit of the mitochondrial respiratory chain complex I, required for mitochondrial ATP production. In our previous study, we found that GRIM-19 immunoreactivity was barely detectable in the subgranular zone, but strongly in the granule cell layer that is densely filled with mature granule cells. It was reported that in mice heterozygous for the alpha-isoform of calcium/calmodulin-dependent protein kinase II (Camk2α), most of the hippocampal granule cells fail to mature and remain in an immature state. Therefore, this study was performed to determine cell types of GRIM-19-positive cells in the dentate gyrus of the Camk2α-heterozygous knockout mice (Camk2α-hKO, 12-week-old). Our immunofluorescence study showed that Calbindin (a mature granule cell marker) immunoreactivity was profoundly decreased while Calretinin (an immature granule cell marker) immunoreactivity was significantly increased in the granule cell layer of Camk2α-hKO mice compared with wild-type mice. In addition, GRIM-19 immunoreactivity was profoundly reduced in the granule cell layer of Camk2α-hKO mice as compared to one of the wild-type. In Camk2α-hKO mice, the degree of reduction of Calbindin immunoreactivity was greater than that of GRIM-19. In wild-type mice, double immunofluorescence staining revealed that GRIM-19 was co-labeled in Calbindin-positive cells, but weakly expressed in Calretinin-positive cells in the hippocampal dentate gyrus. In Camk2α-hKO mice, the number of GRIM-19-positive cells co-localized with Calbindin was significantly decreased. Unexpectedly, there was no difference in the number of GRIM-19-positive cells co-localized with Calretinin between wild-type- and Camk2α-hKO mice. Taken together, our data suggest that Camk2α deficiency affects GRIM-19-positive granule neuron maturation in the adult mouse dentate gyrus.

Disclosures: **S. Hwang:** None. **J. Kim:** None. **S. Kim:** None.

Poster

569. Ischemic Stroke IV

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 569.17/G36

Topic: A.01. Neurogenesis and Gliogenesis

Support: This work was supported by the National Research Foundation of Korea (NRF) grant NRF-2017R1A2B4002704.

Title: Differential expression of GRIM-19 (gene associated with retinoid-interferon induced mortality-19) in the dentate gyrus of mouse hippocampus following pilocarpine-induced SE

Authors: *J.-C. KIM, S.-N. HWANG, S. KIM;
The Catholic Univ. of Korea, Seoul, Korea, Republic of

Abstract: Gene associated with retinoid-interferon-induced mortality-19 (GRIM-19), which was previously identified as a tumor suppressor associated with cell proliferation and apoptosis, contributes to the switch between oxidative and glycolytic pathways. Meanwhile, a metabolic switch from glycolysis to oxidative phosphorylation has arisen as key actors of neurogenesis. Recent studies showed that neuronal differentiation is accompanied by a metabolic switch from glycolysis in neural progenitor cell to neuronal oxidative phosphorylation. Thus, the present study investigated the GRIM-19 expression of the mice dentate gyrus in the pilocarpine-induced SE model, leading to increased neurogenesis. Male C57BL/6 mice (10-week-old) were treated with pilocarpine (280 mg/kg, intraperitoneally) and monitored to evaluate seizure stage based on Racine scale. After 2 hours of SE, which was defined as a continuous motor seizure of stage 5 (rearing and falling), diazepam was administered to terminate seizure. The mice which received saline instead of pilocarpine served as control. In our previous study, we found that GRIM-19 was expressed mainly in mature granule cells and in some immature cells, but barely expressed in proliferating cells in the dentate gyrus under normal condition. In the present study, we performed immunohistochemistry and immunofluorescence staining to examine GRIM-19 expression pattern in the dentate gyrus. In addition, double immunofluorescence staining was performed using various cellular markers representing distinct stages of adult neurogenesis: Ki-67 (a cell proliferation marker), Calretinin (an immature granule cell marker) and Calbindin (a mature granule cell marker). After SE, compared with control animals, immunoreactivity of Ki-67 and Calretinin was significantly increased, while Calbindin was dramatically reduced in the dentate gyrus. At that time, GRIM-19 immunoreactivity was markedly decreased in the dentate gyrus following SE. Taken together, these results indicate that GRIM-19 immunoreactivity was correlated with granule cell maturation. From these results, we can raise the possibility that the decreased expression of GRIM-19 affects maturation of granule cells in the adult hippocampus,

probably through inhibiting the metabolic switching from glycolysis to oxidative phosphorylation.

Disclosures: **J. Kim:** None. **S. Hwang:** None. **S. Kim:** None.

Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.01/G37

Topic: C.10. Brain Injury and Trauma

Support: The Department of Defense W81XWH-16-2-0008, BA150111 CDMRP JPC-6.

Title: Long-term preclinical safety evaluation of clinical-grade human neural stem cells in an experimental model of traumatic brain injury

Authors: *A. SIRSY[1], M. SPURLOCK[1], Z. HU[2], A. MAHAVADI[1], M. BOULINA[1], L. QUESADA[1], E. MONEXE[1], M. ANDREU[1], S. GAJAVELLI[3], S. H. GULTEKIN[1], D. A. SHEAR[4], R. M. BULLOCK[1];
[1]Miami Project to Cure Paralysis; Univ. of Miami, Miami, FL; [2]Dept. of Neurosurg., Sun Yat-Sen Mem. Hospital, Sun Yat-Sen Univ., Guangzhou, China; [3]Miami Proj Cure Paral, Univ. Miami, Miami, FL; [4]Ctr. for Military Psychiatry and Neurosci., Walter Reed Army Inst. of Res., Silver Spring, MD

Abstract: Traumatic brain injury (TBI) is a progressive disease, characteristic of disability amongst its survivors due to loss of neural tissue. Transplantation of neural stem cells (NSCs) is an option to potentially mitigate progressive neural damage and restore function following severe TBI. Recently we established a protocol for robust durable engraftment of human fetal neural stem cells (hNSC; Neuralstem Inc.) that have been approved by the FDA-approved for use in Phase I/II clinical trials for other central nervous system injury indications (i.e. amyotrophic sclerosis & spinal cord injury). However, safety/tumorigenicity studies are needed in order to obtain FDA approval for a TBI clinical indication. For this purpose, the goal of the current study was to evaluate the potential tumorigenicity of the transplanted cells in immune-compromised rats subjected to penetrating ballistic-like brain injury (PBBI).
Adult male athymic Sprague Dawley rats were subjected to unilateral PTBI via rapid inflation of an elastic balloon attached to a perforated probe that was stereotactically inserted through the right frontal cortex. Animals were randomized to two groups (n=20 per group). At one-week post-injury, animals received perilesional stereotactic microinjection of vehicle (Group A) or 3 million green fluorescent protein (GFP) expressing hNSCs (Group B). Animals were euthanized at 6 months post-transplantation and tumorigenecity potential was assessed by examining brain and peripheral organ sections for oncogenic features such as abnormal mitoses, nuclear atypia,

and necrosis in hematoxylin eosin (HE) stained section as well as quantitation of Ki67 positive mitotic figures in brains and spinal cords.
The transplanted cells within brain sections showed pleomorphic density with seamless boundaries and no signs of tumorigenicity. Neither morphological nor immunohistochemical indicators indicative of preneoplastic or neoplastic growth were evident in transplanted cells. No abnormal masses were detected in peripheral tissues. While some peripheral tissue masses were detected, these were found to be benign neoplasms common to this species of rodents.
In summary, the current data supports the notion that hNSC can be considered a safe cell therapy option for TBI patients.
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Disclosures: **A. Sirsy:** None. **M. Spurlock:** None. **Z. Hu:** None. **A. Mahavadi:** None. **M. Boulina:** None. **L. Quesada:** None. **E. Monexe:** None. **M. Andreu:** None. **S. Gajavelli:** None. **S.H. Gultekin:** None. **D.A. Shear:** None. **R.M. Bullock:** None.

Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.02/G38

Topic: C.10. Brain Injury and Trauma

Support: NIH grant RO1NS089901

Title: Elevating microRNA-122 in blood for treatment of ischemic stroke, traumatic brain injury, and intracerebral hemorrhage in rats

Authors: *D. LIU[1], X. CHENG[2], B. P. ANDER[4], H. HULL[4], X. ZHAN[5], F. R. SHARP[6], B. STAMOVA[7], G. JICKLING[8], B. G. LYETH[3];
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Abstract: MicroRNAs (miRs) are very promising new generation drug targets due to their unique miR-target binding that is different from the traditional ligand-receptor. A single miR binds to complementary bases in the 3' untranslated regions (3'UTR) of hundreds of target genes and down-regulates these genes.
Our previous studies showed that intravenous (i.v.) miR-122 mimic (2.4mg/kg, wrapped in PEG-liposomes) improves outcomes after suture middle cerebral artery occlusion (MCAO)-induced ischemic stroke (IS) with a 6 hour time window. In pilot whole genome miR expression studies,

we demonstrated that microRNA-122 (miR-122) is the most significantly decreased miR in blood after both lateral fluid percussion -induced traumatic brain injury (TBI) and intraventricular autologous fresh blood-induced intracerebral hemorrhage (ICH) in rats. As compared to sham operation controls, miR-122 decreased 7 fold at 3 hrs, 39 fold at 24 hrs, 21 fold at 7 days and 24 fold at 14 days in blood after TBI in rats. In comparison, miR-122 decreased 28 fold at 3 hrs, 34 fold at 24 hrs, 31 fold at 7 days and 19 fold at 14 days in blood after ICH in rats. These miR-122 expression data suggest that elevating miR-122 in blood has great potential to treat TBI and ICH.
Therefore, we hypothesized that i.v. miR-122 mimic improves outcomes after TBI and ICH, in addition to IS. Using experimental TBI and ICH models, our data show that miR-122 mimic (2.4 mg/kg, i.v.) decreases BBB disruption at 24 hours after ICH and reduces cognitive deficits at 11-15 days after TBI. Our miR-122 targetome studies show that a set of miR-122 target genes (Pla2g2a, Vcam1, Nos2, Rhbdf1, Olig1, Nrep) are responsible for the therapeutic efficacy of miR-122 mimic on ischemic stroke, while another set (Pla2g5, Ywhaq, Grm1) account for efficacy in ICH. Using 3'UTR luciferase reporter assays and anti-sense Morpholino Oligos (MOs), we show that miR-122 binds to 3'UTR of its target genes Pla2g2a and Vcam1, rather than Nos2. In addition, *in vivo* MO-miR-122-Pla2g2a blocks miR-122 mimic treatment-induced decrease of Pla2g2a in blood cells after ischemic stroke. Although the targetome study of miR-122 on TBI is still ongoing, we predict that a different set of miR-122 target genes are responsible for the efficacy of miR-122 mimic to improve TBI outcomes.
In summary, our data suggest miR-122 mimic can treat IS, TBI and ICH. Therefore, the miR-122 mimic treatment for these acute brain injuries could likely be performed without brain imaging (e.g. in the ambulance, on the battlefield) since it is equally efficacious for IS, TBI, ICH.
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Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.03/G39

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant NS095116

Title: Intranasal insulin improves cognitive function and reduces anxiety-like behavior after repeated mild brain injury

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Abstract: Following a mild traumatic brain injury (mTBI) there is a period of vulnerability to repeated injury, during which a second impact may have worsened outcomes. Our previous research shows that a second impact at 24 hours after an initial mTBI will significantly worsen function and histopathological measures of injury, and that this may be due to a period of depressed cerebral glucose uptake. We have also shown that intranasal insulin can significantly improve outcome after moderate TBI. In order to determine if insulin delivery during the period of vulnerability can improve outcome after a repeated mTBI (rmTBI), we performed a mild lateral fluid percussion (LFP) injury in adult male Sprague Dawley rats followed by intranasal saline (vehicle) or insulin at 4 hours and 24 hours post-injury. A second mild LFP was then performed and behavioral tests assessed. Cognitive function was assessed with the Morris Water Maze task at days 11 - 14 post-injury. While a rmTBI did not significantly affect latency to find a hidden platform, it did significantly alter search strategy in the probe trial test in comparison to naïve rats. This altered search strategy was returned to naïve levels with insulin administration between the 2 mTBI impacts. To assess post-injury anxiety-like function, Open Field, Light-Dark Box and Elevated Zero Maze tests were performed. Rats exposed to rmTBI and saline administration showed a significant increase in anxiety-like behavior, with less time in the center of the open field and more grooming behavior in the periphery of the test. Insulin administration between mTBI impacts significantly increased time in the center of the open field and reduced grooming behavior. While rmTBI rats showed significant reductions in entries into the light area with the Light-Dark box in comparison to naïve rats, insulin did not alter this behavior. No significant effect of injury was noted in the Elevated Zero Maze test. These data demonstrate that rmTBI can negatively affect aspects of memory and anxiety, and that insulin administration during the vulnerable period can reverse these effects. Additional assessment is needed to fully understand the pathophysiology of this response and of insulin's mechanism. However, these data show the promise of intranasal insulin in the treatment of rmTBI.

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Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.04/G40

Topic: C.10. Brain Injury and Trauma

Support: This work is supported by Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (AMRF) to ES and AS

Title: Chemokine receptors CCR5 & CXCR4: Potential targets for enhancing recovery after traumatic brain injury

Authors: *Y. FRIEDMAN-LEVI[1], S. LIRAZ-ZALTSMAN[2,1], G. GINCBERG[1], E. L. KESNER[1], A. J. SILVA[3], E. SHOHAMI[1];
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Abstract: **Background**: In recent years, chemokine receptors CCR5 and CXCR4, have been investigated in the context of cognitive deficits, neuropathic pain, HIV-associate neurocognitive disorders and stroke-related learning and memory dysfunction in human and rodents. CCR5 was shown to negatively regulate CREB activation, and inhibition of CCR5 signaling enhanced learning, memory and plasticity processes in hippocampal and cortical circuits (Zhou et al. eLife 2016). Moreover, mice with CCR5 knockdown and patients with a naturally occurring CCR5Δ32 loss of function mutation were found to have enhanced motor recovery and reduced cognitive deficits after stroke and traumatic brain injury (TBI) (Joy et al. Cell 2019). In the present study we investigated changes in the expression of CCR5 and CXCR4 after TBI in mice. To this effect we used flow cytometry analysis to measure the expression and co-expression of these receptors in several different time points post closed head injury (CHI) on cortical and hippocampal neurons, astrocytes and microglia. Additionally, we examined the effect of pharmacological blockers Maraviroc (for CCR5) and Plerixafor (for CXCR4), both FDA-approved drugs, on expression levels of these receptors, on motor and cognitive functions and on biochemical and pathological features in the brain. Finally, we investigated the immune response of the treated mice post CHI. **Results:** Cortical and hippocampal CCR5 and CXCR4 levels increased after CHI and the most significant changes in all 3 cell types were found on days 3 and 11. We found that Maraviroc and Plerixafor lead to significant improvement in post-CHI cognitive functions, and Plerixafor also improved motor function. Moreover, we demonstrated a significant increase in the number of hippocampal neurons and hippocampal area, reduced lesion volume and ventricular size, and increased phosphorylation level of the NR1 subunit of NMDAR. Changes in levels of CCR5 and CXCR4 expression on neurons, astrocytes and microglia were also noted along with reduction in the levels of infiltrating cells into the cortex. **Conclusions:** In this study we have elucidated the negative effect CCR5 and CXCR4 chemokine receptors exert on recovery after CHI and recognized these receptors as new potential targets for enhancing recovery following TBI. We identified the time points post CHI in which the expression of these receptors is maximal, and were able to design effective treatments based on FDA - approved drugs, that block these receptors and may serve as potential treatment for individuals suffering from functional decline after TBI.

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Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.05/G41

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant 1R01NS100710-01A1

Title: Mesenchymal stem cell-derived exosomes improve functional recovery in female rats after traumatic brain injury

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Abstract: Background: Our previous study has demonstrated that exosomes derived from bone marrow mesenchymal stem cells improve functional recovery in male rats subjected to traumatic brain injury (TBI). The aim of this study was to determine the therapeutic effects of exosomes on functional recovery in female rats subjected to TBI. **Methods:** Anesthetized female age-matched young rats (2-3 months) subjected to moderate TBI induced by controlled cortical impact over the left parietal cortex were randomly divided into the following treatment groups (n=8/group): 1) phosphate-buffered saline (PBS as Vehicle group); and 2) exosomes administered at 1 day (Exo group) post TBI. PBS or exosomes at a dose of 100 μg/rat were injected via a tail vein in 0.5 ml PBS for 5 min starting at 1 day after TBI. Sham female animals with surgery without treatment were included as TBI controls (Sham, n=8). We performed the functional tests 1 day and then weekly post-injury including footfault, adhesive removal, modified neurological severity score (mNSS) and Morris water maze tests (MWM). Animals were sacrificed at day 35 after TBI for future histology study of the brains. **Results:** We found that female TBI rats exhibited spontaneous functional recovery specifically for forelimb footfault and adhesive removal tests and these functions were fully recovered at 28 days post injury, and there was no difference in footfault and adhesive removal functions between Vehicle and Exo groups. However, treatment with exosomes at a dose of 100 μg/rat starting 1 day post TBI significantly reduced mNSS score at 28 days and 35 days compared to Vehicle group ($p<0.05$). Importantly, exosome treatment significantly improved cognitive function (reduced the latency and increased % time spent in the correct quadrant in the MWM test) in female TBI rats compared to Vehicle-treated TBI rats ($p<0.05$). **Conclusion**s: Our data demonstrate that exosome treatment initiated at 1 day post-injury at a dose of 100 μg/rat provides a significant therapeutic effect on functional and cognitive recovery in female rats after TBI.

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Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.06/G42

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant R03DE025906

Title: Unrepaired open craniectomy worsens motor skill impairment in a rat traumatic brain injury model

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Abstract: Decompressive craniectomy (DC) is often required to manage intracranial pressure (ICP) after traumatic brain injury (TBI). Traditionally it involves cranial bone removal at the time of TBI followed by cranioplasty in a delayed fashion. In humans, this can lead to neurological morbidities called syndrome of the trephined. Our long-term goal is to evaluate the use of novel expansile materials that allow for a single stage DC and cranioplasty in the hopes of averting two operations and complications of syndrome of the trephined. In our initial studies, we are utilizing a rodent model of traumatic brain injury (TBI) to test these new materials. The purpose of the present study was to characterize neurological impairment following TBI in rats with an unrepaired craniectomy (DC group) and rats with a closed cranium using a standard non-expansive acrylic following TBI (Cranioplasty group). Long Evans male rats received a controlled cortical impact (CCI) over the caudal forelimb area (CFA) of the motor cortex using a commercial impact device with a 3mm dia. rod with a 1.5 m/s impact velocity delivered at a 2 mm depth from the dura with an impact time of 100 milliseconds. The CFA was exposed with intact dura using a 5 mm cranial trephination. Immediately after CCI rats received either a larger 1 cm craniectomy over the damaged hemisphere (DC group) or an acrylic cranioplasty sealing the cranial vault immediately after impact (Cranioplasty group). Motor performance was assessed on a skilled reaching task on post-CCI weeks 1 - 4, 8, 12 and 16. Three weeks after the CCI injury, the cranioplasty group showed more improvement in motor skill than the DC group. The cranioplasty group continued to perform better than the DC group throughout weeks 4, 8, 12 and 16. Post-mortem assessment of the dorsal surface of the brains from each group 4 mos. after the CCI revealed cortical swelling. The DC group showed more extensive swelling then the cranioplasty group with brain parenchyma protruding through the open cranial vault. The

protracted recovery of motor skills seen after the large craniectomy suggests this model may be beneficial for testing the efficacy of new materials for cranioplasty in rodent TBI models.

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Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.07/G43

Topic: C.10. Brain Injury and Trauma

Support: MOST 104-2923-B-038-004 -MY2
MOST 107-2314-B-038-063
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TMU 106-5310-001-400

Title: Targeted and improved homing of mesenchymal stem cells overexpressing fibroblast growth factor 21 to injury site in a mouse model of traumatic brain injury: Real-time MRI tracking study

Authors: *R. A. SHAHROR[1,2,3], A. ALI[4], C.-C. WU[5,6,3], Y.-H. CHIANG[1,3,5,6], K.-Y. CHEN[1,2,3];
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Abstract: Mesenchymal stem cells (MSCs) are emerging as a potential therapeutic intervention for brain injury due to their neuroprotective effects and safe profile. However, the homing ability of MSCs to injury sites still needs to be improved. Fibroblast Growth Factor 21 was recently reported to enhance cells migration in different cells type. In this study, we investigated whether MSCs that overexpressing FGF21 (MSC-FGF21) could exhibit enhanced homing efficacy in brain injury. We used novel Molday IONEverGreen™ (MIEG) as cell labeling probe that enables a non-invasive, high-sensitive and real-time MRI tracking. Using a mouse model of traumatic brain injury (TBI), MIEG labeled MSCs were transplanted into the contralateral lateral ventricle followed by real-time MRI tracking. FGF21 retained MSC abilities of proliferation and morphology. MSC-FGF21 showed significantly greater migration in transwell assay compared to control MSC. MIEG labelling showed no effects on MSCs' viability, proliferation and

differentiation. MRI revealed that FGF21 significantly enhances the homing of MSC toward injury site. Histological analysis further confirmed the MRI findings. Taken together, these results show that FGF21 overexpression and MIEG labelling of MSC enhances their homing abilities and enables non-invasive real time tracking of the transplanted cells, provides a promising approach for MSC based therapy and tracking in TBI.

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Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.08/G44

Topic: C.10. Brain Injury and Trauma

Support: The Miami Project to Cure Paralysis
NIH/NINDS NS069721

Title: Dual allosteric modulator reverses traumatic brain injury induced cognitive impairments

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Abstract: Traumatic brain injury (TBI) causes long-term neurocognitive disabilities in a significant number of chronic survivors. Thus, effective therapeutic strategies to ameliorate chronic learning and memory deficits after TBI are greatly needed. α5 subunit-containing $GABA_A$ receptors ($GABA_ARs$) and α7 nicotinic acetylcholine receptors (nAChRs) are key regulators of hippocampal network activity and mediate hippocampal dependent learning and memory. Simultaneous allosteric modulation of both the α7 nAChR and α5 $GABA_AR$ with the drug 522-054 induces long-term potentiation (LTP) and enhances cognitive functioning in normal animals. In the present study, we tested the effects of 522-054 on the reversal of deficits in hippocampal synaptic plasticity, and learning and memory in the chronic recovery period of TBI. Adult male Sprague Dawley rats received moderate parasagittal fluid-percussion brain injury or sham surgery. At 3 months after recovery, basal synaptic transmission and LTP at the Schaffer collateral-CA1 synapse was assessed in acute hippocampal slices. TBI caused a significant reduction in basal synaptic transmission and expression of LTP. Bath application of 522-054 (0.1 μM) reduced deficits in basal synaptic transmission and reversed the impairments in LTP expression. Given the reversal of LTP deficits with 522-054 treatment, we tested whether hippocampal dependent learning and memory after TBI could be restored. At 3 months after

recovery, animals received vehicle or drug 522-054 (0.03 mg/kg, intraperitoneally) at 30 minutes prior to training on contextual and cue fear conditioning and the water maze task. TBI significantly impaired cue and contextual fear conditioning as well as water maze acquisition and retention. Treatment with 522-054 during training on both of these tasks reduced deficits in cue and contextual fear memory and water maze acquisition and retention. These results suggest that dual allosteric modulation of cholinergic and GABAergic signaling may be a potential therapeutic to reverse the deficits in hippocampal synaptic plasticity and restore cognitive functioning after TBI.

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Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.09/H1

Topic: C.10. Brain Injury and Trauma

Support: CANDS Grant HU0001-14-1-0030

Title: A ketone mono-ester, 3-hydroxybutyl-3-hydroxybutyrate, attenuates sensory and motor deficits in a CCI model of TBI in male Sprague-Dawley rats

Authors: *C. P. ALMEIDA-SUHETT[1,3], A. NAMBOODIRI[2], K. CLARKE[4], P. DEUSTER[1]; [1]Consortium for Hlth. and Military Performance, Dept. of Military Emergency Med., [2]Dept. of Anatomy, Physiology, and Genet., Uniformed Services Univ. of the Hlth. Scienc, Bethesda, MD; [3]Henry M. Jackson Fndn. for the Advancement of Military Med., Bethesda, MD; [4]Dept. of Physiology, Anat. & Genet. (DPAG), Univ. of Oxford, Oxford, United Kingdom

Abstract: Introduction: Traumatic brain injury (TBI) is a leading cause of death and disability and can lead to long-term morphological and functional deficits. There is no effective therapy to control the progression of injury and prevent the development of neurological deficits after TBI. Ketone-ester supplementation has been shown to be neuroprotective in animal models of neurodegenerative disorders. However, its efficacy in reducing TBI pathophysiology is yet to be determined. **Methods:** A 2x2 factorial design was used to assess the neuroprotective effect of the ketone ester, 3-hydroxybutyl-3-hydroxybutyrate (ΔG®), in male Sprague-Dawley rats (n=32; 8 rats/group) submitted to a controlled cortical impact (CCI) model of TBI. Sham animals were exposed to the CCI surgical procedure but did not receive the brain impact. The rat diet was supplemented with either water or ΔG® by oral gavage (0.5 mL/kg/day) and in water at 0.3% concentration ad libitum. At 28 days post injury, the Neurological Severity Scale-Revised (NSS-R) test was used to assess neurological motor and sensory damage in all rats. Animals were then

perfused, their brains removed, frozen and sliced at 40 μm. A 1-in-5 series of brain sections were stained in cresyl violet and used for stereological quantification of the lesion volume. Data were analyzed using analysis of variance (ANOVA) and analysis of covariance (ANCOVA). **Results:** NSS-R test scores in the CCI group with ΔG® supplementation were 1.16 (SD=0.44), significantly ($p<0.05$) lower than the CCI group with a control vehicle (water) at 4.43 (SD=0.46). There were no significant differences found between the CCI + ΔG®, Sham + ΔG®, and Sham + Control Vehicle (water) groups. Similarly, NSS-R motor scores in the CCI + ΔG® group (0.62+/-0.74) were significantly lower ($p<0.05$) compared to CCI group scores (2.87+/-1.45). There were no significant differences found between the CCI + ΔG®, Sham + ΔG®, and Sham + Control Vehicle (water) groups for both NSS-R total and motor scores. The mean volume of the lesion reduced from 17.32 mm^3 (SEM=10.6) in the CCI group with a control vehicle (water) to 10.1 mm^3 (SEM=3.1) in the CCI group with ΔG® supplementation ($p < 0.001$). **Conclusion:** Ketone ester supplementation improved sensory and motor reflexive behavior in the NSS-R assessment and reduced the lesion volume. Our data suggest that ΔG® supplementation is neuroprotective against TBI-induced morphological and functional deficits. **Disclaimer:** The views expressed are those of the authors and do not reflect an official position of the Uniformed Services University or the United States Department of Defense. Authors have no financial interests or relationships to disclose.

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Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.10/H2

Topic: C.10. Brain Injury and Trauma

Support: Minnesota Office of Higher Education Spinal Cord Injury/Traumatic Brain Injury Grant Program

Title: Human non-hematopoietic umbilical cord blood stem cell treatment reduces inflammation following traumatic brain injury in rats

Authors: *M. R. CHROSTEK[1], A. T. CRANE[1], V. D. KRISHNA[2], N. L. EMMITT[2], N. G. TOMAN[3], W. J. SWANSON[4], E. G. FELLOWS[3], M. L. SHIAO[1], M. C. CHEERAN[2], W. C. LOW[1], A. W. GRANDE[1];
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Abstract: There are an estimated 2.9 million traumatic brain injuries (TBI) reported in the United States each year. Many patients who suffer TBI develop long-term motor and cognitive deficits but have few available treatment options. Following trauma to the brain, a neuroinflammatory response is generated which can exacerbate the initial injury and cause further damage. Chronic neuroinflammation following TBI is associated with neurological decline and offers a target for therapeutic intervention. By modulating the immune response following TBI, neuroinflammation may be reduced leading to improved neurological function and recovery. Here we tested the immunomodulatory effects of human non-hematopoietic umbilical cord blood stem cell (nh-UCBSC) therapy in a rat TBI model. Female Sprague-Dawley rats received a unilateral, controlled cortical impact injury to the primary and secondary motor cortices. Two days after injury rats received either 1 million nh-UCBSC or a vehicle administered through the femoral artery. Different groups of rats were sacrificed at two, seven, and thirty days post-treatment, and assessed using flow cytometry and immunohistochemistry to examine immune system response. Additionally, behavioral testing was conducted to evaluate functional recovery. Following TBI, compared to naïve uninjured controls, there were increased numbers of inflammatory immune cells, primarily neutrophils, in the injured, ipsilateral region of the brain. In the periphery higher neutrophil counts were also noted in the blood. nh-UCBSC treatment of rats with TBI returned neutrophil counts in the brain and blood to the levels similar to the naïve uninjured controls. TBI rats with nh-UCBSC treatment also had increased lymphocyte and NK cell levels in the brain. These results indicate that nh-UCBSC treatment can modulate the immune system following TBI and reduce neuroinflammation which may lead to improved recovery. Of additional interest, the changes in neutrophil numbers in the blood may offer a biomarker which could be useful for monitoring neuroinflammation and evaluating anti-inflammatory treatments.

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Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.11/H3

Topic: C.10. Brain Injury and Trauma

Title: Daily contextual manipulations are critical for success in a hippocampal dependent rehabilitation task following experimental traumatic brain injury

Authors: *L. M. LAW[1], D. R. GRIFFITHS[1], J. LIFSHITZ[2];
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Abstract: Traumatic brain injury (TBI) is not a transient event from which all people recover; the resulting damage can evolve into neurological disease. As with patients, experimental TBI disrupts rodent memory circuits, evident as impaired cognitive performance. Experimental rehabilitation strategies, such as enriched environment and exercise, have partial success in alleviating symptoms. New rehabilitation strategies are necessary to demonstrate therapeutic efficacy and explore cellular mechanisms that promote recovery. Diffuse brain injury by midline fluid percussion leads to cognitive impairments by 1-month post-injury, permitting a timeframe to implement and investigate delayed interventions. Rehabilitation occurs in a box with a peg-board floor that allows for 10cm plastic pegs to be inserted at 2.5cm intervals in designated layouts; termed Peg Forest Rehabilitation (PFR). Brain-injured rats were exposed to PFR (15 min/day), allowing free navigation through either random daily layouts or the same layout daily in the peg-filled arena for 10 days over 2 weeks. The current study compared random daily PFR (dynamic) layouts versus the same PFR (static) layout for two weeks in male and female brain injured rats. We hypothesized that dynamic daily arrangements, not static, are necessary to prevent the onset of injury-induced memory impairments by challenging the limbic memory circuit. Previous results show that 2 weeks of PFR prevents the onset of cognitive deficits in injured rats for short-term, long-term, and working memory. Preliminary data revealed no differences between males and females, so they were combined for analyses. As previously shown, brain injured rats exposed to the dynamic PFR did not exhibit any deficits on 3 cognitive assessments. Interestingly, rats exposed to the static PFR were impaired when compared to the dynamic condition rats. Thus, passive, dynamic, intermittent rehabilitation targeting specific circuitry can prevent cognitive symptomatology. The Peg Forest is a viable rehabilitation strategy to explore cellular and molecular mechanisms to preserve neurological function.

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Poster

570. Traumatic Brain Injury: Therapeutic Strategies

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Program #/Poster #: 570.12/H4

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant T32AI132164
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VA Merit Award 1I01RX001141
VA Merit Award 1BX001218

Title: Reversing cognitive decline in chronic traumatic brain injury with targeted complement modulation

Authors: *K. MALLAH[1], A. ALAWIEH[1], R. CHALHOUB[2], F. LANGLEY[1], M. YORK[1], H. BROOME[1], S. TOMLINSON[1];
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Abstract: Introduction: Cognitive decline is a major chronic complication of traumatic brain injury (TBI). There are no therapeutic interventions for post-TBI dementia due to poor understanding of the pathophysiological mechanisms linking TBI to cognitive decline. We investigated the role of complement-driven neuroinflammation in neurodegeneration post-TBI, and investigated the effect of complement inhibition in cognitive recovery post-TBI. **Methods:** TBI was induced in adult mice using controlled cortical impact (CCI). Animals were housed for 1 or 2 months before administration of CR2-Crry, an injury-site targeted complement inhibitor, administered by a single or repeated intraperitoneal injections. Animals were then housed in enriched environments (to model rehabilitation therapy) and monitored for 2-6 months after CCI. Cognitive (Barnes maze) and motor testing (neurological deficit, ladder task) were performed. Brains were extracted for histological analyses. **Results:** Following CCI, cognitive performance on spatial learning task continued to deteriorate over 6 months of recovery. There was continued perilesional complement C3d deposition for 6 months after CCI, and significant microgliosis and astrogliosis that involved bilateral brain hemispheres. We observed a significant increase in size of astrogliotic scar at 90d compared to 7d and 30d after CCI. Repeat dosing with CR2-Crry starting either 1 or 2 months after CCI resulted in reversal of cognitive decline compared to vehicle treated animals. Treatment with CR2-Crry did not reduce lesion size after CCI, but significantly reduced the extent of microgliosis in the brain at 2-6 months after CCI. Declining cognitive performance in vehicle treated animals was associated with complement-dependent synaptic loss, which was inhibited by CR2-Crry treatment. **Conclusion:** Cognitive decline after TBI is dependent on ongoing neuroinflammation that can be inhibited with targeted complement inhibition as late as 2 months after injury. Complement inhibition may be a potential treatment for patients with chronic TBI who start to demonstrate signs of cognitive decline.

Disclosures: K. Mallah: None. **A. Alawieh:** None. **R. Chalhoub:** None. **F. Langley:** None. **M. York:** None. **H. Broome:** None. **S. Tomlinson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stephen Tomlinson is an inventor on a licensed patent for CR2-targeted complement inhibition..

Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.13/H5

Topic: C.10. Brain Injury and Trauma

Title: Nmda receptor modulation with NYX-458 rescues cognitive impairment and peripheral growth hormone levels in a clinically relevant rat model of repeat concussion

Authors: *L. P. CACHEAUX[1], K. LEADERBRAND[1], R. J. WILSON[1], J. S. BURGDORF[1,2], M. E. SCHMIDT[1], S. U. SAHU[2], J. R. MOSKAL[1,2];
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Abstract: N-Methyl-D-Aspartate receptors (NMDARs) are a family of ligand-gated ionotropic glutamate receptors that are highly expressed in the central nervous system (CNS). NMDAR-mediated excitotoxicity, and later NMDAR hypofunction, have been implicated in the neurobehavioral sequelae of traumatic brain injury (TBI). NYX-458 is a synthetic, small-molecule, orally bioavailable NMDAR modulator that facilitates hippocampal long-term potentiation and enhances performance in several learning and memory tasks in rodents. Here, a model of repeat closed head injury in adult rats was first characterized and then employed to evaluate the therapeutic potential of NYX-458 in TBI. Compared to sham treatment, repeat TBI resulted in glial activation and altered central cytokine and chemokine expression profiles, as well as reduced NMDAR expression and phosphorylation. Relative phosphorylation of several NMDAR-associated intracellular signaling molecules, including CaMKII and ERK1/2, was also reduced in this model. Behaviorally, TBI rats demonstrated deficits in the forced alternation Y-maze and positive emotional learning tasks. Pituitary dysfunction, and in particular growth hormone deficiency, is often seen in humans with TBI and is associated with cognitive deficits in these patients. Serum growth hormone was significantly reduced in TBI *versus* sham-treated rats, and this effect, as well as performance in both behavioral assays, were rescued by systemic administration of NYX-458. Finally, there was a trend towards elevated serum corticosterone in TBI rats compared to sham-treated rats, and in TBI rats, NYX-458 treatment significantly reduced corticosterone compared to vehicle treatment. Together, these data support the further investigation of NYX-458 in ameliorating cognitive and pituitary dysfunction as a result of head trauma. NYX-458 is in clinical development for the treatment of Parkinson's disease cognitive impairment and demonstrated a favorable safety, tolerability, and pharmacokinetic profile in a Phase 1 study in healthy volunteers.

Disclosures: L.P. Cacheaux: A. Employment/Salary (full or part-time):; Aptinyx Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx Inc. **K. Leaderbrand:** A. Employment/Salary (full or part-time):; Aptinyx Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx Inc. **R.J. Wilson:** A. Employment/Salary (full or part-time):; Aptinyx Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx Inc. **J.S. Burgdorf:** A. Employment/Salary (full or part-time):; Aptinyx Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx Inc. **M.E. Schmidt:** A. Employment/Salary (full or part-time):; Aptinyx Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx Inc.. **S.U. Sahu:** None. **J.R. Moskal:** A. Employment/Salary (full or

part-time):; Aptinyx Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx Inc..

Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.14/H6

Topic: C.10. Brain Injury and Trauma

Support: MOST 107-2314-B-038-042

Title: Neural protection and regeneration by inhibition of cholinesterase in TBI animals

Authors: *Y.-H. CHIANG[1], S.-C. HSUEH[2], W.-C. CHANG[3], C.-C. WU[1], K.-Y. CHEN[2]; [1]Dept. of Surgery, Sch. of Medicine, Col. of Med., [2]The Ph.D. Program For Neural Regenerative Med., [3]Grad. Inst. of Med. Sciences, Col. of Med., Taipei Med. Univ., Taipei, Taiwan

Abstract: Traumatic brain injury (TBI) is a leading cause of death and long-term physical or mental condition disability in the developed world. By 2020 TBI will comprise the third largest portion of the global disease. Within the first year after injury, 70-90% of patients continue to manifest prolonged and constantly permanent neurocognitive dysfunctions. Recently, the emerging evidence indicates that this process of TBI can lead to early onset of dementia. TBI is a strong environmental risk factor for development of Alzheimer's disease (AD). Our previous data have shown that (-)-phenserine (Phen), an acetylcholinesterase inhibitor originally designed and tested in clinical Phase III trials for Alzheimer's disease (AD), can reduce neurodegeneration after mild TBI. In addition, Phen can also inhibit neuronal apoptosis following ischemia/reperfusion injury. Here, we used a mouse model of moderate to severe TBI by controlled cortical impact (CCI) to assess the neuroprotective effects of Phen. Animals were treated with Phen (2.5 mg/kg, IP, BID) for 5 days and the effects were evaluated by behavioral histological and western blot examinations at 1 and 2 weeks after injury. Phen significantly attenuated TBI-induced contusion volume, enlargement of the lateral ventricle, and behavioral impairments in motor asymmetry, sensorimotor functions, motor coordination and balance functions. After injury, the morphology of microglia was shifted to an active from a resting form, and Phen dramatically reduced the ratio of activated to resting microglia, suggesting that Phen can diminishes neuroinflammation after TBI. While Phen has potent anti-acetylcholinesterase activity, its (+) isomer Posiphen shares many neuroprotective properties but is almost completely devoid of anti-acetylcholinesterase activity. We evaluated Posiphen at a similar dose to Phen and found similar mitigation in lateral ventricular size increase, motor asymmetry, motor coordination, and balance function, suggesting the improvement of these histological and behavioral tests by Phen treatment occur via pathways other than anti-acetylcholinesterase (AChE) inhibition. However, the reduction of lesion size and improvement of sensorimotor

function by Posiphen were much smaller than with equivalent doses of Phen. Taken together, these results show that post-injury treatment with Phen over 5 days significantly reduces the effects of TBI, suggesting Phen might be a potential compound for clinical use in TBI therapy.

Disclosures: Y. Chiang: None. **S. Hsueh:** None. **W. Chang:** None. **C. Wu:** None. **K. Chen:** None.

Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.15/H7

Topic: C.10. Brain Injury and Trauma

Support: National Health Research Institutes and Central Government S & T Grant 06A1-NPSP06-034
National Health Research Institutes and Central Government S & T Grant 07A1-NPSP11-034
National Health Research Institutes Grant 06A1-CSPP10-014
National Health Research Institutes Grant 07A1-CSPP10-014

Title: Divergent effects of gliptins on the pathological outcomes in a mouse model of traumatic brain injury

Authors: *Y.-W. HUNG, Y. WANG, S.-L. LEE;
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Abstract: Traumatic brain injury (TBI) causes severe disability and mortality. Limited direct therapies are available. Modulation of incretin level seems to offer therapeutic effects against several neurodegenerative disorders. It is, thus, hypothesized that active incretin enhancement by gliptins through inhibiting dipeptidyl peptidase-4 (DPP-4) may also reduce the neuropathological progression caused by mechanical trauma. In the present study, we explored the therapeutic effects of two structurally different gliptins in a controlled cortical impact model of TBI. A moderate TBI was stereotaxically delivered to the right sensorimotor cortex of mice. Gliptins were fed to the animals daily following the injury. Sitagliptin and vildaglptin augmented similar level of active glucagon-like peptide-1 in blood and brain. Only sitagliptin mitigated neurological impairment, brain lesions, and microglial activation. Expression of the anti-inflammatory cytokine IL-10 was elevated by sitagliptin in damaged cortex and striatum. In contrast, a structurally-different DPP-4 inhibitor vildagliptin did not produce similar neuroprotective or anti-inflammatory effects. Our data support a favorable protective effect of sitagliptin against TBI.

Disclosures: **Y. Hung:** None. **Y. Wang:** None. **S. Lee:** None.

Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.16/H8

Topic: C.10. Brain Injury and Trauma

Support: NIH grant 1 R01 NS111037-01
NIH grant P20GM103444
SC-SCIRF grant 2017 B-01

Title: Rolipram loaded polymeric micelle nanocarrier reduces inflammatory response and apoptosis after traumatic brain injury

Authors: ***C. MACKS**[1], D. JEONG[1], M. LYNN[2], J. LEE[1];
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Abstract: Traumatic brain injury (TBI) is a leading cause of hospitalization and death with many patients living with long-term disability. Following injury to the CNS, the level of cyclic adenosine monophosphate (cAMP) drops due to increased degradation by phosphodiesterase 4 (PDE4). The cAMP level in the CNS is linked with neural growth cone development, regenerative capacity of adult neurons, and reduced levels of pro-inflammatory cytokines. Additionally, many extracellular inhibitors of neuroplasticity, including chondroitin sulfate proteoglycans and myelin associated inhibitors, act through the RhoA and Rho kinase (ROCK) pathway. Rolipram (Rm), a hydrophobic drug, restores cAMP level by inhibiting PDE4 and can improve functional recovery, reduce cell apoptosis, and reduce inflammatory cell infiltration. The goal of our work is to develop a nanotherapeutic for combinatorial delivery of Rm and siRNA targeting RhoA. To accompl ish this goal, we synthesized a cationic, amphiphilic, copolymer (poly(lactide-co-glycolide)-graft-polyethylenimine: PgP) capable of loading hydrophobic drugs and complexing nucleic acids. In this study we investigate the effect of cAMP restoration by Rm-PgP on secondary injury in a rat controlled cortical impact injury (CCI) model for TBI. The Rm was loaded to the hydrophobic core of PgP through solvent evaporation method and the amount of Rm loading was determined by HPLC. A craniotomy (5 mm diameter) centered at 3.5mm posterior and 3.5mm lateral of the bregma was performed and the injury generated using an Impactor at 3.5m/s and a depth of 2mm using a 3mm tip. Animals were divided into 3 groups: Sham, untreated TBI (20µL, Saline), and Rm-PgP (20µL, 16µg Rm). Immediately after injury, Rm-PgP was administered by intraparenchymal injection in the lesion site. At 7days post-injury, brains were retrieved for cAMP level by ELISA assay. For histological analysis, rats were euthanized at 7days post-injury by caridac perfusion with 4% PFA, brains collected, and cryosectioned (30µm). Sections were stained with cresyl violet for

lesion volume and by IHC for ED1 (macrophages/microglia) and GFAP (astrocytes). To assess apoptosis, TUNEL assay was performed. We demonstrated that Rm-PgP treatment restores cAMP to a level not significantly different from sham level for up to 3days post-injury. Additionally, we demonstrated that cAMP restoration by Rm-PgP significantly decreased lesion volume, improved neuronal survival, reduced inflammatory cell infiltration, and reduced astrogliosis compared to untreated TBI. In the future, we will evaluate the synergistic effect of Rm-PgP and PgP/siRhoA treatment on secondary injury in a rat CCI TBI model.

Disclosures: C. Macks: None. **D. Jeong:** None. **M. Lynn:** None. **J. Lee:** None.

Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.17/H9

Topic: C.10. Brain Injury and Trauma

Support: CAPES
CNPQ
FAPERJ

Title: Intravitreal injection of mesenchymal stem cells expressing hIGF-1 increases mouse retinal ganglion cells survival and axonal regeneration in a model of optic nerve crush

Authors: *J. F. VASQUES[1], C. A. ABREU[1], L. CHIMELI-ORMONDE[1], B. S. F. SOUZA[3], M. B. P. SOARES[3], R. MENDEZ-OTERO[2];
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Abstract: Introduction and objectives: Retinal ganglion cells (RGCs) are the output neurons of vertebrate retina, and their axons form the optic nerve. RGCs present poor regenerative capacity and their axons do not regenerate at long distances after damaged. Also, axonal damage leads to death by apoptosis of most of RGCs. There are actually no clinically applicable therapies to protect RGCs and restore axonal integrity in an efficient and sustainable way. Therefore, cell therapy emerges as a promising approach that can be easily translated to clinical practice. Recently, bone marrow-derived cells have been used to promote cell survival and regeneration in several preclinical models. In rat model of optic nerve crush, our group recently demonstrated that mesenchymal stem cells (MSC) intravitreally injected remained in eye at least for 18 weeks, leading to sustained protection of RGCs and robust axonal regeneration. However, no visual function recovery was detected. In the present work our goal is to potentiate the protective and regenerative effect of MSC therapy. Considering that many effects evoked by MSC therapy were associated with the trophic factor, cytokines and other molecules secreted by those cells, a novel

promising tool is the genetic modification of cells in order to overexpress specific molecules of interest. Regarding SNC lesions, the insulin-like growth factor-1 (IGF-1) is a potential candidate, due to its neuroprotective and neuroregenerative actions. Therefore, we used mouse transgenic MSC line expressing the human trophic factor IGF-1 (mMSC-hIGF1). Methodology: SvEv129 adult mice were submitted to optic nerve crush and simultaneous intravitreal injection of vehicle, 200.000 mMSC-hIGF1 or control-mMSC. 14 days after surgery eyes and nerves were removed. Retinas were dissected and immunohistochemistry for TUJ1, marker of RGCs, was performed. Axonal regeneration was measured by CTB incorporation, injected intravitreally. Results and discussion: Injection of 200.000 mMSC-IGF1 cells lead to a significant increase (90% higher than vehicle) in RGC survival after optic nerve crush. This neuroprotective effect was more robust than the evoked by control-mMSC, which was already significant in relation to non-treated animals Moreover, axonal regeneration was also increased in mMSC-IGF1 animals, in relation to control-mMSC and vehicle groups. Also, axons from mMSC-IGF1 animals reached further distances in optic nerve. Our data suggests that IGF-1 is capable to potentiate neuroprotective and proregenerative actions of MSCs. It remains to be determined whether this effect is sustained and if it also results in functional recovery.

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Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.18/H10

Topic: C.10. Brain Injury and Trauma

Support: MN Office for Higher Education: Spinal Cord Injury/Traumatic Brain Injury Grant Program

Title: Viral reprogramming of reactive astrocytes to neurons as a therapy for cerebral injury

Authors: *E. G. FELLOWS, A. T. CRANE, N. G. TOMAN, A. R. STEEVENS, M. R. CHROSTEK, A. W. GRANDE;
Neurosurg., Univ. of Minnesota Med. Sch., Minneapolis, MN

Abstract: Cerebral injury is a leading cause of long-term disability and death worldwide. Common neurological hallmarks of cerebral injury include neuronal loss and reactive astrocytosis. However, current treatments fail to target cellular disruption and improve functional recovery. A novel approach to address neuronal loss is direct reprogramming of reactive astrocytes to neurons following injury. In this method, viral vectors designed to transduce astrocytes force the expression of proneural genes, thereby promoting direct transdifferentiation

into a neuronal lineage. We hypothesize that astrocytes can be reprogrammed to neurons using adeno-associated virus (AAV) and that the penumbra of the lesion can be targeted using stereotactic surgical injections to induce reprogramming and promote functional recovery. We have seen successful reprogramming *in vitro* and *in vivo*. Specifically, we observed canine astrocytes expressing immature neuronal markers following transduction with AAVrh10 expressing either Ascl1 or Ngn2 under the Gfap or Ng2 promoters. In preliminary *in vivo* studies, AAVrh10 expressing Ascl1 and an mKate2 fluorescent reporter under the Gfap promoter was injected into the cortex of rats 7 days following ischemic injury. At 7- and 14- days post AAV injection, we observed mKate2-expressing cells in the cortex and striatum. Importantly, a subset of mKate2-expressing cells also expressed mature neuronal marker NeuN, but not GFAP, indicating a reprogrammed state. These results support the feasibility and efficacy of AAV in stroke models. We are also investigating the mechanisms of reprogramming in traumatic brain injury using the cre-lox system in transgenic mice. After traumatic brain injury, behavior tests were performed at 24hrs, 7 days, and 21 days post-reprogramming to evaluate functional outcome. Immunostaining will be used evaluate infection efficiency and the presence of neuronal markers post-infection. *In vitro* studies using cell cultures isolated from the transgenic mice will be performed for further analysis. In conclusion, AAV has great potential to promote brain repair following cerebral injury.

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Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.19/H11

Topic: C.10. Brain Injury and Trauma

Support: Ischemix Inc.

Title: CMX-2043 improves neurological outcomes after moderate focal traumatic brain injury

Authors: *T. HALLOWELL[1], N. DELSO[1], K. BROWNE[2], M. STOLOW[1], J. STARR[1], M. J. MCMANUS[3], D. CULLEN[2], T. KILBAUGH[1];
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Abstract: Traumatic brain injury (TBI) is a leading cause of death and acquired disability in children in the United States. Despite breakthroughs in rodent TBI models, there has been little translational therapeutic success. Although TBI is a multi-faceted injury model, reactive oxygen

species (ROS) have been identified as causing significant secondary injury following TBI. Alpha lipoic acid (ALA) is a naturally occurring compound that has been shown to act as a neuroprotective therapeutic by reducing ROS. This study aimed to identify the efficacy of the drug CMX-2043 (Ischemix Pharmaceuticals), an analog of ALA, in an immature swine model with a five day survival period. Delivery of CMX-2043 was randomized and blinded. A tunneled central venous catheter was placed in immature piglets between 26 and 28 days old to allow for drug delivery and blood collection for biomarker analysis. A moderate focal TBI was delivered using an engineered, piston-driven controlled cortical impact (CCI) device attached directly to the skull. The drug was delivered at designated time points during the five day survival period. MRI scans were taken at the completion of the survival period to allow for quantification of neurological damage. Mitochondrial respirometry was conducted to identify ROS in brain tissue following treatment. Piglets were also outfitted with accelerometers which were used to measure actigraphy characteristics. Animals treated with CMX-2043 demonstrated a 55% decrease in ROS 24 hours post-TBI ($p<0.05$), a 40% decrease in volume of injury ($p<0.1$), a 30% improvement in microstructural tissue integrity ($p<0.05$), a 55% decrease in lactate levels as measured by magnetic resonance spectroscopic imaging ($p<0.05$), improved rest efficiency, and decreased periods of nighttime activity when compared to placebo animals. Lipid peroxidation and protein carbonyl levels confirmed that attenuation of excess mitochondrial ROS (mtROS) production by CMX-2043 was sufficient to protect the brain tissue. Mitochondrial control ratio (RCR), a measure of overall mitochondrial function, also demonstrated a 40% improvement compared to placebo animals ($p<0.05$). Differences in dosing schedules allowed for the distinction of mitochondrial bioenergetic effects (processes?) due to TBI and identified changes in these mechanisms due to treatment. The outcomes of this study provide clinicians with a potential novel avenue for treatment of TBI and shed new light on tissue energetics following TBI. These results suggest that treatment of moderate focal TBI with CMX-2043 significantly improves neurological outcomes in an immature swine model with identifiable translational applications.

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Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.20/H12

Topic: C.10. Brain Injury and Trauma

Support: NINDS R21-NS107985

Title: HDACi nanotherapeutics to treat traumatic brain injury

Authors: *G. MOUSA[1], C. COPELAND[1], B. I. MARTINEZ[1], K. LEKA[1], G. R. BJORKLUND[1], K. T. HOUSEHOLDER[2], J. NEWBERN[1], R. W. SIRIANNI[2], S. E. STABENFELDT[1];
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Abstract: Traumatic brain injury (TBI) is a major cause of disability, with approximately 1.7 million incidents reported annually. Following a TBI, patients are likely to sustain cognitive and sensorimotor impairments and are at an increased risk of developing neurodegenerative diseases later in life. Despite TBI's prevalence and enduring effects, robust therapies that treat TBI neuropathology are not available in the clinic. One emerging approach is to target epigenetic mediators that modulate a variety of molecular regulatory events acutely following injury. Specifically, previous studies demonstrated that histone deacetylase inhibitor (HDACi) administration following TBI enhanced functional outcomes, reduced inflammation, and was neuroprotective. Here, we evaluated a novel quisinostat-loaded poly(D,L-lactide)-b-methoxy poly(ethylene glycol) (PLA-PEG) nanoparticle (QNP) therapy. This nanoparticle system was previously developed for glioblastoma; QNP administration slowed tumor growth and prolonged animal survival more effectively than free quisinostat. To assess QNP intervention in the context of TBI, a controlled cortical impact (CCI) model was used on adult C57BL/6 mice (2 mm tip diameter, 6.0 m/s over the frontoparietal cortex); all experiments were approved by ASU IACUC. Briefly, we evaluated initial pharmacodynamics via cortical histone acetylation levels following CCI and administration of QNPs. A second cohort of mice underwent a battery of behavioral assessment over the course of a month following injury and QNP intervention (rotarod, open field, gridwalk, and Morris water maze). We observed that QNP administration acutely following CCI increased histone acetylation specifically within the injury penumbra, as detected by Western blot analysis. Initial behavioral results indicate that QNP treatment dampened motor deficits as measured by increased rotarod latency to fall relative to blank nanoparticle- and saline-treated injured controls. Additionally, open field data show that QNP intervention altered locomotion following injury. These results suggest that HDACi therapies are a beneficial therapeutic strategy following neural injury and demonstrate the utility for nanoparticle formulations as a mode for HDACi delivery following TBI.

Disclosures: G. Mousa: None. **C. Copeland:** None. **B.I. Martinez:** None. **K. Leka:** None. **G.R. Bjorklund:** None. **K.T. Householder:** None. **J. Newbern:** None. **R.W. Sirianni:** None. **S.E. Stabenfeldt:** None.

Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.21/H13

Topic: C.10. Brain Injury and Trauma

Title: Cognitive improvement by deep cerebellar stimulation in a traumatic brain injury model of rodents

Authors: N. D. MATHEWS[1], H. H. CHAN[2], O. HOGUE[1], C. WYANT[1], R. CHIOMINTO[1], A. MCCREERY[1], R. KUNDALIA[1], D. P. FLODEN[3], A. G. MACHADO[4], *K. B. BAKER[5]; [1]Cleveland Clin. Fndn., Cleveland, OH; [2]Neurosciences, [3]Ctr. for Neurolog. Restoration, [4]Ctr. Neurolog. Restoration, [5]Cleveland Clin., Cleveland, OH

Abstract: Many traumatic brain injury (TBI) survivors live with persistent chronic cognitive deficits despite contemporary rehabilitation services, underscoring the need for novel treatment. We have previously shown that deep brain stimulation (DBS) of the lateral cerebellar nucleus (LCN) can enhance post-fluid percussion injury motor recovery and increase the expression of markers of long-term potentiation in perilesional cerebral cortex. We hypothesize that a similar beneficial effect will be for cognitive deficits induced by controlled cortical impact (CCI) in rodents through long-term potentiation-based mechanisms. Twenty male Long Evans rats with a DBS macroelectrode in the LCN underwent CCI over the medial frontal cortex. After 8 weeks of spontaneous recovery, DBS treatment was applied for 4 weeks, with the Barnes maze and baited Y maze used to evaluate cognitive performance. All animals were euthanized and tissue harvested for further analysis by histology and immunohistochemistry. All animals in both cohorts, with or without LCN DBS generally had the performance on Barnes maze improved. However, by analyzing the variance of performance, only the treated group demonstrated a steady performance while the untreated group displayed a fluctuated performance ($p<0.01$). There is also a better performance on the baited Y-maze in the treated group when compared to that in untreated. The LCN DBS reversed the loss of BDNF+ cells at the perilesional area induced by the CCI lesion in the treated group, accompanying with the reversal of loss of p75NTR+ signal in the same area. Finally, CCI induced the proliferation of c-fos+ cells at the perilesional area which was further increased by the LCN DBS. The current study supports the hypothesis that LCN DBS improves the cognitive deficits by maintaining the health of perilesional neurons and their excitability.

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Poster

570. Traumatic Brain Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 570.22/H14

Topic: C.10. Brain Injury and Trauma

Title: Effects of exercise as a pre-treatment for TBI in juvenile rats

Authors: *R. C. HOLDEN[1], M. J. HYLIN[2];
[1]Psychology, Southern Illinois Univ. Carbondale, Carbondale, IL; [2]Psychology, Southern Illinois Univ. Carbondale Dept. of Psychology, Carbondale, IL

Abstract: Traumatic brain injury (TBI) is the leading cause of death and disability in the juvenile population. As of yet, there is no clear "gold standard" rehabilitative therapy that maximizes long-term, functional recovery. In fact, most TBI interventions focus on secondary injury mechanisms as targets of treatment and have neglected an important avenue of therapy research: pre-treatment. While other injury models such as stroke have thoroughly investigated various pre-treatment interventions, the TBI model remains relatively unexplored. Exercise has been well-established as a beneficial strategy for brain injury rehabilitation due to its positive impact on neurogenesis, angiogenesis, and synaptic plasticity. Moreover, stroke research has indicated that pre-injury exercise reduces infarct size and benefits overall functional recovery. Therefore, the current study investigated the effects of exercise as a pre-treatment for juvenile TBI. To test this, male Sprague-Dawley rats were divided into three groups: injury+exercise pre-treatment, injury+no treatment, and shams. After being weaned on post-natal day 17, rats in the exercise group were pair-housed in running wheel cages until the injury. On post-natal day 28, rats were anesthetized and received either a controlled cortical impact (CCI) or a sham surgery. Following surgery, rats in the running wheel cages were returned to standard housing. In order to assess the effects of the pre-treatment exercise on recovery, rats underwent cognitive testing on the Morris Water Maze two weeks following injury. Results revealed that the pre-treatment group performed significantly better in the water maze compared to the no treatment group, such that the rats that received exercise showed significantly lower latencies to the hidden platform. These findings indicate that exercise before TBI may help to mitigate the cognitive effects of the damage and that it needs to be further explored as a pre-treatment intervention. Lesion verification to assess the impact of pre-treatment exercise on contusion size is currently underway.

Disclosures: R.C. Holden: None. **M.J. Hylin:** None.

Poster

571. Spinal Cord Injury II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 571.01/H15

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIDILRR Grant 90ARHF0002

Title: Investigating effects of transcutaneous spinal stimulation in restoring upper extremity function in people with spinal cord injury

Authors: *F. ZHANG, A. RAMANUJAM, K. MOMENI, M. RAVI, R. PILKAR, J. CARNAHAN, G. F. FORREST;
Kessler Fndn., West Orange, NJ

Abstract: Recovery of hand and arm functions is a high priority for individuals with spinal cord injury (SCI), because upper extremity function closely integrates with activities of daily living and determines the quality of their life. It is hypothesized that transcutaneous spinal stimulation (TSS), as an innovative and non-invasive technique, can change the excitability of spinal circuitry and neuro-modulate the spinal networks into physiological states that facilitate the restoration of paralyzed limb functions. Recently, the idea of applying stimulation to cervical spinal network to facilitate restoration of upper extremity function has gained increasing interest, but related research is limited so far. Therefore, this study aims to investigate the effects of TSS for restoring upper extremity and hand function in people with SCI. Individuals with a chronic cervical SCI received TSS intervention combined with hand function training for a 2-month period. Sub-threshold, tonic stimulation (monophasic, 1ms rectangular pulses at 30Hz, and 10kHz carrier frequency) was delivered using a pair of self-adhesive electrodes placed over cervical spinous processes and a pair of reference electrodes at anterior iliac crests. Hand training was supervised by physical therapists and focused on functional tasks aiming to address bilateral hand grasp and dexterity. Functional outcome measures and neuromuscular synergies (calculated from surface EMG signals) of upper extremities and hands were quantified at pre and post training points to determine the effects of TSS-based intervention. Pilot results from one motor complete SCI individual showed that TSS yielded immediate enhancement in grip strength (increased by 122.2±39.3% and 150.0±82.0%, bilaterally), as compared to baseline without stimulation. Voluntary motor control also improved where the participant was able to successfully lift water bottle and grasp tennis ball with stimulation enabled, which were not possible without stimulation. More importantly, the participant demonstrated progressive improvements in a series of hand outcome measures (i.e. grip and pinch strength test, and box and blocks test) over the course of intervention. These data suggest that TSS has the therapeutic potential of promoting neuroplasticity in upper extremity for SCI individuals.

Disclosures: F. Zhang: None. **A. Ramanujam:** None. **K. Momeni:** None. **M. Ravi:** None. **R. Pilkar:** None. **J. Carnahan:** None. **G.F. Forrest:** None.

Poster

571. Spinal Cord Injury II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 571.02/H16

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIDILRR, RERC Grant (90RE5021-01-00)

Kessler Foundation, Center for Spinal Stimulation

Title: Transcutaneous spinal stimulation augments excitability of spinal circuitry during maximal voluntary contraction

Authors: *K. MOMENI[1,2], M. RAVI[1,2], A. RAMANUJAM[1,2], R. PILKAR[2], F. ZHANG[1,2], E. GARBARINI[1,2], G. F. FORREST[1,2];
[1]Ctr. for Spinal Stimulation, [2]Ctr. for Mobility and Rehabil. Engin. Res., Kessler Fndn., West Orange, NJ

Abstract: Transcutaneous spinal stimulation (TSS) for modulation of the neural networks has increased volitional control for motor complete and incomplete spinal cord injury. The objective of this study was to determine: i) the optimal spinal sites of stimulation and ii) optimal parameters of stimulation to modulate spinal networks for an isometric maximum voluntary contraction. A series of trials were performed with and without stimulation, including: i) maximal isometric knee extension (MVC) and ii) multiple repetitions within each trial. Monophasic pulses were delivered at varying frequencies for different amplitudes to spinal sites between C4/5 and S1/2 (as cathodes), concomitant with isometric knee extension task. Anodes were placed on anterior iliac crests, bilaterally. During spatiotemporal spinal mapping sessions, stimulation amplitudes corresponding to peak EMG responses were identified (A_P). Knee extensor torque values were recorded. At peak amplitude parameters (A_P), peak knee extensor torque increased by 16%, compared to baseline torque without stimulation. At sub-peak amplitude parameters (A_S, lower than A_P), peak torque increased by 36%, compared to baseline. Regardless of stimulation sites, peak torque increased for sub-peak amplitude parameters (A_S), compared to peak amplitude parameters (A_P). Peak knee extensor torque values with and without stimulation increased continually throughout the testing sessions. No neuromuscular fatigue was observed. TSS, with the presence of intent, can significantly augment human spinal motor-neuron excitability and motor pools recruitment rate during task-specific training. Improvements were evident in volitional production of greater isometric torque. These findings support that TSS could facilitate acute plastic changes in the spinal circuitry and, possibly, lead to improvements in functional motor performance.

Disclosures: K. Momeni: None. **M. Ravi:** None. **A. Ramanujam:** None. **R. Pilkar:** None. **F. Zhang:** None. **E. Garbarini:** None. **G.F. Forrest:** None.

Poster

571. Spinal Cord Injury II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 571.03/H17

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIDILRR, RERC Grant 90RE5010-01-00
Kessler Foundation, Center for Spinal Stimulation

Title: Spinal mapping identifies optimal parameters to target specific motor pools through existing spinal networks after SCI

Authors: *M. RAVI[1,2], K. MOMENI[1,2], A. RAMANUJAM[1,2], R. PILKAR[2], F. ZHANG[1,2], E. GARBARINI[1,2], G. F. FORREST[1,2];
[1]Ctr. for Spinal Stimulation, [2]Ctr. for Mobility and Rehabil. Engin. Res., Kessler Fndn., West Orange, NJ

Abstract: Spinal cord injury (SCI) affects the nervous system in various ways including causing affected individuals to suffer loss of mobility and sensation below the level of lesion. Activity based training therapies have long been the only therapeutic choice available to SCI individuals. However, more recently, researchers have shown that combining electrical stimulation with the aforementioned training therapies can lead to significant functional recovery for tasks such as standing, walking etc. The hypothesis is that even after SCI, the spinal sensorimotor networks that are non-functional can be activated or enabled when stimulation is used on the corresponding spinal roots. One of the challenges of using stimulation is finding optimal parameters for an individual. We systematically applied non-invasive transcutaneous spinal stimulation (TSS) on the spinal cord at roots between C4/5 and S1/2 with the anodes placed on the anterior iliac crests, and EMG was recorded on lower limb muscles. The stimulation waveforms (pulse width of 1ms) were either 'monophasic,' which consisted of a 10KHz pulse acting as a carrier wave or 'rectified,' which did not have the carrier wave. Systematic modulations of amplitude and frequency induced specific EMG responses for different spinal roots. Post processing involved a specialized, novel algorithm based on empirical mode decomposition to remove the artifact of stimulation pulses from the EMGs . Analysis of the muscle activity showed that the flexor muscles such as the Tibialis Anterior had a directly proportional relationship to stimulation frequency whereas the extensor muscles such as Vastus Lateralis and Gastrocnemius had an inversely proportional relationship with stimulation frequency. Researchers when using epidural stimulation found similar results. For the majority of muscles tested, muscle activity peaked at a given amplitude precipitating a decrease in muscle activity at increased amplitudes indicating that there exists an optimal stimulation amplitude or maximum motor threshold for different muscles. Our results show that spatiotemporal spinal cord mapping could be an essential step in finding optimal TSS parameters to target specific motor pools through the existing spinal networks after SCI.

Disclosures: M. Ravi: None. **K. Momeni:** None. **A. Ramanujam:** None. **R. Pilkar:** None. **E. Garbarini:** None. **G.F. Forrest:** None. **F. Zhang:** None.

Poster

571. Spinal Cord Injury II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 571.04/H18

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIDILRR, RERC Grant 90RE5021-01-00
Kessler Foundation, Center for Spinal Stimulation

Title: Neuromuscular response to transcutaneous spinal stimulation during overground walking

Authors: *A. RAMANUJAM[1,2], K. MOMENI[1,2], M. RAVI[1,2], R. PILKAR[2], F. ZHANG[1,2], E. GARBARINI[1,2], G. F. FORREST[1,2];
[1]Ctr. for Spinal Stimulation, [2]Ctr. for Mobility and Rehabil. Engin. Res., Kessler Fndn., West Orange, NJ

Abstract: Tonic transcutaneous spinal stimulation (TSS) applied to afferent fibers within L2-S2 posterior (30Hz), below motor threshold have shown immediate positive effects on the leg EMG and reproducibly modified gait kinematics during voluntary treadmill stepping for individuals with incomplete spinal cord injury. Our laboratory has been piloting the intervention of TSS with overground training and exoskeleton training to show that the modulation of spinal networks leads to an increase in excitability of the spinal cord and afferent input during training. Participants completed a series of training sessions with and without stimulation. TSS was delivered between the spinous processes of C4-C5 and L1-L2 vertebrae as cathodes. Anodes were placed on anterior iliac crests. Before training, spatiotemporal spinal mapping sessions were performed by systematically modulating frequency, amplitude, and pulse-width at various spinal sites. Muscle activation data, obtained simultaneously during spinal mapping, provided targeted configurations to enable voluntary motor outputs for training. The stimulation waveform consisted of monophasic rectangular pulse with 10 kHz carrier frequency. Immediate effect of stimulation illustrated an increase in reciprocal and appropriate inter- and intra-limb leg muscle activation and symmetry of bilateral loading. During independent gait, without stimulation, bilateral lower limb motor pools fired simultaneously for an impaired gait pattern. With stimulation, there was a greater inter-limb reciprocal muscle activation for these lower limb pools; Intra-limb coefficient of variation for hip and knee kinematics decreased by 60% and 23%, respectively. Overall gait speed increased by 24%. Data suggested overground training enhanced with TSS and combined with high dosage of stepping can potentially lead to improved gait function.

Disclosures: A. Ramanujam: None. **K. Momeni:** None. **M. Ravi:** None. **R. Pilkar:** None. **G.F. Forrest:** None. **F. Zhang:** None. **E. Garbarini:** None.

Poster

571. Spinal Cord Injury II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 571.05/H19

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NJCSCR-CSCR14ERG007

Title: Neuromuscular responses to electrical stimulation profiles of varying amplitudes and frequency

Authors: *R. PILKAR, K. MOMENI, A. RAMANUJAM, E. GARBARINI, G. FORREST; Ctr. for Mobility & Rehabil. Engin., Kessler Fndn., West Orange, NJ

Abstract: During neuromuscular electrical stimulation (NMES), electrical current is applied to a nerve to elicit action potentials in denervated, peripheral muscles. NMES has been used to assist or restore neuromuscular function to paralyzed muscle after spinal cord injury (SCI). Further, chronic application of electrical stimulation (ES) has been shown to have a therapeutic effect on tissue health and voluntary function. Surface electromyography (EMG) provides an effective way to analyze underlying muscle activity. However, the overpowering presence of electrical stimulus artifact limits the assessment of the direct effect of ES on a muscle or nerve. Recent advances in biomedical signal processing have yielded algorithms that show significant success in removing ES artifacts from EMG signals recorded from the electrically stimulated muscle. Previously, we showed the effectiveness of a custom-developed computational algorithm, utilizing empirical mode decomposition (EMD) and notch filtering, to remove the ES artifact from EMG recordings of the electrically stimulated (35 Hz, 300μs) rectus femoris muscle (RF). We showed distinguishable, artifact-free muscle activations during two conditions of "ES-alone" and "ES+VOL," which is ES combined with the volitional effort to contract the muscle, in SCI (n=5) and able-bodied (n=5) participants. In this investigation, we extend our analysis to examine the neuromuscular responses to ES with ramping profiles at 35 Hz, and ES of 35 Hz, 55 Hz, and 75 Hz at constant amplitudes by studying the novel outcomes derived from artifact-free EMG activities in SCI (n=5) and able-bodied (n=5) participants. We confirm our findings by assessing concurrent torque profiles, measured using an isokinetic dynamometer. This investigation will help with the development of novel neuromuscular mapping techniques to elicit ES thresholds for specific motor pool activation. This could be significant as such relationships have only been established using mechanical outputs such as torque which could be the result of contributions from multiple muscle groups.

Disclosures: R. Pilkar: None. **K. Momeni:** None. **A. Ramanujam:** None. **E. Garbarini:** None. **G. Forrest:** None.

Poster

571. Spinal Cord Injury II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 571.06/H20

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Kosair Charities
Craig H Neilsen Foundation
The Leona M and Harry B Helmsley Charitable Trust
Todd Crawford Foundation

Title: Contribution of trunk muscles to upright sitting with segmental support in children with spinal cord injury

Authors: *G. SINGH, L. MENDEZ, B. UGILIWENEZA, A. BEHRMAN;
Univ. of Louisville, Louisville, KY

Abstract: Objective: Trunk muscles innervated by the thoracic and lumbar spine are critical for mobility as they are involved in virtually all movements requiring an upright posture whether seated, standing, or walking. Spinal cord injury (SCI) at cervical and upper thoracic levels results in paralysis or paresis of trunk muscles, as well as the upper and lower extremities, resulting in an inability to maintain upright balance during sitting and standing. Understanding the effects of SCI on trunk muscles should be one of the primary focuses in rehabilitation research to change the trajectory of outcomes in children with SCI. The aim of this study was to examine and compare trunk motor control and patterns of trunk muscle activation during sitting with segmental support in children with SCI to typically developing (TD) children. We selected to test children during the static control component of the Segmental Assessment of Trunk Control (SATCo) test while recording trunk muscle activity. We hypothesized that children with SCI would show significant differences in patterns of trunk muscle activation at the same segmental level of static control when compared to age-matched TD children. **Methods:** Twenty TD children (11f & 9m, age 7±2 years) were recruited from the community. Twenty-six children with chronic SCI (9f & 17m, age 5 ± 2 years) were recruited for this study. Surface electromyography (normalized amplitude) was collected from various trunk muscles. **Results:** Thoracic paraspinal muscle activation was significantly higher ($p < 0.05$) in SCI group from over lower ribs static control (OLRSC) to no support static control (NSSC) level. Lumbar paraspinal muscle was significantly higher in SCI group at pelvis and NSSC level. Rectus abdominus muscle was significantly higher in SCI group at from OLRSC to NSSC pelvis. External oblique was significantly higher in SCI group at pelvis static control (PSC) and NSSC levels. Intercostal muscle was significantly higher in TD group at OLRSC and below ribs static control (BRSC) level. Pectoralis major was significantly higher in SCI group at BRSC level. **Conclusion:**

Children with SCI produced unexpected activation of trunk muscles below injury level. Also, this activation was higher in SCI group than produced by TD group. However, TD children sustained low level of trunk muscle activation (tonic) at each static SATCo level. This information is useful to clinicians and therapist to plan therapies that target activation of truck muscles below the injury level.

Disclosures: G. Singh: None. **L. Mendez:** None. **B. Ugiliweneza:** None. **A. Behrman:** None.

Poster

571. Spinal Cord Injury II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 571.07/H21

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Kosair Charities Center for Pediatric NeuroRecovery
Christopher and Dana Reeve Foundation NeuroRecovery Network

Title: Unexpected recovery in a 3 year old with chronic, cervical spinal cord injury and ventilator dependent during activity-based therapy program

Authors: *M. ROBERTS[1], D. STOUT[1], S. BICKEL[2], M. CALVERY[2], K. BROTHERS[2], K. MCNAMARA[1], G. SINGH[3], A. BEHRMAN[3];
[1]Frazier Rehabil. Inst., Louisville, KY; [2]Pediatrics, [3]Neurolog. Surgery and Kentucky Spinal Cord Injury Res. Ctr., Univ. of Louisville, Louisville, KY

Abstract: Background
Paralysis after high, cervical pediatric spinal cord injury (SCI) may include predicted life-long ventilator dependence. Those injured <5 years old are at greater health risk. Activity-based therapies (ABT) may promote activation of the neuromuscular system and recovery post-SCI even in the most severely impaired children.
Case presentation
A premature infant with SCI at 18 days from epidural abscess/compression from C4-sacrum received a tracheostomy at 3 months. At 2 years 7 months an inquiry of the impact of ABT on this child's health and function began.
Evaluative tests/assessments included respiration, number of suctions/capping during therapy, trunk control (Segmental Assessment of Trunk Control, SATCo), upper extremity (UE) capacity observation, development (Bayley-III), parent interviews.
Intervention
Child entered daily ABT program (IRB approval for data collection) including AB-Locomotor Training 1.5 hours/day (144 sessions) and UE/trunk neuromuscular electrical stimulation for 1 hour/day (90 sessions). Ventilator weaning initiated.

Outcomes:
Suctioning rate in therapy decreased, tracheostomy capping during sessions initiated and progressed. Concurrent decrease in respiratory rate over 4 months, 60 to 30 breaths/min. Sleep study confirmed gains and decannulation planned within 3 months. SATCo score increased (0/20-5/20) with head and upper thoracic control. UE use improved from none to volitional intent for reach and targeting. Parent report briefly summarized: "We can have a normal life; he can have a normal life now" further substantiated by significant social-emotional and non-verbal cognitive gains per Bayley-III assessments.
Discussion:
In a child with chronic SCI, predicted to be life-long ventilator-dependent, and described as 'just present', ABTs facilitated plasticity of the neuromuscular/respiratory systems resulting in an engaged, purposeful child, breathing independently with head/trunk control, able to sit on his parent's lap and play.

Disclosures: **M. Roberts:** A. Employment/Salary (full or part-time):; Frazier Rehab Institute. **D. Stout:** A. Employment/Salary (full or part-time):; Frazier Rehab Institute. **S. Bickel:** A. Employment/Salary (full or part-time):; Dept of Pediatrics, University of Louisville. **M. Calvery:** A. Employment/Salary (full or part-time):; Dept of Pediatrics, University of Louisville. **K. Brothers:** A. Employment/Salary (full or part-time):; Dept of Pediatrics, University of Louisville. **K. McNamara:** A. Employment/Salary (full or part-time):; Frazier Rehab Institute. **G. Singh:** A. Employment/Salary (full or part-time):; Dept. of Neurosurgery, University of Louisville. **A. Behrman:** A. Employment/Salary (full or part-time):; Dept. of Neurosurgery, University of Louisville. 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.; PI: Kosair Charities Center for Pediatric NeuroRecovery, co-Director, Reeve Foundation NeuroRecovery Network. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oxford University Press, royalties. Other; President, NeuroRecovery Learning, Inc..

Poster

571. Spinal Cord Injury II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 571.08/H22

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Todd Crawford Foundation to Cure Paralysis

Title: Differences in resting state functional connectivity between low and high levels of physical activity in healthy school-aged children

Authors: *L. R. ALVARADO[1], A. L. BEHRMAN[2], B. E. DEPUE[3];
[1]Anatom. Sci. and Neurobio., [2]Neurosurg., [3]Psychological and Brain Sci., Univ. of Louisville, Louisville, KY

Abstract: Regular physical activity has been associated with changes in the structure, function, and connectivity of the adult brain. However, fewer studies have explored the effects of physical activity on the pediatric brain; moreover, they have generally focused on pediatric populations with neurological disorders. The present study aimed to test the hypothesis that levels of physical activity affect resting-state functional connectivity (rsFC) of cortical and subcortical sensorimotor centers of healthy school-aged children. Here we compare rsFC in a sample of healthy school-aged children with low levels of physical activity and a group with high levels of physical activity. This cross-sectional study used data from the Child Mind Institute Healthy Brain Network (HBN) biobank, available through the 1,000 Functional Connectomes Project. The HBN biobank houses phenotypical and multimodal brain imaging data from 1151 children and adolescents who consented to the distribution of their anonymized data. Sixty-two children (29 males and 33 females, 10.5 ± 1.7 years) who fulfilled the following criteria were included in the current analysis: 1) ages 8-14 years; 2) available data for the Physical Activity Questionnaire for Older Children (PAQ-C), FitnessGram assessment, age, sex, height, and body mass index; 3) available T1-weighted MRI and resting-state fMRI scans; and 4) no recorded diagnoses. Images were processed using the CONN functional connectivity toolbox v18.b default pipeline for volume-based analyses. Several potentially confounding sources of signal variation were removed by linear regression before undertaking ROI-to-ROI rsFC analysis by seeding the motor cortex, supplementary motor cortex, somatosensory cortex, thalamus, and basal ganglia nuclei. Higher levels of physical activity were associated with higher rsFC among the supplementary motor cortex, precentral gyri, and postcentral gyri. In addition, higher physical activity was associated with higher rsFC between these cortical sensorimotor centers and the thalamus, caudate, putamen, and pallidum. In sum, the rsFC strength of cortical and subcortical sensorimotor centers correlate with levels of physical activities among healthy school-aged children. These findings highlight the robust sensitivity of rsFC analysis in detecting the impact of inactivity on the healthy pediatric brain.

Disclosures: L.R. Alvarado: None. **A.L. Behrman:** A. Employment/Salary (full or part-time):; Dept of Neurosurgery, University of Louisville.. 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.; PI: Kosiar Charities Center for Pediatric NeuroRecovery, Co-Director, Reeve Foundation NeuroRecovery Network. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oxfor University Press, royalties. Other; President, NeuroRecovery Learning, Inc.. **B.E. Depue:** None.

Poster

571. Spinal Cord Injury II

Location: Hall A

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Program #/Poster #: 571.09/H23

Topic: C.11. Spinal Cord Injury and Plasticity

Support: The Leona M and Harry B Helmsley Charitable Trust

Title: The impact of an activity-based therapy program on pediatric patients with SCI and families

Authors: *K. C. MCNAMARA[1], K. BROTHERS[2], M. L. CALVERY[2], A. L. BEHRMAN[3]; [1]Frazier Rehabil. Inst., Louisville, KY; [2]Dept. of Pediatrics, [3]Dept. of Neurosurg., Univ. of Louisville, Louisville, KY

Abstract: Introduction: When asked "What has participation in this research study meant to your child and your family?" a parent responded, "*You let me out of prison*". This impromptu conversation with a parent catalyzed our exploration of the parent and patient experience in the Pediatric NeuroRecovery Program through a qualitative approach. **Methods**: Participants were the caregivers of patients (1-12 years of age) with acquired SCI who were enrolled in the Pediatric Neurorecovery Program at Frazier Rehab Institute. Patients received Activity Based Therapy for trunk and lower limb capacity and neuromuscular electrical stimulation for upper limb capacity, each 5x/wk for 1.5 hrs/day. In this IRB approved study, semi-structured interviews of caregivers were conducted by PI or trained staff at initial evaluation, after 60-90 sessions of ABT, at discharge and follow-up evaluation time points. Interviews were transcribed, de-identified and uploaded into Dedoose for analysis. An Open Coding Strategy was used to analyze the data. **Results** Temes centered on chid physical and physiological outcomes, psychological impact on the caregiver and developmental changes for the child. **Conclusion:** The developmental trajectory for children and the parent-child relationship is altered after spinal cord injury. Per parent report, gains in child capacity via ABT altered the caregiver role, shifting it from caregiver to parent. The resultant model illustrates a new perspective with regards to the readjustment in the developmental trajectory for child and parent.

Disclosures: K.C. McNamara: A. Employment/Salary (full or part-time):; Frazier Rehabilitation Institute, Kentucky One Health. **K. Brothers:** A. Employment/Salary (full or part-time):; Department of Pediatrics, University of Louisville. **M.L. Calvery:** A. Employment/Salary (full or part-time):; Department of Pediatrics, University of Louisville. **A.L. Behrman:** A. Employment/Salary (full or part-time):; Department of Neurosurgery, University Of Louisville. 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.; Kosiar Charities Center for

Pediatric NeuroRecovery. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oxfor University Press, royalties. Other; President, NeuroRecovery Learning, Inc..

Poster

571. Spinal Cord Injury II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 571.10/H24

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Kosair Charities
The Leona M and Harry B Helmsley Charitable Trust
Craig H. Neilsen Foundation
Todd Crawford Foundation

Title: Continuous beat-by-beat blood pressure and heart rate recording to assess autonomic regulation of the cardiovascular system in typically developing and in children with spinal cord injury

Authors: *A. KELLER, G. SINGH, A. BEHRMAN;
Univ. of Louisville, Louisville, KY

Abstract: Individuals with spinal cord injury (SCI) have a four-time increased risk for developing cardiovascular disease (CVD) above that of general population. Like adults, children with SCI have higher risk for developing CVD. The risk is potentially magnified by a relatively earlier onset of sedentary lifestyle and longer life expectancy. Lack of high quality prospective empirical studies assessing cardiovascular (CV) function in children with SCI hinders our understanding of the extent and severity that the SCI and paralysis-induced immobility holds for the CV health of this “at-high-risk” group. The goal of this study, as a first step, is to establish a protocol for the assessment of autonomic regulation of the CV system in children with SCI. Previously, 5 second maximal expiratory maneuver (MEP) in sitting has been validated as a method for the assessment of autonomic CV function in adults with SCI. Specifically, continuous beat-by-beat blood pressure (BP) and heart rate (HR) recorded via electrocardiogram (ECG) during this respiratory maneuver can be used to calculate baroreflex sensitivity (BRS) index to measure baroreflex function. Baroreflex is key for maintaining BP homeostasis and represents a critical point of integration of the vascular and neural components. Furthermore, BRS holds predictive value for the CV-related morbidity and mortality. Therefore, the goal of this study was to establish a protocol for the assessment of baroreflex function during 5-s MEP maneuver performed by children with SCI and compare them to typically developing age-matched children. Continuous beat-by-beat BP was recorded using finger cuff (Finapres, Netherlands). HR was recorded with 3-lead ECG (AD instruments) during 5-s MEP maneuver in

TD and children with SCI. At least 3 attempts of maximal expiration for the duration of 5 seconds through three-way valve system with tube mouthpiece and 1.5 mm diameter leak to prevent glottis closure were performed to ensure the quality of the signal. BRS was calculated as a slope and correlation coefficient between BP and R-R peak interval. We demonstrate the feasibility of the non-invasive method of the continuous blood pressure and heart rate monitoring during a maximal expiratory pressure maneuver to be used for the assessment of baroreflex function in children with spinal cord injury.

Disclosures: **A. Keller:** None. **G. Singh:** None. **A. Behrman:** None.

Poster

571. Spinal Cord Injury II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 571.11/H25

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Canadian Institutes of Health Research
Wings for Life Foundation

Title: Functional contribution of the mesencephalic locomotor region to locomotor recovery after spinal cord injury

Authors: ***M. ROUSSEL**[1], H. GODET[1], G. CLAIN[1], D. LAFRANCE-ZOUBGA[2], M. LEMIEUX[1], F. BRETZNER[1];
[1]Axe Neurosciences, Ctr. de recherche CHU de Québec-Université Laval, Québec, QC, Canada; [2]Univ. Laval, Québec, QC, Canada

Abstract: Recently, electrical stimulation of the mesencephalic locomotor region has been shown to improve locomotor recovery after spinal cord injury (SCI). The cuneiform nucleus (CnF), a cluster of glutamatergic neurons, and the pedunculopontine nucleus (PPN), a cluster of glutamatergic and cholinergic neurons, are part of this functional region. It has been shown that these three neuronal populations provide distinct contributions to locomotor control: glutamatergic neurons of the CnF can initiate and accelerate locomotion, whereas cholinergic and glutamatergic neurons of the PPN decelerate and stop locomotion. Here, we propose to identify and characterize the functional contribution of these distinct neuronal populations to locomotor recovery after SCI. Using transgenic mice expressing ChR2 in glutamatergic (VGluT2) neurons, we photostimulated VGluT2+CnF or PPN neurons before and after a thoracic lateral hemisection. Seven weeks after SCI, the ipsilesional limb still showed functional deficits including a slower locomotor rhythm, a decrease in the amplitude of intralimb coordination, and episodes of dorsal stepping. During treadmill locomotion, long photostimulation (10 ms pulses at 20 Hz for 1 s) of VGluT2+CnF neurons accelerated locomotor rhythm, increased postural tone,

and improved plantar stepping, whereas photostimulation of VGluT2+PPN neurons evoked deceleration and locomotor arrest. During swimming, long photostimulation of VGluT2+CnF neurons also accelerated locomotor rhythm and increased the maximal angular excursion of the hip, knee, and ankle, resulting in functional locomotor improvement of the ipsilesional limb. In summary, our results suggest that VGluT2+CnF neurons could be a neurological target for improving functional locomotor recovery following SCI.

Disclosures: M. Roussel: None. **H. Godet:** None. **D. Lafrance-Zoubga:** None. **M. Lemieux:** None. **F. Bretzner:** None. **G. Clain:** None.

Poster

571. Spinal Cord Injury II

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Program #/Poster #: 571.12/H26

Topic: C.11. Spinal Cord Injury and Plasticity

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NIH Grant R01 NS090919

Title: Central control of speed-dependent gait expression in intact rats and following spinal cord injury

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Abstract: Animals express different locomotor gaits in a speed-dependent manner. As speed increases intact rats exhibit sequential gait transitions that can be described by the phase-relationships between the limbs. The underlying neural control involves rhythm generating circuits for each limb (RGs) interacting through a variety of at-level commissural interneurons (CINs) and both ascending and descending long-propriospinal neurons (LPNs) providing communication between the enlargements. The objective of this study was to investigate and characterize the specific changes in over-ground speed-dependent gait expression in intact rats and following two different spinal cord injuries, a mid-line T9 contusion and a T9 lateral hemisection. To help us understand the specific changes in neural circuity interactions underlying gait expression, we developed a computational model with four RGs, CINs and LPNs. Locomotor speed in the model is defined by brainstem drive to the RGs.
Intact rats sequentially expressed lateral-sequence walk, trot, gallop, half-bound and bound in a speed-dependent manner. In addition, canter occurred during the transition between trot and

gallop. The asymmetric gaits (gallop, canter and half-bound) occurred with either limb as the lead, although there was a preference for the left. After either the contusion or hemisection injury the maximal and average speeds and stepping frequency were lower. Hemisected animals did not express bound or half-bound gaits, and gallop became more prevalent, but only with the limb ipsilateral to the injury (right) as the lead. Contused animals expressed only alternating gaits (gallop, bound and half-bound were lost), while the variability in phase between the homolateral and diagonal limbs increased. Interestingly, this resulted in the expression of gaits not observed in intact rats: diagonal-sequence walk and pace.
By varying both brainstem and LPN drive to/from the lumbar circuitry to simulate the contusion and hemisection injuries, our computational model was able to reproduce the experimentally observed changes in speed-dependent gait expression for both intact and injured rats, including gait transitions and the loss/appearance of specific gaits. Thus, model analysis allowed us to identify potential neural mechanisms underlying the observed gait changes and to propose mechanistic explanations for the experimental results.

Disclosures: S.M. Danner: None. **I.A. Rybak:** None. **D.S.K. Magnuson:** None. **C.T. Shepard:** None.

Poster

571. Spinal Cord Injury II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 571.13/H27

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH NINDS NS054894
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Craig Neilsen Foundation

Title: Optogeneticially mediated neuromodulation of trunk motor cortex paired with exercise based rehabilitation and viral BDNF leads to axial reflex changes below a complete T9/T10 spinal cord injury

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Abstract: After a complete T9/T10 spinal cord injury (SCI) in adult rats, trunk control becomes very important for postural stability, and crucial for function if stepping of hindlimbs is enabled. We have developed a neuromodulatory technique aimed at promoting plasticity and motor learning in the trunk motor cortex after SCI, by using subthreshold optogenetic stimulation of cortex via virally delivered Channelrhodopsin (ChR2). Virally delivered enhanced yellow

fluorescent protein (EYFP) is used as a control. When optogenetically mediated neuromodulation is paired with a 25 day robot assisted rehabilitation paradigm, motor mapping studies reveal a significant increase in cortical representation of trunk muscle segments below the injury (1-way ANOVA with Tukey-Kramer post-hoc comparisons, $p<0.05$) in the ChR2+robot rats, both with BDNF induced spinal stepping (N=8) and without (N=8), but not in EYFP+robot rats with (N=8) or without (N=8) spinal stepping enabled by BDNF. Activation of caudal trunk enabled by these representational changes likely also causes plastic changes in spinal circuitry below the injury by influencing sensory input and motor output from the spinal cord caudal to injury.
Monosynaptic reflex testing and Frequency Dependent Depression (FDD) is used widely to test spinal excitability. To understand chronic spinal circuit-level changes mediating trunk reflexes below injury in external oblique and longissimus, we implant a stimulating cuff around the T13 spinal nerve, and monitor trunk muscle responses through 13 paired trunk electromyogram electrodes, spaced both above and below injury, over the course of robot rehabilitation. Due to the proximity of the stimulating cuff to the spinal cord, in ipsilateral muscle segments caudal to injury, the motor response and the reflex response overlap. Artificial neural networks can be used to separate the two signals. However, we have also discovered a contralateral reflex of comparable latency, believed to be monosynaptic, which is also readily analyzed. Effects of neuromodulation of trunk motor cortex on the exhibited chronic spinal excitability and FDD below the injury are observed.
This work has been supported by NIH NINDS NS054894, and NS072651 and the Craig Neilsen Foundation.

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Poster

571. Spinal Cord Injury II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 571.14/H28

Topic: C.11. Spinal Cord Injury and Plasticity

Support: GM103507
NS089324
The Kentucky Spinal Cord and Head Injury Research Trust
Commonwealth of Kentucky Challenge for Excellence

Title: Silencing long ascending propriospinal neurons improves hindlimb coordination and stepping precision after incomplete SCI

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Abstract: Central pattern generators (CPGs) are neuronal networks that generate motor output associated with rhythmic behaviors, such as breathing and locomotion. The functional roles of discrete pathways associated with known locomotor CPGs after spinal cord injury (SCI) are poorly understood. Further, the specific anatomical characteristics of these pathways are largely unknown. In the mammalian spinal cord, long ascending propriospinal neurons (LAPNs) are part of an inter-enlargement pathway that anatomically connects the lumbar and cervical enlargements. The dendritic trees of these neurons are relatively simple with minimal branching and their axons ascend through the outermost layers of lateral and ventral white matter, which is often spared following injury. Previously, we found that LAPNs play a pivotal role in interlimb, but not intralimb, coordination of the hindlimbs and forelimbs during overground stepping in uninjured animals. We hypothesized that conditional silencing of LAPNs after mild/moderate SCI would further impair recovered locomotor function. Contrary to our hypothesis, silencing LAPNs after SCI resulted in improved hindlimb stepping precision and interlimb coordination of the hindlimb pair with no change in coordination between the hindlimb-forelimb pairs. Intralimb coordination showed modest improvements. Together, these data suggest that LAPNs cannot reliably distribute appropriate temporal information between the lumbar and cervical CPGs after incomplete SCI. However, removal of LAPNs from the inter-enlargement CPG circuitry leads to increased independence of the hindlimb and forelimb CPGs, such that they are able to achieve improved coordination of their respective limb pairs. Studies to explore the anatomical plasticity of LAPNs and their inputs after injury are ongoing and will contribute to our understanding of the altered role of LAPNs after SCI. These findings may be critical to understanding the therapeutic efficacy of various forms of spinal stimulation and rehabilitation in SCI patients. Supported by GM103507, NS089324, The Kentucky Spinal Cord and Head Injury Research Trust, and the Commonwealth of Kentucky Challenge for Excellence.

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Poster

571. Spinal Cord Injury II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 571.15/H29

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NSF Grant 1739800

Title: A hybrid neuroprosthesis for standing and walking balance in people with spinal cord injuries

Authors: *M. J. NANDOR[1], R. D. QUINN[2], M. AUDU[1];
[2]Mechanical and Aerospace Engin., [1]Case Western Reserve Univ., Cleveland, OH

Abstract: Gait restoration in people with spinal cord injuries has been an important area of research for many years. Two approaches have been traditionally been utilized – Functional Electrical Stimulation of the users own muscles has been shown to provide health benefits, but is difficult to control, as stimulated muscle is non-linear, time varying (due to muscle fatigue), and slow to respond. By contrast, in the recent years, commercial exoskeletons have been developed that move the users joints through a proscribed trajectory in a much more predictable manner. We have developed a system that aims to combine the best of both worlds, with a mechanical exoskeleton specifically designed with low friction joints to integrated joint torque provided by stimulation. Additionally, while current exoskeleton systems require the user to provide balance through their upper extremities, our system aims to provide hands free balance during gait through the integration ankle torques (both robotic and stimulation). To prove the feasibility of such a system, a control system for bipedal walking in the sagittal plan was developed in simulation. A deep deterministic policy gradient (DDPG) neural network was trained in GAZEBO to predict the ideal foot placement to maintain stable walking despite external disturbances. The simulated biped was able to achieve 1 m/s gait speed, and able to maintain stability while a 30 kg*m/sec. impulse disturbance was applied to the torso. While the controller was trained on a 1.8 meter tall model, it was also able to successfully stabilized models from 1.4 meter to 2.3 meters tall. This simulation work shows controller viability and robustness, and future work will look to integrate and test with human subjects.

Disclosures: M.J. Nandor: None. **R.D. Quinn:** None. **M. Audu:** None.

Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 572.01/H30

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Interaction of peripheral-nerve electrical stimulation with central pattern generators in dogs with naturally-occurring complete spinal cord injury

Authors: M. YEO[1], N. JEFFERY[2], *H. PARK[1];
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Abstract: It is well established concept that the central pattern generator (CPG) in the spinal cord can generate walking rhythm without supraspinal input. Indeed, spinalized animals can recover functional walking rhythms or even ambulate unaided. However, perhaps for evolutionary reasons, the human spinal cord is more severely affected by the loss of supraspinal input and there is limited ability to generate a walking rhythm. To compensate for the lack of supraspinal input after spinal cord injury (SCI) and better activate the CPG, either direct spinal cord excitation by epidural or intraspinal stimulation or indirect spinal cord excitation by sensory augmentation is needed. Of these, sensory augmentation for spinal cord excitation has been underexplored and often consists of mechanical interventions which can constrain motor output. Instead, we propose peripheral-nerve electrical stimulation to activate the dormant CPG after SCI. The objective of this study is to determine whether the peripherally-generated walking rhythm evoked by peripheral-nerve electrical stimulation will coordinate with the inherent rhythmicity of the CPG, depending upon specific stimulation amplitude/frequency parameters. Our preliminary work in dogs with naturally-occurring complete SCI showed that transcutaneous electrical stimulation over a range of 0.3 to 3 Hz, alternately applied onto the left and right leg, could generate a walking rhythm. The stimulation site was selected as the skin below the caudal aspect of the medial malleolus, to target distal-tibial nerve. As stimulation parameters, bi-phasic electrical stimulus were used with 2.5 mA current amplitude and 100 Hz carrier frequency. Also, tail pinch, which induced air stepping at ~2 Hz in the hindlegs without peripheral-nerve electrical stimulation, inhibited the walking rhythm induced by peripheral stimulation at 0.3 Hz. We believe that tail pinch excited the CPG and peripheral stimulation at 0.3 Hz was out of the range required to entrain the self-generated CPG rhythm. Using this canine model with peripheral-nerve electrical stimulation, we will further investigate the interaction between the spinal cord excitation and peripheral intervention using electrical stimulation.

Disclosures: M. Yeo: None. **N. Jeffery:** None. **H. Park:** None.

Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 572.02/H31

Topic: C.11. Spinal Cord Injury and Plasticity

Title: A fully-implantable closed-loop stance detection and plantar cutaneous augmentation system to promote gait rehabilitation after spinal cord injury

Authors: *A. SHON[1], K. BRAKEL[2], M. HOOK[2], H. PARK[1];
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Abstract: The contribution of sensory feedback from the leg for walking has been well established with the two-level half-center central pattern generator (CPG) model. Several gait therapies have also been introduced to evaluate the efficacy of motion-dependent sensory feedback from the leg on gait rehabilitation after spinal cord injury (SCI). For example, robotic devices or motorized belts move paralyzed lower limbs, in turn generating motion-dependent feedback. These body-weight supported treadmill training (BWSTT) interventions show positive effects on gait rehabilitation in both rats and humans after SCI. However, the efficacy of BWSTT on human gait rehabilitation is limited. Recent studies suggest that this may be due to insufficient peripheral sensory feedback. The fact that gait rehabilitation with BWSTT becomes more effective with sensory augmentation, produced with epidural stimulation or vibration on leg muscles, supports the notion. Indeed, the reduced loading of the legs with body-weight support reduces the force-dependent feedback. To compensate for this reduced leg loading, which might be the clearest sensory deficit for BWSTT, the current study aimed to augment tactile feedback from the foot sole, by stimulating the distal-tibial nerve as seen in human and cat studies, and ultimately to test whether the plantar cutaneous augmentation could compensate for reduced leg loading and promote gait rehabilitation. First, we developed a fully-implantable stance detection and plantar cutaneous augmentation system. As a proof of concept, we conducted experiments with two intact rats. We tested that the implantable system could record electromyography from the Soleus muscle, which was used for stance phase detection. Second, we measured compound action potentials from the proximal-tibial nerve while applying electrical stimulation to the distal-tibial nerve. Based on the propagation speed of the measured action potential and the plantar innervation of distal-tibial nerve, we believe that the electrical stimulation on distal-tibial nerve could augment plantar cutaneous feedback.

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Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

Location: Hall A

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Program #/Poster #: 572.03/H32

Topic: C.11. Spinal Cord Injury and Plasticity

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Eurostars No. E11834, GTXmedical
National Center of Competence in Research (NCCR) Robotics of the Swiss National Foundation

Title: Targeted epidural spinal stimulation after spinal cord injury: Personalized, computationally-guided stimulation protocols

Authors: *A. ROWALD[1,3], S. KOMI[1,3], R. DEMESMAEKER[1,3], E. BAAKLINI[1,3], H. LORACH[1,3], E. KURT[5], F. BECCE[4], B. LLOYD[6], A. M. CASSARA[6], H. MONTANARO[6,7], A. WATRIN[8], M. CABAN[2,8], M. D´ERCOLE[8], M. VAT[3], L. MCCRACKEN[1,3], S. MANDIJA[9], M. FROELING[9], E. PAOLES[8], D. GANTY[8], M. VAN´T KLOOSTER[8], J. BAKKER[8], C. A T VAN DEN BERG[9], V. DELATTRE[8], H. LAMBERT[8], N. KUSTER[6,7], E. NEUFELD[6], M. CAPOGROSSO[10], F. B. WAGNER[1], J. BLOCH[3], G. COURTINE[1,3];
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Abstract: Epidural Electrical Stimulation (EES) applied over the lumbosacral spinal cord enables supraspinal control over the activity of leg motor neuron pools in individuals with spinal cord injury (SCI). EES recruits large-diameter afferent fibers within the posterior roots, which leads to the modulation of motor neuron pools through the activation of proprioceptive feedback circuits. In turn, targeting individual posterior roots enables the specific modulation of motor neuron pools located in the spinal segment innervated by each root. However, inter-subject variability, limited specificity and time-consuming optimization procedures hinder large-scale clinical deployment of this technology. Here, we present new hardware and software to optimize stimulation protocols. First, we exploited anatomical analyses and computational modeling to design a new electrode array with electrode configurations that are optimized to target the individual posterior roots in a broad range of human spinal cords. Second, we established a computational platform that supports the semi-automated creation of hybrid computational models from high-resolution 3-T MRI datasets of individual patients. These models combine personalized, geometrically realistic 3D finite element models of the lumbosacral spinal cord with realistic compartmental cable models and network models of proprioceptive feedback circuits. We established a computational pipeline to obtain anisotropic tissue property maps, discretize the model, perform simulations using an electro-quasi-static solver and couple these simulations with NEURON-based electrophysiology models. This computational pipeline can determine the optimal site of electrode array implantation, predict the specificity of the stimulation, and discover effective configurations of electrodes. The infrastructure is also in place to use the pipeline for automatized implant design optimization. The safety and efficacy of

the newly designed spinal implant and the computational treatment optimization is under evaluation in patients with SCI.

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Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 572.04/H33

Topic: C.11. Spinal Cord Injury and Plasticity

Title: Targeted epidural spinal stimulation after spinal cord injury: Multi-center clinical trial in patients with subacute injuries

Authors: *R. DEMESMAEKER[1,2], S. KOMI[1,2], M. D'ERCOLE[4], E. BAAKLINI[1,2], H. LORACH[1,2], M. CABAN[4,5], A. YULZARI[4], M. VAN 'T KLOOSTER[4], A. WATRIN[4], R. BUSCHMAN[6], J. VON ZITZEWITZ[4], V. DELATTRE[4], H. LAMBERT[4], F. B. WAGNER[1,2], J. BLOCH[2,3], G. COURTINE[1,2,3];
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Abstract: Recent studies from independent research teams have shown that epidural electrical stimulation applied to the lumbar spinal cord during intensive motor rehabilitation could restore leg motor control in several individuals with chronic spinal cord injury (SCI). Preclinical studies showed that this intervention is markedly more efficient when initiated in the subacute phase after injury. Here, we present the preparation of a multi-center clinical trial to test the safety, feasibility and preliminary efficacy of this intervention for the recovery of leg motor control in individuals with subacute SCI (less than 6 months after injury). Specifically, we present the development of a single-system multi-purpose software platform that is intuitive and easy to use by the patient and for the optimization of electrical stimulation protocols in clinical settings, while integrating the necessary flexibility to support technological and therapeutic innovations. The software includes user interfaces adapted to the needs of patients, therapists and scientists. It allows to intuitively set up, individualize and execute spatial and temporal stimulation programs for different motor tasks ranging from single-joint movements to cycling-like exercises and walking with real-time closed-loop control based on body-worn sensors. The system receives electromyographic and kinematic data streams that are synchronized with the stimulation. While the option of online visualization provides real-time feedback on the effect of the stimulation during the optimization process, multimodal recordings allow the quantified evaluations of motor performance throughout the rehabilitation program. Furthermore, the software platform integrates units that can support the rapid prototyping of novel automated stimulation optimization and closed-loop control algorithms. For example, the software can integrate electroencephalographic signals to perform brain-actuated spinal cord stimulation. These developments will play a key role for the smooth execution of a multi-center clinical trial in the complex period that follows a SCI.

Disclosures: R. Demesmaeker: None. **S. Komi:** None. **M. D'Ercole:** A. Employment/Salary (full or part-time):; GTXmedical. **E. Baaklini:** None. **H. Lorach:** None. **M. Caban:** A. Employment/Salary (full or part-time):; GTXmedical. **A. Yulzari:** A. Employment/Salary (full or part-time):; GTXmedical. **M. van 't Klooster:** A. Employment/Salary (full or part-time):; GTXmedical. **A. Watrin:** A. Employment/Salary (full or part-time):; GTXmedical. **R. Buschman:** A. Employment/Salary (full or part-time):; Medtronic. **J. von Zitzewitz:** A. Employment/Salary (full or part-time):; GTXmedical. **V. Delattre:** A. Employment/Salary (full or part-time):; GTXmedical. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GTXmedical. **H. Lambert:** A. Employment/Salary (full or part-time):; GTXmedical. E. Ownership Interest

(stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GTXmedical. **F.B. Wagner:** None. **J. Bloch:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GTXmedical. **G. Courtine:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GTXmedical.

Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 572.05/H34

Topic: C.11. Spinal Cord Injury and Plasticity

Title: A novel robotic platform for forelimb motor rehabilitation in rats

Authors: *M. PASQUINI[1], N. D. JAMES[2], G. COURTINE[3], S. MICERA[4];
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Abstract: Robot-assisted technologies are increasingly integrated in neurorehabilitation programs. Nevertheless, the relationships between specific robot-assisted training protocols and the augmentation of neuroplasticity remain unclear. Rat models provide a suitable solution to investigate the mechanisms underlying the therapeutic impact of robotic rehabilitation. Here, we present a robotic platform able to provide different levels of assistance during an upper limb reaching task. The device gently clamps the wrist of the rat and guides the movement of the forelimb, providing assistance-as-needed, in order to receive a reward. The system has four degrees-of-freedom (DOF), three translational DOF and one rotational DOF to allow the pronation/supination movement of the forelimb of the animal. The workspace of the robot has been calculated to overlap with the kinematics of rat reaching behaviour, corresponding approximately to an area of 56 x 40 x 20 mm^3. In the vertical plane the movement is driven by a parallel cinematic chain, the design is based on the Pantograph. Horizontal movement and pronation/supination are guided by a linear slide and a parallel shift gear mechanism, respectively. The robot is actuated by three brushed rotary DC motors and one brushless motor coupled with a spindle drive. Two different restrainers allow the rat in a bipedal or quadrupedal position. The first one restrains the rat within a trunk jacket. The other is a head-mounted restrainer. The position of the restrainer is regulated by two micrometric translational stages. Moreover, this platform allows the quantitative assessment of reaching movements. Specifically, a 6-axis load cell records the force signal. The platform is embedded in a system enabling recordings of forelimb kinematic, muscle activity and calcium imaging of brain signals. We are

using this platform to monitor how the brain responds to different training paradigms, both in healthy rats and in rats with severe contusion of the cervical spinal cord.

Disclosures: **M. Pasquini:** None. **N.D. James:** None. **G. Courtine:** None. **S. Micera:** None.

Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

Location: Hall A

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Program #/Poster #: 572.06/H35

Topic: C.11. Spinal Cord Injury and Plasticity

Support: CIHR Research Fellowship
ERC Consolidator Grant
SNF Project Grant

Title: The application of whole organ clearing techniques to spinal cord injury: Unique challenges and solutions

Authors: ***N. CHO**[1], L. BATTI[2], S. PAGÈS[2], M. A. ANDERSON[1], K. BARTHOLDI[1], Q. BARRAUD[1], G. COURTINE[1,3];
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Abstract: The advent of whole organ clearing techniques has made it possible to visualize whole brains and spinal cords en bloc in three-dimensions. Questions specific to spinal cord injury (SCI) present unique challenges related to clearing, and clearing techniques related to SCI have not been well established. To address this gap, we optimized a number of clearing techniques utilized on the rodent central nervous system to answer specific questions related to SCI. We identified the challenges and found reproducible solutions to clear the rodent spinal cord, visualize regenerating fibres through the hostile environment of complete lesions, preserve the integrity and image more delicate tridimensional structures such as spinal dorsal root ganglia, and achieve *in situ* hybridization on whole spinal cord segments. These clearing methods provide reliable solutions to study SCI pathology, mechanisms of recovery and spinal cord repair interventions.

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Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 572.07/H36

Topic: C.11. Spinal Cord Injury and Plasticity

Support: ERC Project Grant
SNSF Ambizione
IRP post-doctoral fellowship

Title: The role of proprioceptive afferents in activity-dependent, spatiotemporal epidural stimulation of the cervical spinal cord

Authors: *N. D. JAMES[1], I. DEWANY[1], L. BAUD[1], S. SHERMAN[1], B. BARRA[2], N. GREINER[2], N. CHO[1], M. CAPOGROSSO[2], G. COURTINE[1];
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Abstract: Contusion of the cervical segments is the most common form of spinal cord injury (SCI). Patients surveys have identified improvements in upper limb function as a top priority for individuals that have suffered this type of injury, but no clinical solution is available for improving the recovery of skilled arm movements. Electrical neuromodulation therapies of the spinal cord have enhanced lower limb function in numerous preclinical models, from rodents to primates, as well as a number of clinical case studies. Despite this success, and the high priority of improved upper limb function for the SCI patient community, efforts to translate this promising technique to the cervical spinal cord and upper limbs have so far been limited. Given the complex patterns of muscle activation required for the execution of skilled arm movements, adaptation of epidural electrical stimulation (EES) to the cervical spinal cord necessitates a thorough understanding of the functional specificity that can be achieved using this technique, as well as the neuronal circuitry that underlies its effect. Here we present functional and anatomical data indicating that lateralised epidural stimulation of the rodent cervical spinal cord effectively targets specific upper limb motor pools, dependent on the rostrocaudal location of the stimulation site. Based on these findings, we have developed and assessed the efficacy of a stimulation paradigm in which cervical EES is delivered in a spatially selective manner and is temporally patterned in accordance with the real time activity of selected upper limb muscles. Furthermore, to gain a greater understanding of key neuronal circuitry we have utilised targeted pharmacological and genetic manipulations, allowing us to demonstrate the pivotal role of proprioceptive feedback circuits in the generation and modulation of motor responses during cervical EES. Taken together, these results establish a conceptual framework for the design and optimisation of targeted cervical implants to facilitate upper limb movements after spinal cord injury.

Disclosures: **N.D. James:** None. **I. Dewany:** None. **L. Baud:** None. **S. Sherman:** None. **B. Barra:** None. **N. Greiner:** None. **N. Cho:** None. **M. Capogrosso:** None. **G. Courtine:** None.

Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 572.08/H37

Topic: C.11. Spinal Cord Injury and Plasticity

Support: CTI 25761.1 PFLS-LS

Title: Targeted epidural spinal stimulation after spinal cord injury: Automated optimization of stimulation protocols

Authors: ***S. KOMI**[1,2], R. DEMESMAEKER[1,2], P. ABRANCHES DE CARVALHO[1,2], I. PERRET[4], H. LORACH[1,2], E. BAAKLINI[1,2], L. MCCRACKEN[1,2], K. MINASSIAN[4], F. B. WAGNER[1,2], J. BLOCH[2,3], G. COURTINE[1,2,3];
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Abstract: A recent study has shown that spatially and temporally patterned epidural electrical stimulation (EES) delivered to the lumbar spinal cord through a multisite electrode array immediately enables walking in individuals with severe spinal cord injury. These spatiotemporal stimulation protocols require the fine-tuning of numerous parameters such as electrode configurations, timing and duration of stimulation bursts, and amplitude / frequency of multiple stimulation waveforms. Hence, determining such complex stimulation protocols requires an optimization process of several days of manual adjustments involving a large multidisciplinary team of engineers, neurophysiologists and therapists. This time- and resource-intensive approach is not practical for large-scale clinical studies, and even less for a broad clinical deployment. Consequently, it is imperative to gain a robust understanding of the effects of each EES parameter, and to leverage this knowledge to build automated methods that render the optimization process time- and cost-efficient. For this purpose, we investigated the effects of bursts of stimulation pulses at increasing frequencies and amplitudes on the recruitment of leg muscle groups. We tested the ability of multiple sets of electrode configurations to target each posterior spinal root specifically while subjects were lying in supine position. We recorded electromyographic activity and kinematics, enabling us to quantify the muscle specificity and functional effects, respectively. All participants exhibited strong posterior root-specific and frequency-dependent properties in the recruitment of the tested muscle groups. These findings immediately translated from supine position to functional use during walking. Subsequently, we

developed a fully automated online machine learning algorithm able to find, in a short time period, electrode configurations and stimulation parameters targeting specific functional muscle groups. This process relies on Bayesian optimization based on Gaussian processes, and embeds the effects observed during previous trials as prior knowledge. These results establish the first steps towards an in-depth understanding of the effects of different stimulation parameters and the development of efficient automated optimization algorithms.

Disclosures: **S. Komi:** None. **R. Demesmaeker:** None. **P. Abranches de Carvalho:** None. **I. Perret:** None. **H. Lorach:** None. **E. Baaklini:** None. **L. McCracken:** None. **K. Minassian:** None. **F.B. Wagner:** None. **J. Bloch:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GTXmedical. **G. Courtine:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GTXmedical.

Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 572.09/H38

Topic: C.11. Spinal Cord Injury and Plasticity

Support: The Craig H. Neilson Foundation #457508
NIH NS 097880

Title: Role of nociceptive afferent input on forelimb reaching and grasping behaviors in the spinal cord injured rat

Authors: *J. R. WALKER, A. ONG, M. R. DETLOFF;
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Abstract: Individuals with spinal cord injury (SCI) suffer a loss of motor and sensory function. The current standard of care to recover fine motor control is rehabilitation focused on a combination of range of motion, aerobic, and strength training (ST). However, limited research has been conducted to determine the role of nociceptive afferent inputs from muscle on spinal plasticity and/or recovery of function. Using a rodent model of SCI strength training rehabilitation, we determined that motor training not only improves forelimb strength and fine motor function but also can modulate the development of neuropathic pain, suggesting that improvements in reaching and grasping may be due, in part, to plasticity of nociceptive afferents. To further explore this, Sprague-Dawley rats received injections of rIB4-conjugated saporin, mu p75-conjugated saporin or unconjugated (vehicle) into the cervical dorsal root ganglia unilaterally to eliminate non-peptidergic and peptidergic nociceptors. There is an uninjured cohort and a group with unilateral C5 SCI. Von Frey and Hargreaves' tests were performed at

baseline and several time points post-injection to assess the efficacy of the nociceptive elimination. Several measures of forelimb strength were recorded over time including the isometric pull task, a single pellet retrieval task and the Montoya staircase test. To confirm the depletion of peptidergic and non-peptidergic nociceptors following saporin injection and/or SCI, cervical DRGs and spinal cords were stained with antibodies against CGRP and isolectin-B4. An understanding of the role of nociceptors in spinal plasticity and functional motor and sensory recovery of SCI patients will guide future research and refine rehabilitation strategies to further improve their quality of life.

Disclosures: J.R. Walker: None. **A. Ong:** None. **M.R. Detloff:** None.

Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 572.10/H39

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation Pilot Grant 457508
NIH Grant NS097880

Title: Rehabilitative strength training induces anatomical and functional plasticity of primary nociceptive neurons after cervical spinal cord injury

Authors: *M. R. DETLOFF, A. ONG, J. R. WALKER, V. ROVIRA ZAMBRANA, T. THAWEERATTANASINP;
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Abstract: More than two-thirds of individuals with spinal cord injury (SCI) develop chronic neuropathic pain. SCI-induced neuropathic pain is associated with both nociceptor hyperexcitability as well as sprouting of primary afferent c fibers that transmit pain information to the spinal cord. We have previously shown that early, aerobic exercise prevents development of neuropathic pain but does not ameliorate it once established. While locomotor training is used in the clinic, the standard of care in post-SCI rehabilitation focuses on improving muscle strength. This project will determine whether early or delayed strength training after SCI can affect nociceptor plasticity and pain development after cervical SCI. Female Sprague-Dawley rats received a C5 unilateral spinal cord contusion corresponding to handedness. A subset of SCI rats underwent isometric forelimb strength training 5 days/week starting at 5 or 42 days post-injury (dpi) for 5 weeks. Briefly, rats complete 50 successful repetitions of at least 50g force in an isometric forelimb pull task to receive a food reward. Mean pulling force returned to near normal after 10 strength training sessions regardless of early or delayed initiation of exercise ($p>.05$ vs baseline). The recovery of forelimb strength corresponded to improvements in reach-

to-grasp behavior as assessed using a single pellet-retrieval task. Delayed strength training reduced paw hypersensitivity and pain behavior as measured by von Frey and mechanical conflict avoidance operant tests compared to unexercised and acute strength training SCI groups ($p<.05$). Preliminary whole cell patch electrophysiology of isolated nociceptors from rats in each group suggest that strength training reduces nociceptor excitability. Another cohort from each group received microinjection of cholera toxin-B into the ulnar nerve to identify large diameter afferents 3 days prior to sacrifice. We are currently completing immunocytochemical experiments assessing the degree of primary afferent sprouting that is associated with forepaw dermatomes. With the results, we hope to better understand the mechanisms underlying SCI-induced pain, allowing for possible refinement of rehabilitation protocols to reduce chronic pain after SCI.

Disclosures: M.R. Detloff: None. **A. Ong:** None. **T. Thaweerattanasinp:** None. **J.R. Walker:** None. **V. Rovira Zambrana:** None.

Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

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Program #/Poster #: 572.11/H40

Topic: C.11. Spinal Cord Injury and Plasticity

Support: WFL-UK-007/15

Title: Boosting production of endogenous stem cells in the spinal cord to enhance recovery from spinal cord injury

Authors: *V. K. LALL[1], J. DEUCHARS[3], S. A. DEUCHARS[2], R. M. ICHIYAMA[3];
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Abstract: The ependymal cell layer surrounding the central canal is an endogenous adult neural stem cell niche. Enhancing this endogenous proliferation could be a lucrative treatment strategy following spinal cord injury. This study investigates the effects of exercise training and of the cholinergic α7 nicotinic receptor positive allosteric modulator PNU 120596, which is known to upregulate cell proliferation of ependymal cells. 4 weeks following moderate spinal cord contusion injury rats were treated with either PNU 120596 or vehicle and either given 24hrs free access to running wheels or not, for 6 weeks. Exercise training revealed vehicle treated rats had a higher mean velocity and increased bouts of activity but no differences were seen in the total distance ran, percentage time spent active or maximum activity durations. At the end of the training period animals in exercise groups displayed significantly higher average BBB sub-scores. The Randall-Selitto paw pressure test revealed that running animals had an increased pain

threshold and had fewer missed steps in the modified step ladder test although the Von Frey hairs test showed no differences between groups. Rats were then transcardially perfused and fixed for immunohistochemical analysis. PNU 120596 treated animals displayed higher numbers of new born cells around the central canal of cervical spinal cord sections in comparison to vehicle treated. Below the lesion this proliferation was attenuated and the exercise trained groups displayed the highest number of new born cells around the central canal region. However, exercise trained animals had fewer new born cells at the lesion site in comparison to non-trained animals. New born cells appear to have migrated well into the white matter in all groups and most of these became GFAP positive astrocytes followed by, APC CC1 positive oligodendrocytes, SoX2 positive neuronal stem cells and only very few were NeuN positive. These results indicate that PNU 120596 is able to augment the proliferative capacity of ependymal cells and that exercise training plays a fundamental role in modulating the spatial proliferation of these cells to enhance recovery of function after chronic spinal cord injury.

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Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 572.12/H41

Topic: C.11. Spinal Cord Injury and Plasticity

Support: ISRT STR118

Title: Combined epidural stimulation, anti-nogo antibody treatment and training in a severe contusion injury

Authors: R. W. KISSANE[1], ***R. G. DICKSON**[2], K. CHEN[3], M. E. SCHWAB[4], S. CHAKRABARTY[2], R. M. ICHIYAMA[2];
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Abstract: Combinatorial therapies for the treatment of spinal cord injury (SCI) are vital if a significant amount of locomotor recovery is to be achieved. Parsing out the behavioral and anatomical changes each treatment is having will allow us to effectively combine therapies needed for SCI recovery. Alone, anti-Nogo-A antibody (11C7), locomotor training, or epidural stimulation of the lumbar spinal cord have been shown to improve locomotor outcomes in animal models of SCI. However combining therapies has not always been successful, with certain treatments, such as training alongside anti-Nogo-A therapy, proving to have negative

combinatorial effects. The current study shows the additive effects of sequential anti-Nogo-A antibody treatment followed by epidural stimulation (ES) and daily locomotor training with body weight support. Adult Sprague-Dawley rats received a severe contusion injury at T9/T10, epidural electrodes implantation at L2 and S1, and intrathecal delivery of either 11C7 or control IgG (osmotic pumps). Animals were randomly assigned to one of cage control, locomotor training, ES (40Hz sub threshold), or combined ES and locomotor training. Pumps and catheters were removed after 2 weeks and training began 3 weeks following injury in order to minimize negative outcomes seen with concurrent combined treatments. Rats in the trained groups stepped bipedally-to-quadrupedally with varying amounts of body weight support at speeds of 7-21cm/s (5 days/week, 20 mins/day) for 8 weeks. 11 weeks after injury kinematic recordings were made and motor cortex BDA injections were completed before terminal electrophysiology. Surprisingly, there were no significant differences in BBB scores between groups throughout the treatment period. However, in the last four weeks there was an increase in weight-supported stepping (BBB≥10) in the training and combination group with 11C7, however 11C7 was found to actually decrease weight supported stepping in the ES alone group. Immunohistochemistry data showed that increases in Ia afferent synapses onto motoneurons with 11C7 treatment were modulated by locomotor training under ES, with fewer direct contacts observed in this group. The varied behavioral results underline the importance of understanding the mechanisms of different treatments in order to be able to combine them in the most effective way.

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Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen NZ:385743
NIH R01NS06004
NYS DOH SCIRB C30606GG
Craig H. Neilsen JHM:261214

Title: Neuron intrinsic growth program activation in response to electrical stimulation of the primary motor cortex

Authors: *N. ZAREEN, H. ALEXANDER, J. H. MARTIN;
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Abstract: Repairing the corticospinal tract (CST) after spinal cord injury (SCI) is difficult due to many factors. SCI is often incomplete, leaving some intact axons that can sprout in injury-dependent manner below injury site, synapsing with denervated spinal motor circuits. Though insufficiently robust to repair the damaged CST, the CST neurons' innate ability to sprout axons can be augmented via chronic electrical stimulation of the primary motor cortex (MCX), resulting in repair and recovery of motor function. We have shown this in rat models of pyramidal tract lesion (PTx) and cervical SCI, making MCX electrical stimulation (MES) an effective repair strategy. The molecular mechanisms of sprouting, unlocked by MES, are not understood well but are beginning to emerge. We have shown that mTOR and the Jak/Stat pathways are needed for CST sprouting resulting from chronic (10 days) MES. The pathways play distinct roles in CST remodeling: mTOR is needed for CST axonal sprouting while Jak/Stat for pre-synaptic boutons formation. The expression level of the mTOR antagonist PTEN is not altered, but level of the inactive phosphorylated PTEN (pPTEN) peaks along with mTOR activity. Thus, chronic MES activates an axon growth-promoting program in the CST neurons. We ask when during chronic MES period does the growth program switches on and if it persists when MES is discontinued. We used MES at various lengths and examined the levels of mTOR and Jak/Stat activaty and inactive pPTEN. mTOR and Jak/Stat activities increase after 1 day of MES. mTOR, but not Jak/Stat, activity remain high for an additional day after MES and drops after 3 days, showing low persistence after short-term MES. Activities of both pathways remain high after 5 days of MES, increasing further after 10 days of MES. PTEN deactivation proceeds gradually from 1 to 10 days of MES. When checked after 20 days after the end of chronic MES, activity levels were found to be comparable to 10 days MES, showing long-term persistence. This may explain data from our published study, showing increased CST sprouting 20 days beyond the chronic MES period. We conclude that short-term MES results in significantly high mTOR activity independent of PTEN activity and the insufficient PTEN deactivation may not activate axon growth-promoting environment. Functional CST remodeling may result from the concurrent increase in mTOR activity and decrease in active PTEN following chronic therapeutic MES. Long-term persistence indicates that a certain length of MES period is sufficient to activate and preserve axon growth program in CST neurons. This may be convenient in clinical settings, eliminating need for SCI patients to undergo MES for indefinite period.

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Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

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NYS DOH SCIRB C30606GG

Title: Combined cortical and spinal neuromodulation strengthens the effectiveness of motor rehabilitation in incomplete cervical spinal cord injury

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Abstract: Physical rehabilitation is the most widely used form of therapy for motor recovery in individuals with spinal cord injury (SCI). However, most forms of rehabilitation only result in modest degrees of functional improvements. This is primarily because after SCI, axons that transmit descending motor commands are too few and weak to produce effective movements. Therefore, in order to enhance the efficacy of rehabilitation, the few spared corticospinal connections must be strengthened to improve functional neural connectivity. We previously showed that intermittent theta burst stimulation (iTBS) of the motor cortex (M1) combined with cathodal trans-spinal direct current stimulation (tsDCS) improved forelimb function and increased corticospinal tract (CST) sprouting following SCI. The purpose of this experiment is to use the same combined neuromodulatory approach to strengthen the effectiveness of rehabilitation following cervical SCI. Female Sprague Dawley rats (n=8 at the time of abstract submission) were trained to run along a horizontal ladder until forelimb error rate was less than 15%. Rats were given a bilateral C4 moderate contusion (200kdyn), damaging the CST and impairing forelimb function. Following 2 weeks of recovery, rats were randomized to receive 10 days of bilateral M1 iTBS+tsDCS followed by rehabilitation (n=4), or rehabilitation alone (n=4). Rehabilitation consisted of 6 weeks, 5 days a week of 24 runs on the horizontal ladder with alternating gaps. Forelimb performance on the same task was tested once a week throughout the 6-week training protocol, and 2 weeks after. The CST was anterogradely traced using BDA (n=8) injections in the M1 forelimb area. Forelimb motor function was impaired in all animals following SCI. Both groups showed improved forelimb performance by the end of the 6-week training period, and improvements were sustained 2 weeks after cessation of training. However, the stimulation+rehab group improved by 67%, whereas the rehabilitation only group improved by 33%. Histology showed complete ablation of the CST in the dorsal column caudal to the lesion. Spared CST axons in the gray matter caudal to the lesion were derived from lateral CST fibers projecting to the intermediate zone. Stimulation increased spared CST axon length in the gray matter caudal to the injury compared to no stimulation. These results suggest that neuromodulation-assisted rehabilitation is more effective than rehabilitation alone in improving motor recovery and activity-dependent axonal growth after incomplete cervical SCI.

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Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

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Topic: C.11. Spinal Cord Injury and Plasticity

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NYS DOH SCIRB C30606GG

Title: Phasic and tonic stimulation of M1 produces morphological and electrophysiological changes in the corticospinal system

Authors: *L. YANG[1], J. H. MARTIN[2];
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Abstract: Neural activity plays an important role in promoting axon growth and synapse formation in activated neurons and pruning connections in non-activated neurons. The potential of neural activity to trigger axon growth becomes especially important for spinal cord injury (SCI) and repair. Studies in our lab show that patterned electrical stimulation(stim) of primary motor cortex (M1) (i.e., iTBS; (intermittent theta burst stimulation)) facilitates motor evoked potentials (MEPs) during and up to 20 minutes post stim. Previously, we used an optogenetic approach to selectively activate ChR2+ neurons in M1 of adult uninjured rats. CST neurons that received 10 days of optical iTBS had increased axon length and axons projected farther into the motor neuron pools compared to non-stimulated neurons. M1 MEPs showed reduced threshold and latency at the optically stimulated site compared to nearby non-stimulated sites. In the current studies, we determined if a tonic increase in M1 neural activity can also promote CST axon outgrowth and targeting with SC neurons. We microinjected AAV- hM3Dq (excitatory DREADD) and AAV-EYFP (for anterograde CST tracing) into forelimb M1. Subjects were tonically stimulated for 10 days via IP injection of the DREADD agonist clozapine n-oxide (CNO). Post stim, tonically-stimulated M1 had lower MEP thresholds than unstimulated M1. Stimulated axons in the contralateral cervical gray matter were longer and extended farther into the motor nuclei. We next determined if phasic and tonic activation promoted establishment of more synapses with spinal interneurons (INs) in a competitive, activity-dependent manner. We examined Chx10+ INs, an abundant excitatory neuron class in the intermediate zone. Optically stimulated axons made significantly more putative synaptic contacts with Chx10+ INs than non-stimulated axons in stimulated animals. Importantly, non-stimulated axons in ChR2+ animals had significantly fewer contacts compared to non-stimulated axons in controls, suggesting that active axons out compete quiescent axons for synaptic contacts. Synaptic contact analysis is in progress for DREADD activated axons. In summary, phasic and tonic stim of M1 produce

similar increases in contralateral CST axon length and decreases in MEP thresholds. Importantly, phasic stim enhances putative connections with a major class of excitatory IN. Analyses are in progress to determine if tonic activation has a similar effect on targeting of CST connections with spinal excitatory INs and M1-to-muscle connection strength. An important question for future experiments is if patterned or tonic stim is more effective in promoting function after injury.

Disclosures: L. Yang: None. **J.H. Martin:** None.

Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: B2316R
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NS097781

Title: Downslope locomotor training - A rehabilitative strategy targeting eccentric components of gait

Authors: *L. R. MONTGOMERY[1,2,4], J. M. NANNEY[2,3], S. F. MCMURTRY[5], A. M. DE BOEF[5], E. KAJTAZ[1,2,5], T. NICHOLS[5], D. R. HOWLAND[1,2,3,4];
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Abstract: Spinal cord injury (SCI) disrupts the intermuscular coordination required for control of knee and ankle flexion during weight acceptance in early stance. This leads to inefficient weight shift and instability, that maybe exacerbated by changes in inhibitory force feedback (iFFB) as seen in our feline SCI model. Currently there are few rehabilitative strategies focused on eccentric activity to restore intermuscular coordination during stance. Downslope walking increases iFFB activity in a decerebrate preparation (Nichols et al 2014), consistent with the prolonged period during stance when the knee and ankle are held in a stable flexed position as the decline angle increases. As a result, our training strategy uses different declining, walking surfaces to target eccentric control of the knee and ankle through iFFB. The goal of this training paradigm is to enhance recovery of weight acceptance and controlled flexion during stance, thereby improving stability and efficiency of gait. In the current work, adult, spayed felines are trained to perform hind limb stepping on a treadmill (TM) and voluntary overground (OG)

locomotion. Slope on each is varied (0º to -26º) and two speeds (0.5 and 0.8 m/s) assessed on TM. After collection of baseline performance data, each receives a low, lateral T9/10 hemisection (LHX) and is placed in trained (TR) or non-trained (NT) groups. Training occurs 5x/wk out to 12 wks. After LHX, yield on flat surfaces and the normal adaptations to slope are disrupted during TM & OG tasks. Impairments are present bilaterally despite SCI asymmetry. Ipsi- and contra-lesional hind limb kinematics however, are not symmetrical suggesting different combinations of functional loss, recovery and compensation across limbs. The TR group adopts a more consistent yield strategy relative to the NT group which displays excessive flexion of distal joints compared to intact animals. Overall step cycle consistency also increases with TR and particularly on TM. Other step cycle features of the TR also more closely resembled intact animals including the stance-swing transition, extent of hip extension at toe off and step cycle duration. These changes were most evident during OG tasks and slower TM speed (0.5 m/s). The iFFB profiles of the TR and NT groups are presented in a companion poster (McMurtry et al.). This work will help guide development of more effective rehabilitative strategies for recovery of effective eccentric control critical for the coordinated weight acceptance and support phases of gait. Spt DVA, RR&D B2316R, B7165R & B9249S, NINDS NS097781, Rebecca F. Hammond Chair. This presentation does not represent the views of the DVA, NIH, US gov.

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Poster

572. Neural Stimulation and Rehabilitation to Treat Spinal Cord Injury

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NINDS NS097781
NICHD HD32571
Rebecca Hammond Chair

Title: Evidence for modulation of force-dependent feedback in cat hindlimb using eccentric training -- A potential mechanism for locomotor recovery

Authors: *S. MCMURTRY[1], A. DE BOEF[1], E. KAJTAZ[1], L. MONTGOMERY[2], J. NANNEY[2,3], D. R. HOWLAND[4,5,3], T. R. NICHOLS[1];
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Abstract: Recent evidence from our lab shows gait deficits, including exaggerated yield, following incomplete spinal cord injury is in part due to the dysregulation of inhibitory force feedback (iFFB) from Golgi tendon organs (GTO). GTO pathways form an intermuscular feedback network in the spinal cord that helps regulate mechanical properties of the limb. Regulation of these properties occurs in a task-dependent manner. Specifically, iFFB is a major control variable for modulation of limb stiffness. In conditions mimicking downhill walking iFFB has been shown to be amplified (Nichols et al., 2014). This upregulation of inhibition increases compliance associated with the braking action during downslope walking. Previous results in our lab utilizing a standing decerebrate prep shows flexible configurations of iFFB patterns in the spinally intact cat (SIC), while cats with chronic lateral hemisection (LHX) show one pattern that indicates amplified inhibition onto ankle extensor muscles. We hypothesize that entraining this iFFB network will reestablish feedback patterns as seen in controls and improve gait. Using the decerebrate cat we measure the strength and distribution of inhibitory feedback between extensor muscles spanning one or more joints of the feline hind limb. The muscles include members of the quadriceps and triceps surae groups, a long toe flexor, and plantaris. The animals received a chronic LHX and a subgroup underwent eccentric training prior to the terminal experiments. Following the decerebration and removal of anesthesia, muscles in pairs, denoted as recipient and donor, were stretched in different combinations and intermuscular inhibition assessed as a decrease in the stretch reflex of the recipient muscle. Blinded analysis involved categorizing 9 cats based on their patterns and magnitude of iFFB. Out of 9 LHX cats so far, we have accurately categorized 8 based on iFFB patterns. Specifically, the trained animals showed iFFB patterns resembling SIC, a more moderate amount of inhibition and less convergence onto the ankle musculature. This return to SIC iFFB patterns in the eccentric training group may restore limb stiffness during gait and be a viable rehabilitation approach to recover gait. We are also looking at the kinematic features of locomotion throughout recovery see SfN companion poster Montgomery et al.

Disclosures: S. McMurtry: None. **A. De Boef:** None. **E. Kajtaz:** None. **L. Montgomery:** None. **J. Nanney:** None. **D.R. Howland:** None. **T.R. Nichols:** None.

Poster

573. Taste: Sensing and Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 573.01/I1

Topic: D.05. Olfaction and Taste

Support: NIH Grant ZIA MH002920-09

Title: Uncovering the spatial representation of taste identity in the human brain

Authors: *J. AVERY, A. G. LIU, C. D. RIDDELL, S. J. GOTTS, J. E. INGEHOLM, A. MARTIN;
Lab. of Brain and Cognition, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: In the mammalian brain, the insula is the primary cortical substrate involved in the perception of taste. Recent imaging studies in rodents have identified a 'gustotopic' organization in the insula, whereby distinct insula regions are selectively responsive to one of the five basic tastes. However, numerous studies in monkeys have reported that gustatory cortical neurons are broadly-tuned to multiple tastes, and tastes are not represented in discrete spatial locations. Neuroimaging studies in humans have thus far been unable to discern between these two models, though this may due to the relatively low spatial resolution employed in taste studies to date. In the present study, we examined the spatial representation of taste within the human brain using ultra-high resolution functional magnetic resonance imaging (MRI) at high magnetic field strength (7-Tesla). During scanning, participants tasted sweet, salty, sour and tasteless liquids, delivered via a custom-built MRI-compatible tastant-delivery system. Our univariate analyses revealed that all tastes (vs. tasteless) activated primary taste cortex within the bilateral dorsal mid-insula (cluster-level p-values << 0.01, corrected via whole-brain permutation test), but no brain region exhibited a consistent preference for any individual taste. However, our multivariate searchlight analyses were able to reliably decode the identity of distinct tastes within those mid-insula regions, as well as brain regions involved in affect and reward, such as the striatum, orbitofrontal cortex, and bilateral amygdala (corrected cluster p-values < 0.05). These results suggest that taste identity is not represented topographically, but by a distributed spatial code, both within primary taste cortex as well as regions involved in processing the hedonic and aversive properties of taste.

Disclosures: J. Avery: None. **A.G. Liu:** None. **C.D. Riddell:** None. **S.J. Gotts:** None. **J.E. Ingeholm:** None. **A. Martin:** None.

Poster

573. Taste: Sensing and Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 573.02/I2

Topic: D.05. Olfaction and Taste

Support: NIH UL1GM118979
NIH TL4GM118980
NIH RL5GM118978

Title: Generalization of conditioned avoidance of 10% ethanol to sucrose, quinine and sucrose-quinine mixtures in male and female rats

Authors: S. R. HESSEL, ***Y. TREESUKOSOL**;
California State Univ. Long Beach, Long Beach, CA

Abstract: Individual variability in taste responsivity contributes to food and fluid acceptance and rejection. Like humans, female rats have a higher propensity to consume ethanol (EtOH), relative to body weight, compared to males. Though humans and rats innately avoid bitter-tasting stimuli, like EtOH, individual variability in orosensory responsivity to ethanol may explain differences in ethanol intake. Previous findings in the literature suggest conditioned avoidance to alcohols generalize to compounds that humans describe as bitter and sweet. The current study was designed to test the hypothesis that the taste qualities of ethanol differ in female and male rats. Here, male [n=16] and female rats [n=16] were presented 10% EtOH followed by administration (i.p.) of either LiCl [n=12] to induce visceral malaise, or saline [n=20], control. Both females ($p = .002$) and males ($p < .001$) demonstrated avoidance of the 10% ethanol across the 4 conditioning trials. After conditioning, generalization was assessed in a brief-access taste test (10-s trials; 30-min sessions). The test array included water, 0.3 M sucrose, 0.03 M sucrose (representing “sweet” compounds), 0.3 mM quinine, 0.03 mM quinine, (representing “bitter” compounds) and mixtures 0.3 M sucrose - 0.03 mM quinine, and 0.03 M sucrose - 0.3 mM quinine, presented in randomized blocks without replacement. Animals could initiate as many trials as possible during the test session. Average number of licks to each test stimulus was used to calculate suppression scores, indicating the degree to which rats generalized the conditioned avoidance of EtOH to each test stimulus. Both male and female LiCl-injected rats showed higher suppression scores to sucrose than quinine. There was more variability in lick responses to mixtures across all rats independent of sex highlighting the importance of further investigating other potential attributing factors. The brief access feature of this procedure provides behavioral measures in which the contribution of postoral factors are minimized. These findings support a role for oral cues in the responses to ethanol.

Disclosures: S.R. Hessel: None. **Y. Treesukosol:** None.

Poster

573. Taste: Sensing and Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 573.03/I3

Topic: D.05. Olfaction and Taste

Support: Problemas Nacionales 464
Productos Medix 3247

Title: Sucrose detection and decision-making coding in the rat anterior insular and orbitofrontal cortex

Authors: *E. FONSECA[1], V. SANDOVAL-HERNÁNDEZ[2], S. MEJÍA-ORTIZ[1], F. ZEPEDA-RUIZ[1], S. A. SIMON[3], R. GUTIERREZ[4];
[1]CINVESTAV, Mexico City, Mexico; [2]Dept. of Physiol., Escuela Nacional de Ciencias Biológicas, IPN, Mexico City, Mexico; [3]Neurobio., Duke Univ. Hosp., Durham, NC; [4]CINVESTAV - IPN, Mexico City, Mexico

Abstract: Sweet taste quality, which predicts immediate energy presence, is suggested to be primarily encoded in the anterior insular cortex (aIC). In contrast, intensity/concentration is known to be encoded throughout the gustatory pathway, including the primary and secondary gustatory cortices: aIC and Orbitofrontal Cortex (OFC). Representation of both attributes is essential to shape a taste percept which will lead the subjects to the most convenient food selection. Studies exploring neural representation of these attributes have been mainly achieved in anesthetized animals, in tasks where subjects only decide whether to ingest or not the gustatory stimuli, or that does not allow a dissection between quality and intensity components. Therefore, we designed a sucrose detection task (Water 0% vs. sucrose 0.5, 1.3, 3.2, 7.9, 20%) that allowed the animal to actively report the presence or absence of sucrose while recording single-unit activity. We found that more than half of neurons recorded, in both cortices, were responsive to cue delivery. Although, at the population level, different modulatory patterns were displayed: aIC responded earlier and with a strong phasic component, whereas OFC neurons exhibited a late tonic response. Only a small (~16.6%) subpopulation of Quality-selective (QS) neurons responded differentially to sucrose in comparison to water. This group contained more information -in the firing rate and spike timing- about the intensity in comparison to Non-selective. Furthermore, QS could respond differently to at least two of sucrose intensities (Intensity-Variant, Var) or very similar to all sucrose intensities (Intensity-Invariant, Inv). The proportion of the Inv neurons was higher in the aIC in comparison to OFC, while Var neurons prevailed in the OFC. We propose that Inv neurons could be important to detect sucrose regardless of its sweetness. In both cortices, a subset of Var neurons linearly modulated their firing rate as a function of intensities. These data confirm that both regions represented sucrose quality and intensity physical dimension: responses covaried with stimulus. On the other hand, we confirmed that the psychological dimension of the sweet taste detection can be encoded in both regions: responses covaried with the animal choice. Finally, other decision-variables such as movement direction and outcome omission were encoded by these two regions. Thus, the taste system uses a compact and distributed code to detect and represent the perceived quality and intensity of sucrose. Moreover, the decision variables, as opposed to other sensory systems, are encoded by both cortices demonstrating they served as multimodal areas.

Disclosures: E. Fonseca: None. **V. Sandoval-Hernández:** None. **S. Mejía-Ortiz:** None. **F. Zepeda-Ruiz:** None. **S.A. Simon:** None. **R. Gutierrez:** A. Employment/Salary (full or part-time):; CINVESTAV-IPN. 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.; Problemas Nacionales 464, Productos Medix 3247.

Poster

573. Taste: Sensing and Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 573.04/I4

Topic: D.05. Olfaction and Taste

Support: NIH Intramural grant

Title: Testing basic principles of gustatory neural coding

Authors: *Y.-S. HUNG, M. A. STOPFER;
NICHD, NIH, Bethesda, MD

Abstract: The sensation of taste (gustation) provides critical information about nutrient content and toxicity of food sources. It is essential for the survival of animals, and in the case of humans, it also enhances our enjoyment of flavoursome foods, the quality of our lives, and our good health. However, the neural mechanisms for encoding and processing taste information are still unclear and controversial within the gustation field. Two major but contradictory hypotheses for taste information coding are widely accepted. The “labeled line” model states that there are a small number of basic taste categories (e.g. sweet, sour, salty, bitter, umami), and that these tastes are encoded, from receptors to brain, via segregated pathways. The other view, the “across fibre pattern” model, asserts that a tastant and its intensity are encoded by interacting ensembles of broadly tuned neurons. Controversy also surrounds the fundamental question of whether the gustatory system senses only basic taste categories, or rather each individual tastant. To understand how taste information is processed in the nervous system, we use fruit flies (Drosophila) to test these fundamental ideas. Taking advantage of genetic tools, we will examine the basic coding hypotheses using both anatomical and physiological approaches. We will identify and characterise the connectivity of gustatory secondary neurons (G2Ns) to different gustatory receptor (GR) expressing neurons, and their responses to a wide variety of tastants. Our preliminary results show that G2Ns connect to more than one type of GR-expressing neuron. The physiological measurements from these cells (by patch clamp and calcium imaging) in flies exposed to various tastants will provide valuable insights into the gustatory coding scheme employed by fruit flies.

Disclosures: Y. Hung: None. **M.A. Stopfer:** None.

Poster

573. Taste: Sensing and Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 573.05/I5

Topic: D.05. Olfaction and Taste

Support: NIH Grant R01GM100027

Title: Functional division of *Drosophila melanogaster* sweet taste neurons underlying behavioral flexibility towards sugars

Authors: *H.-L. CHEN[1], U. STERN[2], R. YANG[2];
[1]Biol., [2]Neurobio., Duke Univ., Durham, NC

Abstract: While *Drosophila* consistently show appetitive responses toward sugars during food searching, their responses towards sugars during egg-laying site selection is context dependent. For example, they readily accept a sucrose substrate for egg-laying when it is the sole option but robustly reject it when a sucrose-free substrate is available. The mechanism by which *Drosophila* sweet taste circuit ensures consistent response towards sugar during one behavior while promotes flexible sugar responses during another is not known. Here, we report that sweet taste neurons on flies' proboscis are divided into two distinct groups that convey opposing values in the context of egg-laying but promote identical values in the context of feeding. First, we found that a specific subset of sweet taste neurons - that is molecularly distinct from the rest - acts specifically to promote rejection of sucrose during egg-laying. Inhibiting this subset of sweet neurons switched females from robustly rejecting to preferring sucrose for egg-laying. Second, both the sensitivity and the functional output of the rejection-promoting sweet neurons are regulated differently from the rest of the sweet neurons. Removing a specific ionotropic receptor (IR) from these neurons but not the rest reduced sucrose rejection. Moreover, reducing two GABA receptors from these neurons did not impact sucrose appraisal whereas reducing the receptors from the rest enhanced sucrose preference for egg-laying. Third, the rejection-promoting group still promotes appetitive response during feeding. Optogenetic activation of these neurons drove robust proboscis extension, a feeding acceptance, as did optogenetic activation of the rest. Finally, the rejection-promoting group and the rest have shared as well as distinct synaptic targets in the brain. Using Trans-Tango, a newly developed synaptic-tracing technique in flies, we found that both groups synapsed with 2nd order neurons that arborize locally in the subesophageal zone (SEZ), a taste center in the brain where motor neurons controlling proboscis extension extend their dendrites, but the rejection-promoting group did not synapse with 2nd order neurons that showed long range projections to several higher brain areas. Together, our collective results revealed the existence of a specific group of sweet taste neurons that is molecularly, cellularly, and anatomically distinct from the rest of sweet taste neurons and its existence enables consistent

appetitive responses during feeding but context-dependent responses during egg-laying site selection.

Disclosures: H. Chen: None. **U. Stern:** None. **R. Yang:** None.

Poster

573. Taste: Sensing and Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 573.06/I6

Topic: D.05. Olfaction and Taste

Support: NIDCD Grant 5R01DC014728

Title: Human taste buds are more densely innervated than those of mice and tree shrews

Authors: *B. HIGH, C. E. WILSON, R. YANG, M. E. JETTÉ, T. E. FINGER;
Dept. Cell & Devel. Biol., Univ. of Colorado, Aurora, CO

Abstract: Gustatory nerve fibers innervate mammalian taste buds and express P2X receptors, reflecting the obligate purinergic nature of gustatory transmission. These fibers arise from the facial nerve to innervate the fungiform papillae and from the glossopharyngeal nerve to innervate the circumvallate and foliate papillae. We utilized immunohistochemistry to visualize P2X3, which labels gustatory fibers as well as subset of mucosal nerve fibers, and electron microscopy to compare the patterns of innervation of fungiform and circumvallate papillae of mice, humans and tree shrews (*Tupaia belangeri*), a member of the Euarchontoglires superorder of mammals. Immunofluorescent images were quantified using trinarization then binarization of P2X3-positive nerve fibers to calculate the density of innervation of taste buds. As another means of assessing innervation density, nerve fiber profiles were counted in randomly selected electron microscopic images of taste buds across species. Although the general pattern of innervation is conserved across all three species, initial measurements show that human taste buds have 2-5 times the density of innervation compared to corresponding taste buds in mice and tree shrews. Further ultrastructural analysis is necessary to determine whether the details of connectivity, such as the number of synaptic contacts, in humans differ from those in mice and tree shrews.

Disclosures: B. High: None. **C.E. Wilson:** None. **R. Yang:** None. **M.E. Jetté:** None. **T.E. Finger:** None.

Poster

573. Taste: Sensing and Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 573.07/I7

Topic: D.05. Olfaction and Taste

Title: Memories are coming: Tracking the neural activity underlying taste aversion learning

Authors: *E. ARIELI[1], N. YOUNES[1], A. MORAN[1,2];
[1]Tel Aviv Univ., Tel Aviv, Israel; [2]Sagol Sch. of Neurosci., Tel Aviv, Israel

Abstract: Neuronal activity in sensory cortices changes following learning, such as in the gustatory cortex (GC) after conditioned taste aversion (CTA) wherein a novel palatable taste becomes aversive following pairing with malaise. These changes, however, have been found using "snapshots" taken 24 hours apart, and thus do not allow a fine temporal description of the response changes over time. Insights about the time course of these changes come from molecular studies showing different molecular cascades that span over hours following the CTA induction. To reveal the neuronal activity changes over time we implanted rats with electrodes in the GC and intraoral cannula for precise taste deliveries, and tracked ensembles of neurons for 48 hours; before, during and after CTA. Our results show that changes in neuronal response dynamics start approximately 1h after CTA induction and end about 8h post CTA, with the main changes occurring 3-6h post CTA. This timing is similar to the time frame of the reported molecular processes. Interestingly, these changes were uncorrelated with changes in their baseline (BL) activity over time. In contrast, high correlations were observed in BL and taste response activity between different neurons, supporting the idea of global changes that govern neuronal activity following learning. Additional analyses of network level synchrony and delta-gamma modulation show similar increases 3 hours post CTA. Together, our results show that long-term electrophysiological changes that occur following taste aversion learning occur at the same time scales of the molecular processes. Moreover, these changes seem to be mainly governed by a network level organization and to a lesser extent by the state of the single neuron.

Disclosures: E. Arieli: None. **N. Younes:** None. **A. Moran:** None.

Poster

573. Taste: Sensing and Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 573.08/I8

Topic: D.05. Olfaction and Taste

Support: This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs, through the Spinal Cord Injury Research Program (SCIRP), Investigator Initiated Research Award (IIRA), under Award No. W81XWH-17-1-0197.

Title: The effects of sleeve gastrectomy on oral and post-oral sucrose preferences in a high fat diet-induced obese rat model of spinal cord injury

Authors: T. TANG, L. B. WILLING, E. N. BLANKE, N. HORVATH, G. M. HOLMES, ***A. HAJNAL**;
Neural and Behavioral Sci., Penn State Univ. Coll Med., Hershey, PA

Abstract: Approximately two-thirds of spinal cord injured (SCI) individuals become overweight or obese. Weight loss/metabolic surgery, including sleeve gastrectomy (SG) is regarded as highly effective in the long-term treatment of obesity and remission of type 2 diabetes. It is, however, unknown if obese individuals with SCI respond to obesogenic diets and SG similarly to the able-bodied. This study used a rat model of SCI to assess sucrose preferences in the context of dietary obesity, and the efficacy of SG. Male Wistar rats received either contusion injuries of the spinal cord (T3-T4) or spinal sham operation (SP-SHAM). After full recovery, all rats were fed a high energy, high fat diet (HFD, 60%kcal from fat) for 6 weeks prior to sleeve gastrectomy (SG) or abdominal sham surgery (AB-SHAM). Taste preferences based on oral and post-oral effects were assessed using automated gustometers for brief-access (10-s) lick rate analysis and two-bottle choice (2BC) tests for sucrose, respectively, at various time points. Pre-HFD, SCI compared to SP-SHAM significantly reduced sweet taste preferences for sucrose (0.6-1.5M) but did not alter 2BC preference. HFD resulted in greater weight gain in SCI rats, an overall blunting of lick responses to low (0.1-0.3M) and increased responses for high sucrose concentrations (0.9-1.5M). Furthermore, SCI rats on HFD showed avoidance to 0.3M sucrose in the 2BC tests. Lastly, SG compared to AB-SHAM reduced sucrose preferences across all concentrations in both SCI and SP-SHAM cohorts with the SCI rats being more sensitive to this effect. SG also restored 2BC sucrose preference in SCI rats. In summary, SCI, compared to sham-surgery, reduced sweet-taste preferences based on brief-access oral stimulation both prior and post HFD, and also abolished preferences for sucrose based on its post-ingestive effects following HFD exposure. Furthermore, SCI rats were more sensitive to the effects of SG on either oral or post-oral sucrose preferences. Remarkably, SG restored diminished post-oral preferences for sucrose in the SCI rats. These findings collectively support the hypothesis that SCI may result in altered taste and gut-brain nutrient/reward sensing, and in turn, may increase the risk for development of diet-induced obesity. Furthermore, these findings represent the first evidence suggesting that SG may restore normal sensing in SCI more efficiently than non-SCI subjects. Future mechanistic studies are warranted to reveal the underlying neural and hormonal mechanisms.

Disclosures: T. Tang: None. **L.B. Willing:** None. **E.N. Blanke:** None. **N. Horvath:** None. **G.M. Holmes:** None. **A. Hajnal:** None.

Poster

573. Taste: Sensing and Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 573.09/I9

Topic: D.05. Olfaction and Taste

Support: NIDCD Grant RO1-DC6013904

Title: High fat diet's influence on body composition and peripheral taste organs persists even after switching to a low fat diet

Authors: F. HARNISCHFEGER[1], M. S. WEISS[3], *P. M. DI LORENZO[4], R. DANDO[2]; [1]Food Sci., [2]Cornell Univ., Ithaca, NY; [3]Psychology, [4]Binghamton Univ., Binghamton, NY

Abstract: Recent studies have shown that weight gain arising from consumption of a high fat diet (HFD) in mice is accompanied by a loss of taste buds (Kaufman et al. PLoS Biol. 16(3):e2001959, 2018). Here, we studied whether a HFD in rats would also result in a loss of taste buds and whether this deficiency would persist after rats were returned to a normal chow diet for a prolonged period. Two groups of adult male rats were fed standard chow (CON) or a HFD (45% fat) for 8 wks. The HFD group was then divided into two groups that were weight matched: the HFD-chow group was switched to standard chow and the HFD-pair fed group was given the same number of calories as their HFD-chow counterparts, but in the form of a HFD. Rats were maintained on this diet regime for an additional 12 wks. All rats were scanned with dual-energy X-ray absorptiometry to assess body composition every 4 wks. At the end of the experiment, rats were sacrificed and perfused with saline and paraformaldehyde. Tongues were removed. The fungiform region was stained with methyl blue and imaged to count fungiform papillae. Circumvallate papillae were processed histologically to allow analyis of taste buds. Groups were compared using independent Kruskal-Wallis ANOVA, with statistical significance assumed at $P < 0.05$. Results showed that all rats on a HFD gained weight and showed an increase in the proportion of body fat compared to CON rats during the 8 wks prior to the dietary switch. After the HFD group was divided, rats in both groups continued to gain weight, with the percent body fat in the HFD-pair fed group continuing to increase despite caloric restriction. Percent body fat in the HFD-chow group decreased but remained elevated compared to CON group. Analyses of taste buds showed a clear and significant decrease in the number of taste buds and in the number of fungiform papillae (Ps < 0.05) in both the HFD-chow and HFD-pair fed groups compared with lean CON rats. Additionally, number of Type II cells, as measured by gustducin, were lower in the HFD-chow and HFD-pair fed groups compared with CON rats ($P < 0.05$). Although not significant, the HFD-pair fed group had slightly increased neutrophil invasion into the circumvallate papillae. These data suggest that consumption of a HFD

compromises the peripheral gustatory apparatus and that this effect persists despite a long-term resumption of a standard diet.

Disclosures: F. Harnischfeger: None. **M.S. Weiss:** None. **P.M. Di Lorenzo:** None. **R. Dando:** None.

Poster

573. Taste: Sensing and Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 573.10/I10

Topic: D.05. Olfaction and Taste

Support: NIH R01 DC006666

Title: State-dependent coding: LiCl-induced sickness alters gustatory oscillatory rhythms and coordinated spiking during taste processing

Authors: *B. T. STONE[1], A. MAHMOOD[1], J.-Y. LIN[1], D. B. KATZ[2];
[1]Neurosci., [2]Dept Psychol, Brandeis Univ., Waltham, MA

Abstract: A large literature addresses how toxicity by way of drug injection (commonly lithium chloride; LiCl) shapes aversive behavior, but few studies have delved into the nature of this powerful state itself. Such states influence an animal's interactions with its environment, potentially affecting its feeding behavior through modifications of taste perception: an animal that is ill, for instance, is less likely to find food appetitive (a fact that can potentially prolong infirmity by demotivating the animal to ingest nutrients). Here, we report the beginning of an investigation into how the spontaneous network state induced by LiCl specifically impacts taste processing, and how the activity underlying this internal state might support learning. Using extracellular (single-neuron and local field potentials; LFPs) recordings during a passive taste delivery task under two (LiCl-induced sickness and Neutral) conditions, I demonstrate evidence that network state changes induced by internal state manipulations are represented in the gustatory cortex (GC). I show that in comparison to a neutral ("healthy") state, rhythmic activity during taste presentation is quenched within 7-12Hz which has previously been reported as reflective of attentiveness to external stimuli. Furthermore, the data show that coordinated spiking activity following taste delivery, as characterized through spike-phase locking within the GC, increases within 4-7Hz while decreases within 7-12Hz; providing evidence that sickness alters the orchestrated communication among neural populations differentially with respect to rhythmic patterns. These results provide powerful evidence towards the function that an animal's welfare has on the establishment and maintenance of natural reward valuation and associative effects of stimuli.

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Poster

573. Taste: Sensing and Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 573.11/I11

Topic: D.05. Olfaction and Taste

Title: Neonatal chorda tympani transection enhances gustatory responses from uninjured nerves in the adult rat parabrachial nucleus of the pons

Authors: *L. J. MARTIN, S. I. SOLLARS;
Univ. of Nebraska At Omaha, Omaha, NE

Abstract: The gustatory chorda tympani nerve (CT) does not regenerate when it is cut in rats at postnatal day 10 (P10) or younger, resulting in a permanent loss of taste input from the anterior tongue. Early CT transection (CTX) alters the organization of intact gustatory nerve terminal fields in the nucleus of the solitary tract (Martin et al., 2019) and stunts the typical developmental shift from preference to avoidance for ammonium chloride (NH_4Cl) solutions (Sollars & Bernstein, 1996). The importance of CT input for the development of central gustatory function is largely unknown. Here, we recorded gustatory responses from single neurons in the third-order gustatory nucleus, the parabrachial nucleus of the pons (PbN), in adult male and female rats following neonatal CTX. At P5, the CT was accessed via a neck incision and was either transected (CTX) or left intact following visualization (Sham). At least 100 days after surgery, rats were anesthetized with urethane and prepared for extracellular electrophysiology. The CT proximal to the site of surgery was then cut in the middle ear in Sham and CTX rats to ensure that all sampled neurons responded to input from taste nerves other than the CT and that neurons were as similar as possible between experimental groups. Glass-insulated tungsten microelectrodes (1-3 MΩ) were lowered into the brain until gustatory PbN neurons were identified. Firing rates to the following stimuli were recorded: 0.1 and 0.5 M NH_4Cl, 0.1 and 0.5 M NaCl, 0.5 M sucrose, 0.01 M citric acid, and 0.01 M quinine. Neural activity and entropy (breadth of tuning to five stimuli) were compared between groups with ANOVAs and Welch's *t*-tests. Responses were recorded for 25 CTX neurons and 25 Sham neurons. Overall, CTX rats had significant higher responses to taste stimuli ($p = .005$), and differences in taste responses between surgical groups dependent on the solution examined ($p = .001$). Specifically, CTX rats had significantly higher responses to 0.1 M NH_4Cl ($p = .021$), 0.5 M NH_4Cl ($p = .001$), 0.1 M NaCl ($p = .013$), 0.5 M NaCl ($p = .005$) M citric acid ($p = .042$). There was a non-significant tendency for CTX rats to have higher activity to 0.5 M sucrose stimulation ($p = .062$), but responses to 0.01 M quinine were not significantly different between groups ($p = .427$). Neurons from CTX rats also had significantly higher spontaneous activity ($p = .032$) and

entropy (p = .044). These findings suggest that the early loss of CT input leads to compensatory amplification of remaining inputs in a stimulus-specific manner. Higher spontaneous activity, elicited responses, and tuning breadth in CTX rats may reflect an increased convergence of inputs onto PbN neurons.

Disclosures: L.J. Martin: None. **S.I. Sollars:** None.

Poster

574. Auditory Processing: Neural Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

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Topic: D.06. Auditory & Vestibular Systems

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Title: Do rat brains discriminate Spanish and English languuages?

Authors: *M. SATO, N. MATSUMOTO, Y. IKEGAYA;
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Abstract: There are difficult tasks that humans are not able to solve even after they are repeatedly trained. For example, many Japanese people have difficulty in discriminating between sounds of L and R although the two types of sounds are represented in distinct cell ensembles in the auditory cortices. Thus, since sensory information is conveyed from sensory organs to each sensory cortex as long as humans are exposed to sensory stimuli, we hypothesized that sensory cortices contain the information required to solve a sensory discrimination task. In the process of sensory information transmission from the sensory organs to the sensory cortices, there is little information loss at least in the primary sensory cortex. Therefore, sensory information in a sensory-relevant task may be decoded from neuronal activity in the primary sensory cortex. We hypothesized that when the human language is presented to rats in an auditory discrimination task, the auditory information (*e.g.*, Spanish or English) can be decoded from neural activity, although rats do not basically discriminate between the phonetic features of spoken English and Spanish languages. To test this hypothesis, we developed a new behavioral task, where we extracellularly recorded neuronal activity (*i.e.*, local field potentials (LFPs)) from the rat primary auditory cortex while a rat was given short phrases of Spanish or English sentences. Then, we tried to decode the language given to the rat from the neural activity. Before we presented voices of human languages to rats, as pilot study, we recorded LFPs from the primary auditory cortex while rats were given pure tones (1500 - 7000 Hz, 3 sec) intervened between silent periods, and found the differences in LFPs between the onsets of the silent and tone periods. We examined

whether deep learning can decode the difference of the pitches and silent periods from LFPs. We found deep learning model with a structure that performs one-dimensional convolution in the time axis direction and the electrode channel direction independently, improved decoding performance partially because the spatiotemporal information of LFPs was efficiently used. We tried to feedback the decoded information to the brain and to enhance what the animals are able to do, which would enhance animals' intelligence.

Disclosures: M. Sato: None. **N. Matsumoto:** None. **Y. Ikegaya:** None.

Poster

574. Auditory Processing: Neural Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 574.02/I13

Topic: D.06. Auditory & Vestibular Systems

Support: DARPA (D15AP00101)

Title: Direct comparison of nonlinear sensory encoding models in ferret primary auditory cortex

Authors: *J. R. PENNINGTON[1], S. V. DAVID[2];
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Abstract: A common framework for describing the function of auditory neurons is the linear-nonlinear spectro-temporal receptive field (LN STRF). This model casts a neuron's sound-evoked activity at each moment in time as the linear weighted sum of the immediately preceding sound spectrogram, followed by nonlinear rectification. However, the LN STRF is an incomplete model since it cannot account for context-dependent encoding or other nonlinear aspects of auditory processing. Two alternative models have improved on the predictive power of the LN STRF by accounting for experimentally observed biological mechanisms: short-term plasticity (STP) and contrast-dependent gain control (GC). While both models improve performance over the LN model, they have never been compared directly. Thus, it is unclear whether they account for separate processes or simply describe the same phenomenon in different ways. To address this question, we recorded the activity of single primary auditory cortical neurons (n = 423) in awake ferrets (n = 7) during the presentation of natural sound stimuli. We then fit STRFs incorporating one nonlinear contextual mechanism (GC or STP) or both mechanisms (STP+GC) on this single dataset. We compared model performance using the correlation coefficient (Pearson's R) between predicted and observed time-varying firing rate for each neuron. Our results indicate that there is no significant performance difference between the STP and GC models, but that the STP+GC model performs significantly better than either individual model. This finding indicates that the STP and GC models contain distinct explanatory power. Further,

the success of the combined model hints that auditory cortical neurons utilize at least two independent mechanisms to adapt encoding properties to different sensory contexts. Future neuromorphic sound processing technologies may therefore improve their performance by incorporating both STP- and GC-based strategies.

Disclosures: **J.R. Pennington:** None. **S.V. David:** None.

Poster

574. Auditory Processing: Neural Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 574.03/I14

Topic: D.06. Auditory & Vestibular Systems

Title: The properties of neural activities by acoustic factors in higher auditory region to sound stimuli in awake and anesthetized finches

Authors: *A. YOSHIDA, M. INDA, K. HOTTA, K. OKA;
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Abstract: Zebra finches (*Taeniopygia guttata*) sing songs to communicate each other. Songs enable the birds to discriminate species and individuals, and the previous study suggested that female finches have high selectivity to individual male songs (Terpstra *et al.*, 2006). In the avian brain, caudomedial nidopallium (NCM), one of higher auditory regions, might play the important roles for memorization and discrimination of songs. In this study, we recorded neural activities to several songs from single NCM neurons in awake finches to investigate the difference between responses to each song. In our experiment, three songs were presented as sound stimuli: direct song (sing for courtship), undirect song (sing in daily life) and hetero-specific song (Bengalese finches' song).We detected the significant differences in awake birds only between the responses to undirect song and those to hetero-specific song. To investigate why there was no significant difference between responses to direct song and those to hetero-specific song, we examined the difference of the several acoustic factors of songs: amplitude, fundamental frequency, mean frequency, frequency modulation and entropy. The comparisons of the effects of these acoustic factors in songs on neural activities indicated that neurons in NCM encode these factors. This result suggests that the difference of acoustic factors could cause the difference of responses.Furthermore, recent studies showed that anesthesia has a great effect on the neural activity (Ruijssevelt *et al*., 2017). We, therefore, recorded the neural activities from single NCM neurons under urethane anesthesia and awaking. In this comparison, there was no significant differences in responses to the whole songs. However, we found the significant differences in the timing and the duration of the responses by syllable base analysis. This suggests the possibility that urethane triggers the response delay of NCM neurons. We approached the influence of anesthesia on the neurons.

Disclosures: **A. Yoshida:** None. **M. Inda:** None. **K. Hotta:** None. **K. Oka:** None.

Poster

574. Auditory Processing: Neural Coding

Location: Hall A

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Program #/Poster #: 574.04/I15

Topic: D.06. Auditory & Vestibular Systems

Support: NIH Grant F32 DC016508
NIH Grant R01 DC014656

Title: Representation of behavioral integration time downstream of auditory cortex

Authors: ***J. YAO**, J. GIMOTO, D. SANES;
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Abstract: The central representations of environmental signals are transformed at each locus of an ascending sensory pathway. One characteristic of this hierarchical processing is that the time required to fully encode a sensory cue (i.e., integration time) increases at ascending levels of the nervous system. Here, we sought to determine how auditory information is transformed downstream from core auditory cortex (ACx), at a location thought to support sensory decisions, the parietal cortex (PC). Gerbils were trained and tested on an appetitive alternative forced-choice (AFC) auditory temporal integration task. Specifically, gerbils were required to discriminate between amplitude modulated (AM) noise at 4 versus 10 Hz across a range AM durations (100-1000 ms). Behavioral integration times were measured by examining how AM discrimination scales with stimulus duration. Task performance was poor at very short AM durations (100-200 ms), improved with longer durations, and reached an optimum at ~600 ms. To determine the downstream projections from gerbil ACx to PC, viral tracing experiments were performed. The data revealed a disynaptic pathway from ACx to dorsal auditory cortex to PC. Thus, we hypothesized that the integration times for AM cues are transformed downstream from ACx, in PC, thereby creating the representation that supports integration time on the AM task. To test this idea, muscimol was bilaterally injected in PC to attenuate activity during task performance. While animals continued to perform the task following muscimol infusion, integration times were increased. To determine whether a PC encoding mechanism could account for these behavioral results, we conducted wireless recordings of single-unit activity from neurons in ACx and PC while gerbils simultaneously performed the auditory temporal integration task. Neural integration times are calculated from discharge patterns obtained during psychometric performance. We predict that ACx integration times for AM signals will be significantly shorter than those displayed behaviorally, whereas the neural representation in PC will yield integration times that match psychometric performance. Collectively, these

experiments will reveal whether the neural representation downstream of ACx, in PC, is necessary and supports the observed behavioral temporal integration times.

Disclosures: J. Yao: None. **J. Gimoto:** None. **D. Sanes:** None.

Poster

574. Auditory Processing: Neural Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 574.05/I16

Topic: D.06. Auditory & Vestibular Systems

Title: Characterization of modularity in the lateral cortex of the mouse inferior colliculus using a combination of optogenetic circuit mapping and *in vivo* two-photon imaging

Authors: *B. A. IBRAHIM[1,2], Y. SHINAGAWA[1,2], A. R. ASILADOR[2,3,4], D. A. LLANO[1,2,3]; [1]Mol. & Integrative Physl, [2]Beckman Inst. for Advanced Sci. and Technol., [3]Neurosci. Program, [4]Sch. of Mol. & Cell Bio, Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: The inferior colliculus (IC) is a critical midbrain structure for the processing of auditory stimuli. The IC is a hub that permits widespread convergence of both bottom-up and top-down projections involving auditory, somatosensory, visual, motor and arousal-related brain regions. One of the non-lemniscal divisions of the IC, the lateral cortex (LC), contains periodic modules of GABAergic cells and terminals which stain strongly for a range of metabolic markers. Anatomically, auditory inputs from the auditory cortex or central nucleus of the IC strongly avoid these inhibitory modules and instead form dense projections to the matrix areas that surround the modules. In addition, these modules receive direct inputs from the somatosensory brain regions. On cell type, GABAergic cells in the modules appear to integrate information between the modules and matrix and therefore may be critical to multisensory integration. However, there is no clear mechanism about the function of these inhibitory modules in sensory processing. Here we show using laser-assisted mapping that AC terminals in the LC made monosynaptic connections with all LC neurons with the exception of GABAergic cells in the modules, which we previously have shown to be the only cell type in the LC to receive substantial intrinsic cross-module inputs. In addition, two-photon imaging was used here to characterize the functional activity of the GABAergic and nonGABAergic cells inside and outside the modules. We observed strong tone-responsiveness in the LC, with a broad array of tuning widths. These data suggest that the module/matrix organization of the lateral cortex has the capacity to process auditory stimuli while being modulated by auditory cortical projections.

Disclosures: B.A. Ibrahim: None. **Y. Shinagawa:** None. **A.R. Asilador:** None. **D.A. Llano:** None.

Poster

574. Auditory Processing: Neural Coding

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Title: Neuronal dynamics of non-classically responsive cortical neurons

Authors: *M. INSANALLY[1], B. DEPASQUALE[2], B. F. ALBANNA[3], K. RAJAN[4], R. C. FROEMKE[1];
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Abstract: Spike trains recorded from the cortex of behaving animals can be complex, highly variable from trial-to-trial and therefore challenging to interpret. A fraction of recorded cells typically exhibit trial-averaged responses with obvious task-related features and can be considered ‘classically-responsive’, such as pure tone frequency tuning in the auditory cortex. However, a substantial number of cells (including cells in primary sensory cortex) do not appear to fire in a task-related manner and are often neglected from analysis (Olshausen & Field 2006). Even classically-responsive cells lose their stimulus representation during task-engagement without impairing behavioral performance (Otazu et al., 2009). These results suggest that non-classically responsive cells may play an underappreciated role in sensory processing and cognition. Using multielectrode arrays we recorded from 103 single-units in the auditory cortex (AC) and 74 single-units in the frontal cortex (FR2) while animals performed a frequency recognition task. While the trial-averaged responses of some cells exhibited obvious and statistically significant task-related features, many cells were non-classically responsive (64/103 AC cells and 43/74 FR2 cells from 15 animals had neither significant tone-modulated activity nor ramping activity; $p < 0.05$, 5,000 bootstraps). Recently, we showed that non-classically responsive cells contained hidden task-relevant information at levels comparable to responsive cells using a novel single-trial spike-timing-based analysis (Insanally et al., 2019). Here we expand our investigation to explore the potential utility and necessity of non-classically

responsive cells and demonstrate: 1) Non-classically responsive cells are better predictors of single-trial behavioral errors. Historically, the capacity to predict behavioral errors on single trials using responsive cells has been limited. Using our novel decoder, we demonstrate that including non-responsive cells significantly improved predictions of behavioral errors in both auditory and frontal cortex indicating that these neglected cells can provide missing insights into behavioral variability. 2) Non-classically responsive activity is necessary for task performance and interacts synergistically with the activity of responsive cells. Using a recurrent neural network model trained to perform our frequency recognition task, we establish that non-classically responsive activity is necessary for successful task performance. Furthermore, we demonstrate that responsive and non-classically responsive subpopulations have a synergistic effect on network behavior.

Disclosures: M. Insanally: None. **B. DePasquale:** None. **B.F. Albanna:** None. **K. Rajan:** None. **R.C. Froemke:** None.

Poster

574. Auditory Processing: Neural Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 574.07/I18

Topic: D.06. Auditory & Vestibular Systems

Title: Data-driven auditory field mapping for mice using naturalistic sounds

Authors: *H. TERASHIMA[1], H. TSUKANO[2,3], S. FURUKAWA[1];
[1]NTT Communication Sci. Labs., Atsugi, Japan; [2]Dept. of Neurophysiol., Brain Res. Institute, Niigata Univ., Niigata, Japan; [3]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Studies on hierarchical cortical processing of auditory information require a precise map of functional fields that constitute the auditory cortex. For the mouse auditory cortex, advances of imaging techniques have resulted in a variety of researcher-dependent field maps (Guo et al., 2012; Issa et al., 2014; Tsukano et al., 2015). These mapping studies were biased in two ways: stimuli were only simple synthetic sounds and analyses of responses were hypothesis-driven. To address the issue, here we drew a new areal map of the mouse auditory cortex using naturalistic complex sounds and data-driven analyses. First, we recorded trans-cranial Ca^{2+} responses to a set of naturalistic sounds from the entire auditory cortex of anaesthetized Emx1-GCaMP8 mice. Considering the hearing range of mice, the naturalistic sound set was constructed by pitch-shifting a set of 165 natural sounds for humans (Norman-Haignere et al., 2015) by four octaves. We decomposed the responses into five components using matrix decomposition technique that maximizes non-Gaussianity of spatial components, which was originally developed for human BOLD signals (Norman-Haignere et al., 2015). Comparison with responses to pure tones reconfirmed the previously known tonotopic fields such as A1, AAF, DM, and A2.

Using regularized linear regression, we characterized each component by acoustic features that can predict its coefficient and found that some components are selective to FM sounds, which correspond to fields known as DA and DP. Moreover, we found a new auditory field on the rostro-dorsal side of the classical auditory cortex, which might be related to high-frequency FM sounds like mice vocalizations. Overall, our findings reconfirmed most of the field map drawn by Tsukano et al. (2015) and extended it with a new field. The results demonstrate how naturalistic sounds combined with machine learning techniques can reveal functional organization of the mouse auditory cortex.

Disclosures: H. Terashima: None. **S. Furukawa:** None. **H. Tsukano:** None.

Poster

574. Auditory Processing: Neural Coding

Location: Hall A

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Program #/Poster #: 574.08/I19

Topic: D.06. Auditory & Vestibular Systems

Support: NSF Grant No. IOS 1354381
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Title: Response properties of the bat primary auditory cortex to frequency-modulated stimuli

Authors: *K. BAKSHI[1,2], S. MACIAS HERRERA[2], M. S. SMOTHERMAN[1,2];
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Abstract: Neural selectivity to the direction and rate of sensory stimuli is a common feature across sensory modalities. In the auditory system, frequency-modulated (FM) sweeps are essential elements of vocal communication in animals and for human speech. Echolocating bats provide an ideal model for studying the neural circuits underpinning FM sweep selectivity due to their reliance on FM sweeps for biosonar. We used multichannel microelectrode arrays in anesthetized Mexican free-tailed bats (*Tadarida brasiliensis*) to evaluate how FM sweeps were encoded in the primary auditory cortex (A1). Pure tone stimuli were presented to determine the response properties of principal cells and their surrounding local field potentials (LFP), including characteristic frequency (CF), best frequency (BF), minimum threshold (MT), best level (BL) at CF, and frequency response area bandwidth (BW). We used these parameters to map the topographical organization of response properties throughout A1, and then investigated how FM sweep selectivity was represented within this map.
Spiking neurons responding to pure tone stimuli were tonotopically organized rostrocaudally with lower CFs represented caudally. Frequency response areas were significantly lower and broader for LFPs than for spikes, indicating that local interneurons receive convergent inputs

from an asymmetrical frequency range to produce a feedforward inhibition that may bias spiking neuron response properties in favor of downward sweeps. The majority of A1 neurons responded preferentially to downward FM sweeps, with more neurons tuned to slower sweep rates. These results are consistent with hypotheses that intracortical inhibitory processes, such as sideband inhibition, shape FM tuning and suggest that in the free-tailed bat, A1 is preferentially sensitized to sounds occuring within the context of downward FM sweeps.

Disclosures: K. Bakshi: None. **S. Macias Herrera:** None. **M.S. Smotherman:** None.

Poster

574. Auditory Processing: Neural Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 574.09/I20

Topic: D.06. Auditory & Vestibular Systems

Title: Auditory neurofeedback for noise suppression and speech enhancement

Authors: Y. DONG, ***Y. G. GAI**;
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Abstract: Cortical entrainment refers to the synchronization of brain activity to external sensory stimuli. For speech input, electroencephalography (EEG) signals may be linearly related to the sound envelope (in the frequency range of 2 to 8 Hz) or other linguistic features. When speech is presented in background noise, our previous study found that brain signals obtained with certain electrodes can suppress response to noise and more or less maintain correlations to the speech component. Here we developed a neurofeedback system to explore if the human subject can actively enhance speech response and suppress noise response. A 64-channel EEG system was used to record brain signals while the subject was presented with speech sentences presented alone in noise. In contrast to conventional neurofeedback systems that mostly measure neural oscillations to monitor the brain's internal states, our system provided the subject with real-time correlations of ongoing EEG signals evoked by speech in noise to a target. This target was either the envelope of the speech alone or pre-recorded EEG evoked by speech alone. Subjects were asked to increase this correlation value by changing their attention or whatever technique they found effective. We observed diverse abilities of subjects in suppressing responses to the background noise. The EEG electrodes that provide the best correlations also differed. The next step of the study is to find out if the auditory neurofeedback training can increase speech intelligibility assessed with behavioral tasks.

Disclosures: Y. Dong: None. **Y.G. Gai:** A. Employment/Salary (full or part-time):; Saint Louis University.

Poster

574. Auditory Processing: Neural Coding

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Program #/Poster #: 574.10/I21

Topic: D.06. Auditory & Vestibular Systems

Support: NIH 1R01DC016363
NIH 5R01DC013906

Title: Dynamics of primate inferior colliculus neurons during the localization of simultaneous sounds

Authors: *S. M. WILLETT[1], S. T. TOKDAR[2], J. M. GROH[3];
[1]Dept. of Neurobiology, Ctr. for Cognitive Neurosci., [2]Dept. of Statistics, [3]Psychology and Neuroscience, Neurobiology, Ctr. for Cognitive Neurosci., Duke Univ., Durham, NC

Abstract: It is unclear how neurons and populations of neurons encode more than one stimulus. Canonically, a possible solution is to have sufficiently selective neurons so stimuli representations could be encoded by specific neural subpopulations. However, this proposed solution ignores the multi-selectivity of many neural populations, the surprisingly broad tuning of neurons, and the complex content of natural stimuli. For example, neurons in the monkey inferior colliculus encode sound location by monotonically increasing their firing rate with sound eccentricity, while they encode sound frequency with circumscribed, but broad, receptive fields. Recent work (Caruso et. al., *Nature Communications,* 2018) proposed an alternative to the selective subpopulation hypothesis and showed that some inferior colliculus neurons alternate between firing rates corresponding to two simultaneously presented sounds within single trials. However, this study only presented sounds of similar frequencies. It remains unclear if these dynamics exist when sounds of dissimilar frequencies are presented, where neural tuning for frequency may potentially carry a larger coding burden. The current study presented simultaneous sounds with variable separation of frequency to investigate the impact of frequency selectivity on the dynamics of single trials neural responses. To determine the response functions of IC neurons, spiking activity from isolated, sound responsive, neurons were recorded while two rhesus macaques (*Macaca mulatta*) performed a dual sound localization task. The task required monkeys to make either a single saccade to the location of one sound or a sequence of saccades to the location of each simultaneously presented sound. Traditional time and trial pooled analyses found many of the neurons average their responses in the presence of two sounds. Upon closer inspection by an analysis using spike count distributions from single trials (whole trial, i.e. 1 bin) revealed some neurons alternate across trials. That is on some trials neurons responded to one sound and on other trials they responded to the other sound. Analyses at finer time scales in

neurons that exhibited intermediate whole trial spike counts but did not show such fluctuations at the single trial level are currently pending.

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Poster

574. Auditory Processing: Neural Coding

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 574.11/I22

Topic: D.06. Auditory & Vestibular Systems

Support: NIH Grant NS104911

Title: Modeling nonlinear dendritic integration in space-specific auditory neurons of barn owls

Authors: J. C. GORMAN[1], A. V. R. MILLER[1], J. L. PENA[2], *B. J. FISCHER[1];
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Abstract: Dendritic integration can take different functional forms depending on the morphology of the neuron and the active properties of the dendrites and spines. The barn owl's external nucleus of the inferior colliculus (ICx) contains spatially selective neurons (SSN) that form a map of auditory space, where nonlinear input integration has been described. Recent anatomical work identified the existence of large diverse spines in SSNs that may integrate many inputs. The anatomical finding of diverse spines in ICx suggests that ICx may consist of neurons with different functional forms of dendritic integration. Here we use a model to investigate the functional implications of different dendritic nonlinearities in SSNs.
Neurons in ICx become tuned to sound location through selectivity for combinations of sound localization cues. The barn owl uses the interaural time difference (ITD) as a cue for the horizontal direction. ITD is detected by neurons that are narrowly tuned to frequency, and thus unable to uniquely represent auditory space. ICx neurons resolve this ambiguity integrating inputs across frequency. As a result, SSNs display ITD tuning curves with a large peak for a single ITD, surrounded by reduced side peaks, termed side peak suppression (SPS).
We used a two-stage model of ICx neurons to study the relationship between frequency integration bandwidth and SPS, consisting of neurons with dendritic subunits with nonlinear integrative properties. The input to ICx originates in the lateral shell of the central nucleus of the inferior colliculus (ICcl). ICcl neurons respond to ITD and are narrowly tuned to frequency. An established model of ICcl as the source of ICx inputs was used. Plausible SPS values were obtained from intracellular *in-vivo* recordings of ICx neurons to constrain the model. We used the model to predict the frequency integration bandwidth that would produce experimentally observed ranges of SPS for ICx neurons with different dendritic subunit nonlinearities.
We found that different model configurations are possible, but there is a predictable relationship

between the bandwidth of frequency integration and the form of subunit nonlinearity required to achieve experimentally observed ITD tuning curve shapes. Specifically, larger frequency integration bandwidth requires a more suppressive dendritic subunit nonlinearity and vice versa. A sigmoid nonlinearity was able to capture both of these requirements since it is expansive for small numbers of inputs and suppressive for large numbers of inputs. This suggests that ICx neurons may integrate inputs over larger frequency ranges than currently predicted by linear models and frequency tuning curves.

Disclosures: **B.J. Fischer:** None. **J.C. Gorman:** None. **A.V.R. Miller:** None. **J.L. Pena:** None.

Poster

574. Auditory Processing: Neural Coding

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 574.12/I23

Topic: D.06. Auditory & Vestibular Systems

Title: Causal relationship between right auditory cortex and speech-evoked frequency following responses: Evidence from tDCS and EEG

Authors: *G. MAI, P. HOWELL;
Dept. of Exptl. Psychology, Univ. Col. London, London, United Kingdom

Abstract: Speech-evoked frequency following responses (FFR) reflect neural fidelity of speech periodicity and act as a clinical biomarker for speech processing disorders. While FFRs are considered to originate mainly from the brainstem, interest in contributions of auditory cortex (AC) to FFRs has increased. Recent research has shown that FFRs are associated with right-asymmetric AC activity (Coffey et al., 2016, 2017), but a causal relationship between AC and FFRs has not been established. This study combined transcranial direct current stimulation (tDCS) and electroencephalography (EEG) to test for such causality. 90 right-handed normal-hearing young adults were assigned at random to 5 groups (18 participants each group; single-blinded) and received 25-min 1-mA tDCS on AC (reference placed above the contralateral eyebrow) during a frequency discrimination task. Groups were (1) anodal on left AC; (2) cathodal on left AC; (3) anodal on right AC; (4) cathodal on right AC; and (5) sham (30-s ramping-up-and-down). An /i/ syllable was repeated monaurally on the left and right ear before and after tDCS and FFRs were obtained via EEG at the vertex. After-effects of tDCS on FFR spectral magnitudes and inter-trial phase-locking values at the fundamental frequency (F_0) were measured. After-effects showed main effects of group in the left but not right ear listening condition. Posthoc t-tests found that anodal and cathodal tDCS on right, but not left, AC resulted in significant after-effects (reduced FFR magnitudes and phase-locking) compared to sham in the left ear condition. In the right ear condition, no significant after-effects were found for tDCS on left or right AC compared to sham. Changes in neural excitability of the right, but not left, AC

altered FFR strengths along the contralateral pathway, hence providing direct evidence for a causal relationship between right AC and speech-evoked FFRs. Current results thus support the right-asymmetric auditory cortical contribution to processing of speech periodicity and facilitate our understanding of how speech is encoded in human auditory systems.

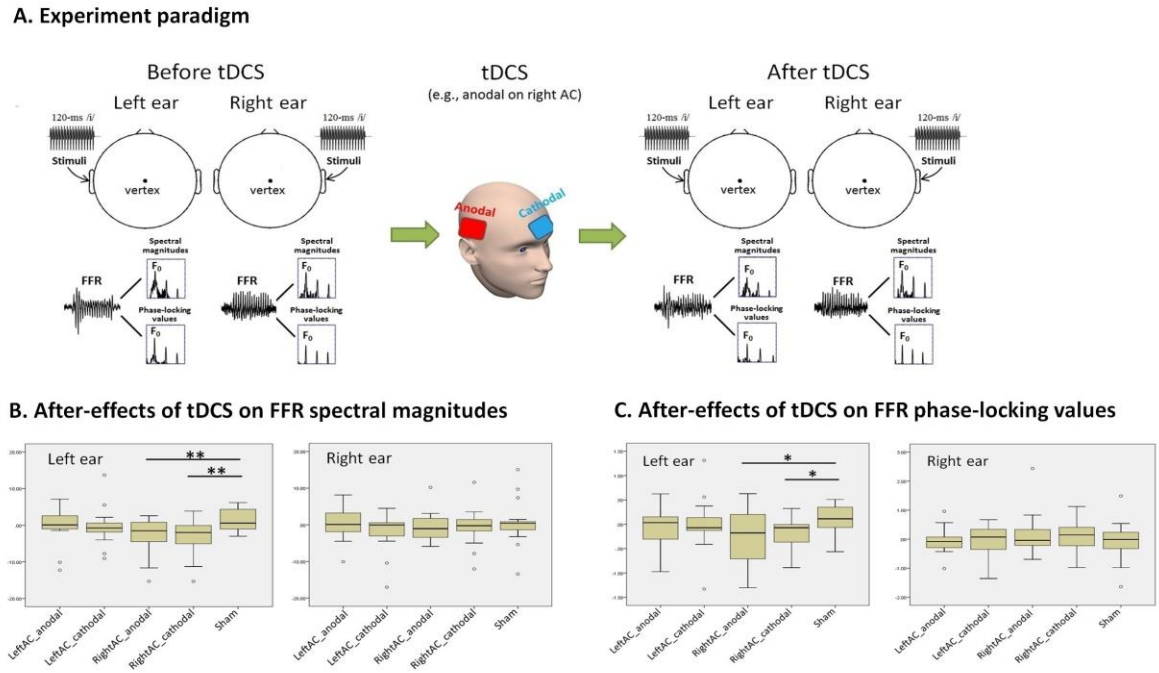

Figure 1. **(A).** Experiment paradigm. Participants listened to a repeated syllable monaurally from the left and right ear while FFRs were obtained from the vertex before and after tDCS. A frequency discrimination task was completed during tDCS. **(B) and (C).** After-effects of tDCS on FFR (B) spectral magnitudes (in *dB*) and (C) phase-locking values (logit-transformed). Significant main effects were found in the left but not right ear condition. Results showed significant after-effects of anodal and cathodal on the right AC compared to sham in the left ear condition. *p < 0.03; **p < 0.01

Disclosures: G. Mai: None. **P. Howell:** None.

Poster

574. Auditory Processing: Neural Coding

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Program #/Poster #: 574.13/I24

Topic: D.06. Auditory & Vestibular Systems

Support: Burroughs Wellcome Fund

Title: Phonological feature and pitch classification with a branched convolutional neural network

Authors: *I. M. GRIFFITH[1], A. LEBEL[2], S. JAIN[3], A. G. HUTH[2,3], L. S. HAMILTON[1,4]; [1]Dept. of Communication Sci. and Disorders, Univ. of Texas At Austin, Austin, TX; [2]Dept. of Neurosci., [3]Dept. of Computer Sci., [4]Dept. of Neurology, Dell Med. Sch., Univ. of Texas at Austin, Austin, TX

Abstract: While processing natural speech, the human brain is able to take a complex acoustic signal and transform it into linguistically meaningful content. This includes encoding of simple acoustic features such as frequency or spectrotemporal modulation content, as well as phonological and prosodic representations. Previous research using invasive intracranial recordings has shown that distinct regions of the superior temporal gyrus encode prosodic and phonetic content (Tang et al. 2017). These regions are sensitive to intonational pitch (both absolute and relative) or phonological features, while being invariant to other stimulus features. However, it is not known how such invariance arises from auditory neural networks. To address this, we used a branched convolutional network trained on several hours of natural speech. Our network architecture consists of separate absolute pitch and phonological feature branches, each receiving input from shared earlier network layers. The network was optimized to simultaneously perform both absolute pitch and phonological feature classification, allowing earlier shared feature maps to inform individual task-specific outputs. Confusion matrices generated during model evaluation on a separate dataset indicate a high degree of accuracy and precision in both absolute pitch and phonological feature classification tasks. We next tested whether the representations learned by the network were able to predict brain responses. Using fMRI data collected from participants as they listened to the same natural speech stimuli, we fit encoding models that predict BOLD signals in each voxel using the activation weights from each layer of the convolutional neural network as stimulus features. Both pitch- and phonological feature-trained branches of the network strongly predicted activity in early auditory cortex in both the left and right hemispheres. We compare the spatial distributions of model performance to find regions of auditory cortex that differentially encode these intermediate to late layer representations. These results have implications for how invariance to complex attributes of speech and other natural sounds arise from earlier acoustic representations.

Disclosures: I.M. Griffith: None. **A. LeBel:** None. **S. Jain:** None. **A.G. Huth:** None. **L.S. Hamilton:** None.

Poster

574. Auditory Processing: Neural Coding

Location: Hall A

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Program #/Poster #: 574.14/I25

Topic: D.06. Auditory & Vestibular Systems

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Title: Neural decoding model of auditory attention in a dichotic listening condition

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Abstract: Human can successfully parse different sound streams and focus on a specific target sound in a cocktail party condition. Recently, several studies have shown that estimating attended sound is feasible with linearly trained neural decoders. In this study, we took the similar approach to build an auditory attention decoder based on human EEG signal recorded during dichotic listening experiment (64 channels, Neuroscan SynAmps RT). Nineteen participants are instructed to attend a speech on the one side of the ear and ignore another speech presented to the opposite side of the ear (order of stimuli presentation is randomly selected). Length of the stimuli was 1 min long and excerpted from a Korean listening comprehension audio samples for college entrance test (Female voice only). Since it has been reported that low-frequency of speech envelope is linearly related to the low-band of EEG, 2-8 Hz band-pass filter was applied to extract low-frequency component of EEG data and 8 Hz low-pass filter was used for extracting speech envelope after applying Hilbert transform. Auditory attention decoder was trained using linear regression method and was validated by leave-one-out validation method. Attended sound stream was selected based on the correlation between envelope of reconstructed speech and that of the original speech. First, we tried to build a subject-specific attention decoder with EEG recordings of all channels. However, most of the trained decoder shows lower performance on auditory attention decoding (mean accuracy of attended decoder: 54.4%, mean accuracy of unattended decoder: 51.4%, 5% of significance level: 67.9%). To increase the accuracy of the trained decoder, we tried forward feature selection method which incrementally searches the feature space and adds effective channels that could give better performance. As a result, we were able to successfully decode auditory attention of each subject (mean best accuracy of attended and unattended decoder: 86.3%). Also, for attended decoder model, channels around temporal region are mostly selected, which could reflect the auditory processing of current auditory attention task. In summary, we have shown that auditory attention can be successfully decoded with neural signals from selected EEG channels. In the future, we are going to try building single decoder model that could be generally applied to different participants without user specific optimization process and also try real-time decoding for applications such as human-robot interaction and hearing aid technology.

Disclosures: **J. Park:** None. **J. Kyong:** None. **J. Choi:** None. **M. Suh:** None. **S. Kim:** None. **Y. Lim:** None.

Poster

574. Auditory Processing: Neural Coding

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Title: Neonatal exposure to mild sound in rats differentially altered FM sensitivities at the auditory cortex and midbrain

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Abstract: Frequency modulated (FM) signals are building blocks of complex sounds including those present in vocalization. The auditory cortex (AC) and midbrain inferior colliculus (IC) are two key neural centers for FM coding and they are known to be plastic during the early postnatal period, with some response characteristics shaped by acoustic experiences. Whether or not, and how FM sensitivities are specifically altered at the AC and IC by the acoustic experience remains unclear. The aim of this study is to study and compare the effects of neonatal sound exposure on the neural responses to FM stimuli recorded at the AC and IC later in adulthood. Young pups were randomly divided into two groups: control and experimental. The experimental group received a month-long tone exposure (4 kHz, 65 dB SPL) starting right after birth. The control group was raised in the same environment but without tone exposure. At postnatal week-10, the rat was urethane-anesthetized, and the 2 electrodes were acutely placed on the left AC and a depth electrode into the ipsilateral IC to record simultaneously FM-evoked potentials (EPs). The stimuli were exponential frequency sweeps with 4 different durations. EPs were processed in the spatiotemporal domain to detect FM-related changes within the gamma-band frequency range. In control, FM stimuli produced a rather strong gamma-band response at both the AC and IC: first to the onset of the stimulus and then over certain parts during the time-course of modulation. Gamma activity was time-locked to the low-frequency region of the modulation envelope (250-800Hz). In experimental, gamma-activities showed basically little time-locked response to the same low FM frequency region. But, an unexpected strong gamma response emerged around

300-350 Hz. In addition, this new gamma band activity occurred throughout the entire time-course of the FM sweep. Such gamma band response that was present at both AC and IC, appeared stronger and more robust at the IC. Results showed that long-term neonatal sound exposure had altered FM sensitivities at both the AC and IC, but not in the same fashion. The new 300-350 Hz gamma band response to FM sweeps, reflecting the complex neural plasticity induced by the acoustic experience, was found here for the first time.

Disclosures: **T. Chiu:** None. **Y. Li:** None. **M. Chang:** None. **T. Wang:** None. **D. Suta:** None.

Poster

574. Auditory Processing: Neural Coding

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Topic: D.06. Auditory & Vestibular Systems

Support: NIH Grant F31-DC014903
NIH Grant R01-DC014656

Title: Reliable envelope coding from unreliable single neurons

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Abstract: While natural acoustic signals, including speech and music, often contain rhythmic elements, the amplitude modulations (AM) composing them are temporally irregular. However, our understanding of AM coding is largely based on periodic stimuli, with responses typically measured from activity averaged over many iterations of each period. Since auditory response properties are sensitive to stimulus history and vary from trial-to-trial, we first asked how temporal regularity impacts coding by individual neurons. Single unit recordings were obtained wirelessly from gerbil auditory cortex (NeuroNexus 16 and 64 channel arrays) as gerbils performed an aversive Go-Nogo detection task in which all modulated stimuli were safe (signaling the availability of a water reward), while unmodulated noise served as the warn signal that predicted a brief electrical shock. Modulated stimuli were either periodically sinusoidally modulated at rates of 2-32 Hz, or aperiodically modulated (i.e., quasi-random sequences of individual periods drawn from the same set of rates). In addition, we characterized responses to vocoded speech stimuli. We found that responses of individual neurons to a given AM period could be modulated by stimulus history, but high trial-to-trial variability led to low discriminability across stimulus history contexts. High response variability raises the question of how neurons can provide a robust representation of the envelope of a complex signal in real time. Our recordings suggest that cortical responses tile the complex envelope. Therefore, our

current analyses focus on assessment of how larger pools of units enhance the representation of irregular AM sequences, including vocoded speech.

Disclosures: K.B. Penikis: None. **D.H. Sanes:** None.

Poster

574. Auditory Processing: Neural Coding

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U19NS107464

Title: Single cell and population encoding in input and associative layers of mouse auditory cortex across strains

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Abstract: Sound stimuli are encoded by populations of neurons in the primary auditory cortex (A1). Sound information arrives at its input layer 4 from where activity propagates to associative layer 2/3. Given the hierarchical structure of A1, the encoding of sound information is thought to be transformed between layers, but the nature of this transformation is unclear. Since stimulus information is represented in populations of neurons, we investigated the spatiotemporal organization of neuronal population activity across layers. Mice on the C57BL/6 background are commonly used to study cortical processing, yet these mice develop high frequency hearing loss with age making them a less optimal choice for auditory research. In contrast, mice on the CBA background retain better hearing sensitivity in old age. Therefore, we performed comparative analysis of neuronal populations from both adult (~10 weeks) C57BL/6 mice and CBA mice. We used *in vivo* 2-photon imaging of pyramidal neurons in cortical layers L4 and L2/3 of awake mouse A1 to characterize the populations of neurons that were active both during tonal stimuli and in the absence of any stimulus. Pure tones recruited neurons of widely ranging frequency selectivity in both layers and strains, with CBA mice exhibiting a higher proportion of selectively tuned neurons. We next characterized the spatiotemporal population activity via neuronal ensembles, defined as neurons being active within or during successive temporal windows at the temporal resolution of our imaging sampling rate. For both layers neuronal ensembles were highly variable in size during both spontaneous activity and during sound presentation. Ensemble sizes distributed according to power laws, the hallmark of neuronal avalanches, and were similar across sound levels. Avalanches evoked by sound were composed

of neurons with diverse tuning preference, yet with selectivity independent of avalanche size. Spontaneous and evoked activity in both L4 and L2/3 of A1 in both strains of mice are composed of neuronal avalanches with similar power law relationships. To further probe the temporal correlations at the population level seen in neuronal ensembles, we utilized functional connectivity measures to quantify network structure in both layers and strains. Our results demonstrate that single cell and ensemble activity is largely similar in A1 of adult C57BL/6 and CBA mice with CBA mice showing more sound-level sensitivity in responses. Moreover, our work shows that these neuronal ensembles exhibit network principles linked to maximal dynamic range, optimal information transfer and matching complexity between L4 and L2/3 to shape population activity in A1.

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Poster

574. Auditory Processing: Neural Coding

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Topic: D.06. Auditory & Vestibular Systems

Support: Duke CTSI
CTSA UL1TR002553

Title: Decision tree based phonetic selectivity using high density µECoG-recordings

Authors: *S. DURAIVEL[1], C.-H. CHIANG[1], K. BARTH[1], I. RACHINSKIY[1], M. HAGLUND[2], D. G. SOUTHWELL[3], S. SINHA[4], J. VIVENTI[1], G. B. COGAN[5];
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Abstract: Previous work has demonstrated that the human auditory cortex encodes the spectrotemporal properties of phonetic information during speech perception. The cortical mapping of these phonetic features can be used to develop effective speech prosthesis using ECoG (Mesgarani et al. 2014), however the micro-scale spatial specificity of these features is unknown. Decision tree analysis is an underutilized and interpretable modeling technique that can characterize the spatial importance of electrodes for spectrotemporal and phonetic feature selectivity (Buitinck et al. 2013). We therefore sought to employ this method to elucidate the phonetic feature selectivity of human µECoG recordings. Firstly, to validate this technique, we use a decision tree model to predict neural responses to auditory tones in the rat auditory cortex, since the tonotopy is well established (Insanally et al. 2016). We recorded cortical signals from an anesthetized rat's auditory cortex using a 60 channel (406 um pitch) µECoG electrode array (Trumpis et al. 2017). We played 60 sets of randomly shuffled 13 tones ranging between 0.5 and

32 kHz during the recording session. The broadband neural response (2 – 100 Hz) was used to build a 5-fold cross-validated classification and regression tree (CART) model, and the decision weight of each electrode is interpreted as a selectivity metric in predicting a particular tone. Our preliminary results reveal an above chance decoding accuracy in tone prediction (63.8%; chance – 7.7%, ROC-AUC: 0.958 ± 0.015), and we observed spatial clustering of decision weights for each tone. We then recorded human cortical signals using a 244 channel (762 um pitch) high-density μECoG electrode array implanted on the superior temporal gyrus (STG) of a single patient undergoing treatment for pharmacologically resistant epilepsy during an anesthetized craniotomy. The subject was presented with a set of bisyllabic words and non-words. To build a CART model for phonetic feature prediction, we used high gamma power (70-150 Hz) as a predictor feature for each phonetic class. The decision weights of the electrodes were translated as the selectivity metrics for a particular cluster of phonetic features. Results demonstrated clustering of decision weights in the spatial domain for certain classes of phonetic features. These findings indicate that phonetic information is spatially selective at the micro-scale in human STG. Furthermore, this suggests that decision tree modeling is a useful technique to interpret the spectrotemporal selectivity of each channel and can be a reliable tool for cortical phonetic feature mapping specifically, and auditory processing in general.

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Poster

574. Auditory Processing: Neural Coding

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Topic: D.06. Auditory & Vestibular Systems

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Title: Effects of arousal on population coding of natural sounds in primary auditory cortex

Authors: *C. R. HELLER, D. SADERI, Z. P. SCHWARTZ, S. V. DAVID;
Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Behavioral state variables such as arousal, task-engagement, and attention have been shown to decrease shared variability, i.e., stimulus-independent, pairwise correlations between neurons, in primary sensory cortices. This change may reflect state-dependent processing that removes noise and enhances faithful sensory encoding. However, many questions remain regarding the origin of shared variability and how, or if, it impacts sensory encoding accuracy.

Here, we investigated the origin of shared cortical variability and its dependence on arousal state in the primary auditory cortex of awake, passively listening ferrets. The simultaneous activity of multiple single units was recorded during the presentation of natural sounds and arousal levels were monitored via pupillometry. We found that that arousal influences correlated variability on multiple, distinct timescales. Consistent with the time course of fluctuations in arousal itself, we observed strong covariation in spike rate from trial to trial, on the order of seconds. This result was expected, given previous work showing that arousal modulates the excitability of cortical neurons. At these slow timescales, we saw no change in the amount of shared variability between high and low arousal states. On timescales faster than one second, however, heightened levels of arousal suppressed shared variability. Notably, the degree of suppression for a given pair was not predicted by tuning similarity. Given previous theoretical work showing that shared variability impairs sensory encoding only when present in co-tuned neurons, our results suggest that arousal dependent reductions in shared variability do not necessarily improve sensory encoding. To test this prediction, ongoing experiments are comparing decoding accuracy of neural populations recorded during high and low arousal states.

Disclosures: **C.R. Heller:** None. **D. Saderi:** None. **Z.P. Schwartz:** None. **S.V. David:** None.

Poster

574. Auditory Processing: Neural Coding

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Title: Differential roles of somatostatin and parvalbumin-positive interneurons in contrast gain control

Authors: *C. F. ANGELONI, X. DING, M. N. GEFFEN;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Sensory systems are composed of neurons with limited dynamic range, but are required to accurately represent a world in which the dynamic range of incoming stimuli can vary wildly. To efficiently encode environments with different dynamic ranges (referred to here

as contrast), sensory neurons adapt the gain of their response function to effectively match their dynamic range to that of the environment. However, it is not known how this gain control arises in the auditory system. Prior work in the visual system shows that modulating inhibitory synaptic currents can induce changes in gain. Here, we expand on this previous work using a multi-compartment circuit model which simulates populations of somatostatin-positive (SOM) and parvalbumin-positive (PV) interneurons, and their synapses onto the dendrites and somas, respectively, of a population of pyramidal neurons. When increasing either SOM or PV inhibition in the model, we observe that gain-like changes occur primarily when modulating SOM neurons, while an overall subtractive effect is observed when modulating PVs. We then validate our model experimentally, by optogenetically activating these two interneuron populations in the auditory cortex of awake mice as they listen to acoustic stimuli of varying contrast. We found that SOMs have a larger effect on the gain of neural responses, while PVs have a smaller effect on gain, and exhibit subtractive inhibition, in agreement with our model predictions. These findings suggest that inhibitory neurons control the sensitivity of cortical neurons in a predictable manner. Our results lay the groundwork for further exploration of the role of circuits in auditory cortex in regulating psycho-acoustical behaviors.

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Poster

574. Auditory Processing: Neural Coding

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Title: Characterizing the nonlinear encoding of speech in the human auditory cortex

Authors: *M. KESHISHIAN[1,2], H. AKBARI[1,2], B. KHALIGHINEJAD[1,2], J. L. HERRERO[3], A. D. MEHTA[4], N. MESGARANI[1,2];
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Abstract: There is a growing interest in characterizing the response properties of sensory neurons under natural stimulus conditions. The majority of previous studies have used linear models to relate the acoustic features of sound to neural responses. Linear models, however, cannot capture the inherent non-linearity of the processes in the brain. Recent advancements in machine learning and computational power have allowed us to utilize deep learning methods in a large variety of tasks. We investigate the utility of deep neural network models to predict neural

responses to speech in human auditory cortex, with the goal of analyzing the learned networks to gain insight into the nonlinear mechanisms of the brain. The neural responses were recorded from the transverse and the superior temporal gyrus of five patients undergoing surgery for the treatment of epilepsy, as they listened to continuous speech. As deep neural networks (DNNs) have shown great promise in capturing non-linear relationships, we trained a convolutional neural network (CNN) with a non-linearity in each layer using the time-frequency representation of the stimulus as the input and the envelope of the high-gamma activity of the neural responses as the output of the model, to study the effect of artificial neural networks.
In comparison to the STRFs, the predicted responses from the neural networks had a higher correlation with the original responses. On average, using CNNs improved performance by 25%. To interpret the nonlinear function that the network applies to the stimulus, we analyze the linear equivalent of the function, at each time point. As a result, we observe three general classes of nonlinear behavior implemented by the network: gain change, feature memory, and shape diversity. The feature memory or "hold" can be interpreted as the network holding on to a response captured by the STRF. Finally, we quantify these properties for all electrodes and try to explain the prediction improvement gained from using the CNN model, through these simple parameters. Furthermore, we studied the relation between these parameters and the electrodes' anatomical locations and other encoding properties.

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Poster

574. Auditory Processing: Neural Coding

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Topic: D.06. Auditory & Vestibular Systems

Title: Multi voxel pattern analysis of auditory oddball as a tool for investigating locus coeruleus modulation of perceptual circuits

Authors: *K. C. YAGHOUBI[1], M. ALIZADEH SHALCHY[1], X. CHEN[2], J. LANGLEY[2], I. J. BENNETT[1], X. P. HU[3], A. R. SEITZ[1], M. A. K. PETERS[3];
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Abstract: The locus coeruleus noradrenergic (LC-NE) system is implicated in many cognitive processes including perception, attention, and decision making. In this study, we aimed to develop and optimize an empirical approach for investigating the relationship among LC activity, neural representations of sensory stimuli, and perceptual performance in humans using multivariate fMRI. We focused on auditory perception, selecting the primary auditory cortex

(A1) as a target region of interest and developing a novel psychometric auditory oddball paradigm; we then evaluated the sensitivity of this paradigm and our computational neuroimaging approach for characterizing the role of the LC-NE circuit in auditory perception. Compared to the standard oddball paradigm that consists of a frequent stimulus and one type of oddball stimulus, our paradigm consists of six different auditory oddball stimuli (1004 Hz - 1128Hz) to facilitate estimation of signal-response functions in behavior and in auditory cortical representations. The resulting psychometric function revealed a fine characterization of behavioral performance. We next used a multi-voxel pattern analysis (MVPA) approach (sparse logistic regression classification) to examine decodability of our psychometric oddball versus frequent stimuli in A1. We showed that we can successfully decode distinct oddball versus frequent neural representations in this area, demonstrating the sensitivity and appropriateness of our behavioral and analytic approach as a tool for characterizing the influence of LC activity on behavioral performance via modulation of neural representations.

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Poster

574. Auditory Processing: Neural Coding

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Program #/Poster #: 574.23/I34

Topic: D.06. Auditory & Vestibular Systems

Title: Vivarium and laboratory noise, ultrasonic noise, and vibration as unrecognized experimental confounds in neuroscience research

Authors: *J. G. TURNER[1,2];
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Abstract: Neuroscience research using laboratory animals is purportedly conducted in highly controlled housing and testing environments. The intention of such control is to limit sources of confounding variability that might negatively impact the research animals themselves or interfere with the tests being conducted. We report here on the noise, ultrasonic noise, and vibration levels sampled from a wide variety of research animal vivarium and laboratory spaces (both between institutions and from room-to-room within an institution) in order to help investigators appreciate the role that such noise and vibration might have on introducing confounding variability into their neuroscience research. We also suggest mechanisms for controlling or minimizing the impact of such noise and vibration.

Disclosures: J.G. Turner: A. Employment/Salary (full or part-time):; Turner Scientific.

Poster

574. Auditory Processing: Neural Coding

Location: Hall A

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Program #/Poster #: 574.24/I35

Topic: D.06. Auditory & Vestibular Systems

Support: MH113041 to TT

Title: Mismatch responses at the scalp and primary auditory cortex of the rhesus macaque: Mismatch negativity, mismatch positivity, stimulus specific adaptation and deviance detection

Authors: *T. TEICHERT;
Psychiatry and Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Background. Mismatch negativity (MMN) has provided important insights into normal brain function. It is also a sensitive and selective marker of altered brain function in schizophrenia. Rhesus macaques are the most established animal model of MMN, and have provided groundbreaking insights into the circuits and pharmacology of MMN. However, several findings have questioned the homology and utility of MMN in the monkey. (1) Recent studies have shown short-latency mismatch responses (MMRs) in humans at latencies around 40 ms after tone onset. MMRs with similarly short latencies have not been identified in monkey EEG. (2) It is unclear whether MMRs in the monkey comprises of two distinct sub-components, stimulus specific adaptation and deviance detection, as is the case in the human. (3) Despite the possibility to record MMRs at the level of EEG and in auditory cortex, MMRs have not been measured in the same animals using both (i) high-density EEG montages and (ii) intracranial depth recordings in auditory cortex. This has limited our understanding of how macroscopic signals that can be readily observed in the human inform our understanding of the microscopic events in auditory cortex that can only be measured in animal models. Methods. To address these questions we recorded MMRs in four rhesus macaques using 32 channel cranial EEG while the animals passively listened to a modified roving standard paradigm. In a subset of two animals, we also recorded MMRs in primary auditory cortex using 24 and 32 channel laminar depth electrodes. Results. We found mismatch responses at the level of EEG in all four animals. A fronto-central mismatch positivity lasted from 20 ms to 60 ms after stimulus onset. A subsequent fronto-central mismatch negativity was observed between 65 and 110 ms after onset. Using the many-standards control condition, we identify both stimulus specific adaptation and deviance detection. Stimulus-specific adaptation emerged earlier and peaked around 30 ms after onset; deviance detection emerged later and peaked around 55 ms after onset. Laminar recordings in A1 confirmed stimulus-specific adaptation and deviance detection at the level of neural firing and post-synaptic potentials. Deviance detection was present in the first wave of cortical activity (20-

45 ms), but was most pronounced in a later period from 70 to 125 ms. This is the first report of mismatch positivity and deviance detection in this species.

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Poster

574. Auditory Processing: Neural Coding

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Title: Laminar origin of evoked ECoG high-gamma activity

Authors: *M. DOUGHERTY[1], A. P. Q. NGUYEN[2], V. BARATHAM[3,1], K. E. BOUCHARD[1]; [1]Biol. Systems & Engin., Lawrence Berkeley Natl. Lab., Berkeley, CA; [2]Dept. of Mathematics, Univ. of Iowa, Iowa City, IA; [3]UC Berkeley, Berkeley, CA

Abstract: The high spatiotemporal resolution and broad coverage of electro-corticography (ECoG) makes it a critical methodology for basic human neuroscience and shows promise for brain machine interfaces. The High-gamma (Hγ) component of cortical surface electrical potentials (CSEPs) from ECoG is a commonly used signal for understanding the human brain, but its interpretation is impeded by a lack of spatial localization. To address this, we develop a novel recording setup combining a micro-ECoG (μECoG) array with laminar polytrodes to record both CSEPs and laminar multi-unit activity (MUA) in rats. Recordings were collected from the auditory cortex of four anesthetized female rats presented with forty millisecond tone-pips of varying frequency and amplitude. These stimuli were used to simultaneously estimate the tuning properties of the cortical surface and each lamina within a cortical column. We demonstrate that stimulus evoked CSEPs carry a multi-modal frequency response, peaking in the Hγ range. Laminar MUA responses exhibited similar tuning to CSEP Hγ directly over the intracortical recording site, suggesting a functional relationship. We fit CSEP Hγ to the simultaneously-recorded laminar MUA using a state-of-the-art sparse multi-linear regression model, UoI_{Lasso} to identify laminar contributions to cortical surface Hγ. Our results indicate that CSEP Hγ recorded by ECoG reflects spiking activity from neurons in layer 3. These results provide initial insight into localizing the sources of CSEPs, which will guide clinical and BMI device decisions.

Disclosures: M. Dougherty: A. Employment/Salary (full or part-time):; Lawrence Berkeley National Lab. **A.P.Q. Nguyen:** None. **V. Baratham:** None. **K.E. Bouchard:** None.

Poster

574. Auditory Processing: Neural Coding

Location: Hall A

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Program #/Poster #: 574.26/I37

Topic: D.06. Auditory & Vestibular Systems

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NIH UL1-RR024979

Title: Evoking potentials without events: Intrinsic response identification in neural recordings using higher-order spectra

Authors: *C. K. KOVACH, K. V. NOURSKI, P. E. GANDER, H. OYA, H. KAWASAKI, M. A. HOWARD, III;
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Abstract: In contrast to micro-scale unit recordings, field potential data typically lack any obvious, well-defined and discrete neural response, akin to the action potential. The absence of such an event-like response makes it relatively difficult to apply and interpret the kinds of reverse-correlation analyses that have been crucial for revealing receptive fields in unit recordings. Instead, conventional analyses of field potentials have been limited to asking, "what kind of response, if any, follows a given event" rather than "what kind of stimulus, if any, evokes a given response?" Here we demonstrate how this limitation may be overcome with a novel decomposition of the bispectrum (Kovach and Howard, 2019). This technique allows a non-Gaussian time series to be explained by the emission of one or more transient waveforms at discrete times. It yields the respective waveforms, times at which the waveforms are emitted, and reconstructed component signals explained by the emitting processes.
We applied the technique to human intracranial data from 59 epilepsy patients, demonstrating its ability to blindly identify the form and timing of auditory event-related potential (ERP) waveforms recorded from Heschl's gyrus with no prior information about the stimulus. Stimuli were repeated acoustic transients (50 Hz click trains) presented at regular intervals. Averaged responses in posteromedial Heschl's gyrus were generated by the post-stimulus emission of the ERP waveform. In contrast, those in anterolateral Heschl's arose predominantly through the transient suppression of waveforms from the background signal, resulting in a negative image of the suppressed waveform within ensemble averages. The latter finding was confirmed in two separate ways: (1) by the inversion of the generating waveform in the average, and (2) by a transient decrease in average power coincident with the averaged waveform. Thus, the bispectrum decomposition approach enabled us to identify a novel mechanism of auditory ERP generation. We consider implications of these findings for the interpretation of averaged evoked responses and their relationship to background activity. In particular, we examine the potential

for the newly identified contribution of waveform suppression in the average to be mischaracterized as phase resetting under conventional techniques of phase analysis.
References
Kovach, C. K. and M. A. Howard, III (2019). Decomposition of higher-order spectra for blind multiple-input deconvolution, pattern identification and separation. arXiv preprint arXiv:1901.11395.

Disclosures: **C.K. Kovach:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Methods described in this work are the subject of U.S. Provisional Patent Application No: 62/695,586. **K.V. Nourski:** None. **P.E. Gander:** None. **H. Oya:** None. **H. Kawasaki:** None. **M.A. Howard:** None.

Poster

574. Auditory Processing: Neural Coding

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Pennsylvania Lions Club Hearing Research Fellowship Maria Neimark Geffen

Title: Neurons in auditory cortex integrate statistical regularities on different time scales

Authors: *L. GARAMI[1], C. F. ANGELONI[2], X. DING[1], M. N. GEFFEN[1];
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Abstract: Auditory objects are often detected through regularities in their acoustical structure. Depending on the complexity, these regularities emerge at various timescales. Our goal is to identify the neuronal circuitry in auditory cortex (AC) that enables the auditory system to detect temporal patterns in sounds with different complexities. On a large scale, human data shows that in both the AC and the pre-frontal brain regions differential brain activity correlates with the predictability (random vs regular) of auditory stimuli. On a smaller scale, responses of individual neurons in AC exhibit sensitivity to temporal regularities in sounds: neurons exhibit stimulus-specific adaptation, a reduction in their response selective to frequently presented inputs. This adaptation may underlie the population sensitivity to more complex spectro-temporal acoustic

regularities, and the rapid perception of such regularities. Here, we adapted a human change-detection paradigm used to test sensitivity to transitions between regular and random acoustic stimuli to test whether and how neurons in mouse AC encode predictable temporal structure. We presented chord pairs and either repeated them (predictable scenes) or distributed them randomly (random scenes). Each trial had a transition, ie. consisted of two scenes picked randomly, while single and multi-unit activity was recorded in AC. Neurons exhibited stimulus-specific adaptation to the spectral content of the chords, as expected. However, this adaptation was enhanced in the regular scenes, indicating that the adaptation on the single neuron level in the auditory cortex can evolve at multiple time scales. In line with the human data, this enhanced adaptation was present as soon as from the second chord pair repetition in regular scenes. The predictability of the preceding scene had a differential effect on firing rate in the first half of the new scene. These results show that while environmental predictability is encoded in AC, the integration time window might be limited at this level, removing information about previous acoustical contexts relatively rapidly as new stimulus statistics are presented.

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Poster

574. Auditory Processing: Neural Coding

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Title: Role of interneurons in populations' neural coding in auditory cortex

Authors: *M. TOBIN, K. WOOD, X. DING, M. N. GEFFEN;
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Abstract: Cortical neuronal networks are comprised of multiple types of excitatory and inhibitory neurons, which perform specific computations. In the auditory cortex (AC), excitatory neurons receive the sound input and transmit the processed signal to other areas, whereas the inhibitory neurons dynamically help shape the response of the excitatory neurons. In the last decade, we have learned specific functions of distinct inhibitory neurons, yet how different interneuron subpopulations affect network dynamics remains unexplored. To establish the role of

different interneuron subpopulations within the cortical network, we stimulated specific interneuron subpopulations, while imaging the network responses to sounds in the AC. We monitored the activity of populations of hundreds of neurons using two-photon calcium imaging and simultaneously increased the activity of a subpopulation of interneurons using optogenetic stimulation. We focused on VIP and SOM inhibitory neurons, which have previously been found to shape cortical responses in a context-dependent fashion (Natan et al, 2015; Pi et al, 2013). Response of neurons activated by sound were enhanced when VIPs were activated, but reduced upon activation of SOMs. The population of cells increasing their activity in response to sound is distinct from the VIP interneuron population, but includes a subset of SOM interneurons. Finally, we observed that sound stimulation reduced the activity of VIP interneurons and increased the activity of SOM interneurons. We conclude that the activation of VIP or SOM interneurons leads to opposite effects on the response of the neural network to sounds in AC.

Disclosures: **M. Tobin:** None. **K. Wood:** None. **M.N. Geffen:** None. **X. Ding:** None.

Poster

574. Auditory Processing: Neural Coding

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Topic: D.06. Auditory & Vestibular Systems

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Title: Reorganization of cortical population neuronal activity following differential auditory fear conditioning

Authors: *K. WOOD[1], R. BETZEL[3], D. S. BASSETT[2], M. N. GEFFEN[1];
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Abstract: Auditory perception relies on learning-driven neuronal plasticity within the auditory pathway. Here, we investigated how associative learning, differential auditory fear conditioning (DAFC), affects neuronal population responses to sounds in auditory cortex (AC). In DAFC, the subject is presented with two different frequency tones, one of which is paired with a foot-shock.

Previously, we found that AC is required for expression of DAFC-driven changes in sound-frequency discrimination acuity (Aizenberg and Geffen, 2013) and that modulating inhibitory neuronal activity in AC leads to similar bi-directional changes in discrimination acuity (Aizenberg, 2015). However, how DAFC affects tone-evoked population neuronal activity remained unknown. We hypothesized that DAFC would drive changes in population tone-evoked neuronal activity corresponding to either and increase or a decrease in neurometric frequency discrimination acuity, as a function of fear learning specificity.To understand the transformation of sound representation in AC before and after DAFC we imaged calcium activity in hundreds of neurons simultaneously in AC of awake, head-fixed mice, tracking the same neurons over days under a two-photon microscope before and after two DAFC sessions. We quantified changes in frequency-dependent responses of individual neurons, as well as in population functional connectivity using network analysis. DAFC drove heterogeneous changes in individual neuronal responses for either shock-paired or unpaired tone frequencies. We used population Fisher Information to calculate the discriminability between the conditioned and control stimulus using frequency tuning curves before and after fear conditioning. We found that discriminability before fear conditioning predicted how well the mouse would learn to discriminate after fear conditioning. Neural discriminability after fear conditioning only showed a weak correlation with behavioral discriminability. Neuronal populations formed clusters driven by correlated activity. The neuronal cluster structure changed between days in the absence of DAFC, but the network structure became more consistent over days following DAFC. These findings suggest that DAFC drives cortical population activity into more stable states.

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Poster

574. Auditory Processing: Neural Coding

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Title: Transformation of sound representations between inferior colliculus and auditory cortex

Authors: *J. BOURG[1], A. KEMPF[1], T. TARPIN[3], B. BATHELLIER[2];
[1]UNIC, CNRS, Gif-sur-Yvette, France; [2]UNIC, CNRS, Gif sur Yvette, France; [3]ENS, Paris, France

Abstract: The auditory system, as other sensory systems, is thought to be hierarchically organized encoding increasingly complex features from peripheral to more central stages. Yet the precise transformations of auditory representations across stages of the most central auditory system are not fully characterized. To start addressing this question in a systematic manner, we used two-photon calcium imaging in awake mice to extensively record auditory responses in the auditory cortex (AC, at depths ranging from 0-600 μm) and the superficial layers of the inferior colliculus (IC, 0-200 μm). To capture both spectral and temporal aspects in auditory coding, we used a wide range of laboratory sounds including pure tones, chords, intensity ramps, amplitude modulated sounds and various frequency chirps. We thereby collected a dataset of 59590 neurons (7 mice, 60 sessions) in the AC, fully sampling the horizontal extent of AC, as assessed with global tonotopic mapping. We also obtained activity from 15311 neurons in the IC (31 mice,101 sessions).
Using model-free clustering to organize this rich dataset, we observed at both levels of the auditory system a large number of complex sound response types, combining specificity for frequency, intensity and their temporal variations. However, particular coding features are markedly enhanced in AC, with the most evident difference appearing in the coding of intensity variations (e.g. onset and offset). While in IC neurons either rapidly reach a response plateau or monotonically increase their response with intensity, in AC it is possible to identify three large neuronal populations non-monotonically tuned to different levels of intensity variations (typically 60,70, 80dB). This tuning allows constructing a rich and divergent representations of the sound envelope, a crucial parameter in sound recognition. In addition, we observe that the two opposite directions of sound frequency modulations (up or down) are represented by less correlated population activity patterns in AC than in IC.
Together these results point towards the progressive emergence of a coding scheme in auditory cortex which captures different temporal features of the sounds into distinct neuronal activity patterns, possibly contributing to perceptual segregation of these features.

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Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.01/I42

Topic: D.07. Vision

Support: MOMRP-Task Area I

Title: Antibodies against lysophosphatidic acid protected against blast-induced ocular dysfunctions

Authors: *P. ARUN[1], A. BATUURE[1], F. ROSSETTI[1], D. WILDER[1], J. DEMAR[1], Y. WANG[1], I. GIST[1], A. MORRIS[2], R. SABBADINI[3], J. LONG[1];
[1]Blast-Induced Neurotrauma, Walter Reed Army Inst. of Res., Silver Spring, MD; [2]Col. of Med., Univ. of Kentucky, Lexington, KY; [3]Dept. of Biol., San Diego State Univ., San Diego, CA

Abstract: Exposure to blast waves has been implicated as the major cause of ocular injuries and resultant visual dysfunctions in veterans involved in recent combat operations. Between 2006 and 2009, 43% of veterans with blast-induced traumatic brain injury (TBI) also had significant closed-eye injuries. While improvised explosive devices have greatly increased the incidence of ocular injuries, no effective countermeasure has been developed thus far. Lysophosphatidic acid (LPA) is a bioactive lysophospholipid released from activated platelets, astrocytes, choroidal plexus cells and microglia and is reported to play major roles in activating inflammatory processes. Acute increase in LPA levels was observed in the cerebrospinal fluid (CSF) of patients after TBI and use of monoclonal antibodies against LPA has been found to be protective against TBI and neuropathic pain in animal models. Since in preliminary studies we observed acute increases in LPA levels in the CSF and plasma of rats after a single blast exposure, we have evaluated the efficacy of anti-LPA monoclonal antibodies for protection against blast-induced ocular injuries. Anesthetized rats were exposed to single blast (19 psi peak total pressure, 4-5 msec duration) using an advanced blast simulator. A single intravenous injection of anti-LPA antibodies (25 mg/kg) was given to rats at 1 hr after blast exposure and ocular functions and retinal pathology were evaluated at different intervals. Visual acuity tests by optokinetics were carried out post-blast on days 2 & 6, electroretinography (ERG) was conducted on days 3 & 7 and retinal pathological evaluations were performed on tissue collected on day 8. H&E staining revealed significant protection against neuronal cell deformation in the retinal photoreceptor and outer nuclear layers after treatment. Immunohistochemical evaluations indicated that the antibody treatment decreased the presence of both activated astrocytes and microglia in the retina. Antibody treatment also significantly improved visual acuity in both eyes on days 2 & 6 post-blast. ERG, as a measure of retinal signaling response to light, showed significant improvements in both A & B waveform amplitudes of the left eyes and B wave of the right eyes on day 7. Our data reveals that LPA plays an important role in ocular injuries following blast and that early intervention with anti-LPA antibodies can provide significant protection against damages to the retina.

Disclosures: P. Arun: None. **A. Batuure:** None. **F. Rossetti:** None. **D. Wilder:** None. **J. Demar:** None. **Y. Wang:** None. **I. Gist:** None. **A. Morris:** None. **R. Sabbadini:** None. **J. Long:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.02/I43

Topic: D.07. Vision

Title: The role of microRNA-150 in the pathogenesis of diabetic retinopathy

Authors: *F. YU[1], S. CHAPMAN[2], M. L. KO[2], G. Y.-P. KO[3];
[1]Vet. Integrative Biosci., [3]Vet Integrative Biosci., [2]Texas A&M Univ., College Station, TX

Abstract: Diabetic retinopathy (DR) is a leading cause of vision impairment in the US. Retinal photoreceptors are suggested to have an important role in the pathogenesis of DR in recent studies, but it is not clear as to how photoreceptors contribute to DR under diabetic insults. MicroRNAs (miRs) represent a set of regulators that impact metabolism, angiogenesis, and inflammation and may link to the development of DR. Among them, decreased miR-150 is observed in diabetic patients. MiR-150 is a powerful regulator of inflammation and angiogenesis. Retinal miR-150 is decreased in eyes with ischemic insults. However, it is not known whether retinal miR-150 plays a role in the pathogenesis of DR. We used 661W cells (a mouse photoreceptor cell line) and miR-150 null (miR-150 KO) mice to test our hypothesis that decreased miR-150 in the retina contributes to obesity-induced type 2 DR. We found that 661W cells treated with palmitic acid (100 μM) had decreased miR-150 by qPCR and increased phosphorylated NFκB (pNFκB) and ERK (pERK) using Western blots. Compared to mice fed with a normal chow, mice fed with a high-fat-diet (HFD) for 3 months developed hyperglycemia, insulin-resistance and glucose-intolerance, and had significantly decreased miR-150 in the serum and retina. Using electroretinogram (ERG) recordings, the miR-150 KO mice under HFD for 1 month showed dampened retinal light responses compared to the WT mice. After six months of HFD, the retinas of miR-150 KO mice had a higher level of pNFκB and pERK (immunofluorescent staining) compared to the WT mice fed with a HFD. After 6-7 months of HFD, we observed degenerated retinal micro-vessels in both WT and miR-150KO mice. Our results indicate that decreased miR-150 in the early diabetic retina aggravates inflammation, which may further exacerbate the pathogenesis of DR.

Disclosures: F. Yu: None. **S. Chapman:** None. **M.L. Ko:** None. **G.Y. Ko:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.03/I44

Topic: D.07. Vision

Title: A retinal photoreceptor distribution model based on an algorithm of the Voronoi diagram

Authors: *K. MIYATAKE, T. KOHAMA;
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Abstract: Recently, simulation studies on human visual information processing using mathematical models have been actively conducted. When simulating visual perception using mathematical models, a simple image information is often used as the input. As the visual information captured by the photoreceptors is processed in the retinal neuron network composed of horizontal, bipolar, amacrine, and ganglion cells, the output from the retina differs from the input image data. To elucidate the mechanism of visual perception using a mathematical model of the visual system, the outputs of the retinal neuron network should be reproduced as the inputs in the model. A more realistic model of retinal neural mechanism has been developed using a honeycomb model of photoreceptor distribution fabricated using an algorithm of the Voronoi diagram (Kubo & Kohama 2018). However, this model limited the distribution of photoreceptors in the central fovea, which is a narrow region containing only cones. Since the characteristics of retinal response are different in the foveal and peripheral visual fields, the Kubo & Kohama model could not be used for the simulation of large visual angles. In this study, we proposed a wide-scale photoreceptor model that reproduces the distribution of the cone and rod cells as a function of retinal eccentricity to simulate the behavior of the visual nervous system to natural scenes. The cone and rod cells differ in density and size depending on the retinal eccentricity. The cone cells are dense and small around the fovea and coarse and large in the peripheral retina. The rod cells have a remarkably low density around the fovea and high density in the peripheral retina. The cone cell density was calculated using a modified Deering model (Kubo et al. 2016), and the size was approximated using a two-dimensional Gaussian distribution as a function of retinal eccentricity. The result of the simulation was consistent with the anatomical evidence of the retina. This indicated that the proposed model could reproduce the visual information received by the retina.

Disclosures: **K. Miyatake:** None. **T. Kohama:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

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Support: National Natural Science Foundation of China (Grant No: 81470626)
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Title: Crx is posttranscriptional regulated by daylight stimulation in postnatal rat retinal neurocytes

Authors: *J. ZHUANG, K. YU, Y. WU, J. QIU, Z. LAI, S. CHEN, M. TANG;
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Abstract: Purpose: Crx plays a key role in the center of regulatory network in retina. Abnormal expression induces retinal disorders. This study focuses on elucidation the underlying mechanism of Crx expression in retina neurocytes with light stimulation.
Method: Primary rat retinal neurocytes from postnatal 1day SD rats were incubated in darkness (D-D) or 12 hours daylight and 12 hours darkness cycle (L-D). The level of mRNA and protein of Crx and its downstream genes in retina neurocytes was assayed by qPCR and Western blot. The inducibility of Crx promoter is measured by transfecting a construct with rat Crx promoter luciferase reporter assay. The expressing of exogenous Crx is assayed by transfecting pcDNA3.1-Crx plasmid. The results are confirmed in 15 days and adult SD rats. The data shown are representative of three independent experiments. Statistical significance was analyzed by the Student's t-test.
Result: The mRNA of Crx keeps stable in retinal neurocytes cultured in daylight or darkness (Light (L), 1; Dark (D), 0.863±0.101; P>0.05). However, Crx protein is increased in neurocytes cultured in darkness compared with the control (daylight) by 2.85-fold (**P<0.01). Moreover, Crx protein shows a light intensity-related decrease in retinal neurocytes (Dark, 1; 200luc, 0.742±0.231; 400luc, 0.648±0.104; 600luc, 0.574±0.0.152; 800luc, 0.538±0.0.042; ** p<0.01), without mRNA changed. Downstream genes of Crx, Arrestin and Rhodopsin, are increased in retinal neurocytes cultured in darkness, compared with that cultured in daylight too. The inducibility assay of Crx promoter doesn't change in retinal neurocytes cultured in daylight or darkness (L, 1; D, 1.044±0.227; P>0.1). Thus, posttranscriptional regulatory mechanism might be involved in Crx expression in retinal neurocytes due to light stimulation. However, the expressing level of exogenous Crx in primary retinal neurocytes cultured in daylight or darkness is not changed (L, pcDNA3.1-Crx, 1.433 ± 0.360; D, pcDNA3.1-Crx, 1.569±0.221. P>0.1), which indicates that the posttranscriptional regulatory mechanism might be specific to endogenous Crx gene. Consistent with the results in vitro, mRNA of Crx is not changed, protein

is increased in P15 rat retina in covered eyes (L, 0.439±0.242; D, 0.990±0.129, **P<0.01). However, the Crx mRNA and protein is not affected in adult rat retina by light stimulation. Thus, this mechanism might be involved in immature retina.
Conclusion: This study not only provides new insights into the mechanism of Crx expression in retina. Moreover, daylight condition should be taken into consideration in the strategy of retinal experiment of in vitro.

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Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

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Topic: D.07. Vision

Support: Pennsylvania Department of Health, Tabacco CURE Funds

Title: Adenosine reduces photoreceptor damage in a zebrafish light-induced damage model of age-related macular degeneration

Authors: *A. KHAN, S. L. STELLA, Jr.;
Neural and Behavioral Sci., Penn State Univ. Col. of Med., Hershey, PA

Abstract: Purpose: Adenosine has been shown to be neuroprotective in the CNS and in retinal ganglion cells in the inner retina. However, the neuroprotective effects of adenosine on outer retinal neurons, in particular photoreceptors, is not known. Age-related macular degeneration (AMD) is a multifactorial disease characterized by the impairment or loss of central vision due to macular dropout and loss of photoreceptors. Adenosine has been shown to inhibit photoreceptor excitability by suppressing Ca^{2+} influx through voltage-gated Ca^{2+} channels, which could lead to cell death. The purpose of this study was to see if adenosine would reduce photoreceptor damage in a light-induced retinal degeneration (LIRD) model in pigmented zebrafish.
Methods: Adult wild-type and *Tg(NeuroD:GFP)* zebrafish (used to GFP label rod photoreceptors) were dark-adapted for 24 hours, followed by intravitreal injections of ~ 0.5 µl (1.67 to 167 µM) of adenosine in both eyes. Controls were injected with saline in both eyes. All zebrafish were exposed to full spectrum high intensity light (8000 lumens) for four days and collected at 0 and 96 hours post dark-adaptation. Immunohistochemical analysis was performed on vertical retinal sections in order to visualize cones, rods, and the outer nuclear layer of the retina. Retinal damage was assessed using confocal microscopy with a TUNEL assay and cell specific markers.
Results: Photoreceptors in control retinas collected at 96 hours exhibited severe truncation or

loss of the outer segments, and swelling of the cell body. Additionally, there was an increase in TUNEL positive cells and a significant decrease in rod and cone photoreceptors in the control retinas. In adenosine-treated retinas collected at 96 hours, photoreceptors exhibited less cell death, reduced truncation of the outer segments, lacked swelling, and had cell morphology similar to retinas collected prior to light exposure.
Conclusion: These findings show that adenosine can prevent light damage to the cell bodies and outer segments of rods and cones, and provide evidence of a potential novel therapeutic target for the treatment of the "dry" form of AMD.

Disclosures: A. Khan: None. **S.L. Stella:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

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Title: Melanopsin (Opn4) regulates retinal neuron diversity during fetal development

Authors: *S. DSOUZA, M.-T. NGUYEN, R. LANG;
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Abstract: The atypical opsin, Melanopsin or Opn4, is expressed within retinal ganglion cells in the mammalian retina where it serves as an input for the circadian clock and regulates scheduled vascular regression of the hyaloid vessel. Although its roles in the adult retina have been well characterized, little is known about the mechanism by which Opn4 signaling functions to regulate the vascular status of the retina. Here, we show that Opn4 regulates retinal diversity as its loss evokes changes in the proportions of various neurons including amacrine cells, bipolar cells, and S-cones in the adult retina. These changes are evident as early as P8 (before eye opening in mice) and depend on gestational light, as dark rearing C57BL/6J mice leads to similar increases in amacrine cells. Additionally, Opn4 appears to drive retinal progenitor cell-fate decisions during development as evident from Ptf1a lineage tracing experiments at E16. These results highlight the importance of fetal light-responsive pathways in driving development and appropriate retinal architecture necessary for visual function.

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Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

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Topic: D.07. Vision

Support: 1SC1MH086070-01

Title: The GABAergic phenotype of horizontal cells in the mouse retina

Authors: *Z. URESTI, M. MIRANDA-ARANGO;
The Univ. of Texas At El Paso, El Paso, TX

Abstract: The inner nuclear layer of the mammalian retina contains the cell bodies of the amacrine, bipolar and horizontal neurons. About 90% of the amacrine neurons are glycinergic and GABAergic and marked by the expression of the vesicular inhibitory amino acid transporter, VIAAT. By contrast, the phenotype in horizontal inhibitory neurons vary among different mammals. In the primate retina, experimental evidence suggests the absence of VIAAT and GABA has been proposed to be released through the GABA transporters. On the other hand, in rodents, the horizontal cells express the VIAAT and carry out vesicle-dependent GABA release. Although the retina cells have been extensively studied, the precise inhibitory repertoire of horizontal cells is not yet fully elucidated. In this study, we provide additional evidence of the GABAergic phenotype of horizontal cells in the mouse retina by using transgenic technology. Immunostaining of retinal sections from a transgenic line that expresses EGFP under the GAD67 promoter suggest that adult horizontal cells are devoid of GAD67 but contain GAD65. In addition, analysis of sections from a mouse expressing ChR2-EYFP under the VIAAT promoter clearly label horizontal and amacrine cells. Undergoing work will better define a GABAergic character of mouse horizontal cells and contribute to the understanding the basic chemo-architecture of the rodent retina.

Disclosures: Z. Uresti: None. **M. Miranda-Arango:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.08/J5

Topic: D.07. Vision

Support: NIH Grant R01EY027077
NIH Grant R01EY027711
NIH Grant 5T32GM063483

Title: Novel roles for encephalopsin (OPN3) within the mammalian central nervous system

Authors: *B. A. UPTON, G. NAYAK, K. ZHANG, R. A. LANG;
Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH

Abstract: Opsins are light-sensitive proteins used for the detection of coherent (i.e. vision-forming) and ambient light. Changes in ambient light occur with regular daily and seasonal patterns and can be used to predict changes in temperature, food and water availability, and as a synchronization cue for behavior, such as migration or reproduction. Atypical (i.e. non-visual) opsins are used to detect these changes in ambient lighting and despite expression in a variety of organ tissue, most mammalian studies have been limited to atypical opsin expression within the eye. Interestingly, opsin-mediated deep brain photoreception has been described in every non-mammalian class of the chordate phylum and there is evidence of atypical opsin expression in the brains of rodents and primates, including human, suggesting that opsin function within the central nervous system is a widespread and evolutionarily conserved process.
Encephalopsin (OPN3) is a highly conserved blue light-sensitive atypical opsin found in a variety of mammalian brain regions, including the cortex, striatum, cerebellum, and hypothalamus. In particular within the hypothalamus, OPN3 is expressed in the paraventricular nucleus, supraoptic nucleus, median preoptic nucleus, and subfornical organ. Despite its broad expression, no functions of OPN3 have been identified to date. Here, we examine the functions of OPN3 in the developing as well as adult mouse brains via gene analysis, behavioral assays, and hemodynamic monitoring. Together, these findings will provide new insight into how blue light and OPN3 shape the development and function of the central nervous system and provide direct evidence for mammalian deep brain photoreception.

Disclosures: B.A. Upton: None. **G. Nayak:** None. **K. Zhang:** None. **R.A. Lang:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.09/J6

Topic: D.07. Vision

Support: NIH Grant EY030360-01
NIH Grant 1DP2EY022584

Title: GABA release by intrinsically photosensitive retinal ganglion cells influences non-image forming vision

Authors: *T. SONODA, T. M. SCHMIDT;
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Abstract: Retinal ganglion cells (RGCs) are the output cells of the retina and innervate over 30 brain areas to influence a wide range of physiological processes. Current evidence points to RGCs executing these functions by primarily releasing the excitatory neurotransmitter glutamate with some RGCs also being able to co-release peptide transmitters. However, previous immunocytochemical and electrophysiological experiments have suggested the presence of GABAergic RGCs in multiple mammalian species including rodents and humans. The purpose of this study was to determine the identity and function of these putative GABAergic RGCs using a combination of mouse genetics, viral circuit tracing and optogenetics. Here, we report that a subpopulation of intrinsically photosensitive retinal ganglion cells (ipRGCs) that project to the suprachiasmatic nucleus (SCN), the intergeniculate leaflet (IGL) and the olivary pretectal nucleus (OPN) are GABAergic. Our preliminary data suggest that GABA release by ipRGCs function to dampen the sensitivity of non-image forming visual functions, especially at low light levels. These results identify a novel inhibitory circuit in the mouse visual system.

Disclosures: **T. Sonoda:** None. **T.M. Schmidt:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.10/J7

Topic: D.07. Vision

Title: Light regulates gut microbiome composition and rhythmicity through ipRGCs

Authors: *T. LU[1], C.-C. LEE[2];
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Abstract: Environmental light dark cycle is an important external cue to modulate many physiological functions of animals including circadian photo-entrainment. Recent studies indicated that aberrant light dark cycle such as dim light at night affects or chronic jet lag can influence the gut microbiome and metabolic status or mice. However, how does light modulate the gut microbiota remain unclear. We collected fecal samples from WT and ipRGC eliminated mice housed under different light dark cycle, and compare the microbiota between different mice and light dark cycle using 16S rRNA Next Generation Sequencing. Our data suggests light influences gut microbiome composition, diversity and rhythmicity. Furthermore, intrinsically

photosensitive retinal ganglion cells (ipRGCs), a group of photoreceptors, act as key role to provide daily light dark cycle input for gut microbiome modulation. External light dark can regulate gut microbiome composition and rhythmicity through ipRGCs.

Disclosures: **T. Lu:** None. **C. Lee:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.11/J8

Topic: D.07. Vision

Support: MOST 106-2311-B-002-033-MY3

Title: Light modulates oxytocin release and sociosexual behavior in mice through ipRGCs

Authors: *J.-H. YU, P.-Y. LIAO, S.-K. CHEN;
Natl. Taiwan Univ., Taipei, Taiwan

Abstract: Over the past decades, oxytocin has been extensively studied for its complex role as a neurohormone that modulates wide aspects of social behavior and conventional physiological functions. In addition to its correlation with stress, how and whether environmental stimulation influence oxytocin release in the plasma and cerebrospinal fluid remain unclear. In the present study, we investigate if light stimuli could influence oxytocin and regulate the downstream sociosexual behavior with mice. We confirmed that a one-hour light pulse can reduce the concentration of oxytocin in the blood. Furthermore, light exposure could also reduce the sociosexual behavior in WT mice, but not in ipRGC genetically eliminated mice. Although the circuit which relays the light signal to regulate the oxytocin release is still under investigation, our results suggest that light can influence the oxytocin level and potentially modulate social behaviors.

Keywords
ipRGC, oxytocin, sociosexual behavior.

Disclosures: **J. Yu:** None. **P. Liao:** None. **S. Chen:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.12/J9

Topic: D.07. Vision

Support: MOST 106-2311-B-002-033-MY3

Title: A mouse training protocol for time perception test

Authors: *F. LIANG, S.-K. CHEN;
Natl. Taiwan Univ., Taipei, Taiwan

Abstract: Light has a strong effect on our lives and physiological functions. In addition to image-forming visual function for animal to perceive our environment, ambient light could also influence many non-imaging-forming functions such as resetting the circadian clock, controlling the pupil size and modulating emotion and cognition functions. It has been shown that intrinsically photosensitive retinal ganglion cells (ipRGCs) play an important role in non-imaging-forming functions. These ipRGC express melanopsin, a special photopigment with principal absorption wavelength around 470 nm (blue light). Recent evidence also indicates that ipRGCs innervate the SCN and deep layer of the superior colliculus, which is involved in the regulation of circadian and the multisensory integration respectively. It has been showed that human exposed to different melanopsin contrast have slightly different perception of time. However, how light could influence the time perception remain unclear. To setup an animal model for further test, we generate a training protocol for mice to perform time perception test using two-alternative forced choice task. Mice first learned to poke the middle hole to start the trial and hold the position under two beeping sounds plays with interview ranging from 0.6 to 2.4 sec. They then next learn to approach the specific choice point to obtain water reward. After 3 weeks of training, we can test the time perception of mice under different background of light. This training protocol showed that we can used two -alternative forced choice task to study time perception of mice model.

Disclosures: F. Liang: None. **S. Chen:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.13/J10

Topic: D.07. Vision

Support: Max Planck Institute

Title: Mouse rod photoreceptor ribbons are essential for the formation of a large pool of primed vesicles

Authors: *C. P. GRABNER[1], T. MOSER[2];
[1]Synaptic Nanophysiology Group, Max Planck Inst. For Biophysical Chem., Goettingen, Germany; [2]Inst. for Auditory Neurosci., Univ. Med. Ctr. Goettingen, Goettingen, Germany

Abstract: Dark adapted animals can perceive very small doses of light. The detection threshold may be set by the activation 0of a few rhodopsin molecules in a single rod. The rod's single synaptic terminal converts the small amplitude photo-currents into synaptic signals. A mouse rod forms a single synaptic ribbon active zone. It is believed that only a subset of ribbon-associated synaptic vesicles (SVs) are available for release onto post-synaptic targets. Whole-cell membrane capacitance (C_m) measurements performed on mature mouse rods made with a high concentration of intracellular Ca^{2+} buffer (10mM EGTA) have reported that ~80 SVs fuse within a 1sec depolarization (Grabner et al., 2015 J. Neurosci.). This result was interpreted to represent release from the ribbon active zone; however, the time course of release and its dependence on intracellular Ca^{2+} buffering were not probed. In the current study, similar recordings were performed using shorter duration stimulations with 0.5 or 10mM EGTA in the pipette. Brief 1 and 3ms steps to -18mV evoked 0.59 and 1.35fF C_m jumps with 10mM EGTA (3 cells), and 1.65 and 3.25fF with 0.5mM EGTA (4 cells). Longer steps to 30ms produced a dC_m of 3.41fF with 0.5mM intracellular EGTA, similar to 3ms step responses, and suggestive of a depleted pool of SVs. Using a C_m value of 40aF for each SV (Grabner and Moser; 2018 PNAS), a total of 85 SVs were estimated to fuse within 30ms. SVs fusing within 3ms (regardless of EGTA conc.) are generally assumed as primed for release (Neher and Brose; Neuron 2018), and those released in 10mM EGTA are within a small Ca^{2+}-nanodomain (< 50nm from Ca_v channels; Burrone et al., 2002 Neuron). To assess the role of the ribbon itself in SV priming, the ribbonless RIBEYE knockout mice were examined (Maxeiner et al., 2016 EMBO J.). In the more permissive release condition of 0.5mM EGTA, 1 and 3ms steps elicited dC_m values of 0.38 and 1.03fF (5 cells), respectively, which were reduced to less than 30% of control values (p values: 0.003 and 0.019 for 1ms steps). This reduction occurred despite similar peak Ca^{2+} currents in rods of RIBEYE ko and wild type mice. The results argue that the synaptic ribbon is critically needed for SV priming, and the findings are congruent with published EM data that revealed the density of SVs

is reduced at the synaptic juncture (Maxeiner et al., 2016 EMBO J.). In summary, the rod's ribbon creates a large pool of ~80 primed SVs, which is equivalent to, or slightly more than, what is commonly viewed as docked at the ribbon's base.

Disclosures: C.P. Grabner: None. **T. Moser:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

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Topic: D.07. Vision

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Title: Cannabinoid receptors as modulators of cell migration in retinoblastoma

Authors: *C. M. VECCHINI-RODRIGUEZ[1,2,3], Y. OQUENDO-ALVARADO[4], F. BIAGGI-HUYKE[5], M. PORTELA-VÁZQUEZ[3], J. FLORES-OTERO[1];
[1]Anat. and Neurobio., Univ. of Puerto Rico Sch. of Med., San Juan, Puerto Rico; [2]Comprehensive Cancer Ctr., San Juan, Puerto Rico; [3]Inst. of Neurobio., San Juan, Puerto Rico; [4]Univ. of Puerto Rico, Cayey, Puerto Rico; [5]Villanova Univ., Philadelphia, PA

Abstract: Retinoblastoma (RB) is an intraocular tumor that develops during childhood. Current therapeutic approaches for RB target DNA synthesis with the goal of decreasing tumor size. However, these therapies fail to control the migration of RB via the optic nerve, which is the primary risk factor for brain metastasis. The survival rate for RB patients with brain metastasis is less than 8%. Recent studies have shown that the cannabinoid receptors (CBRs) and their ligands display anti-cancer roles including the prevention of metastasis by targeting cell migration. Moreover, the expression of the CBRs has been described in the retina of different animal models. Our main objective is to define how we can interfere with RB cell migration to prevent brain metastasis via modulation of the CBRs. Preliminary data from our lab using Western blot assays demonstrate than in contrast to the upregulation of CB2Rs, CB1Rs are downregulated in RB human tumors when compared to fetal retina (Two-way ANOVA, control; $p<0.001$ and $p<0.01$, respectively). Immunohistochemistry results validate the expression of CB1Rs and CB2Rs in murine retina. We hypothesize that RB migration can be modulated by targeting CBRs. To determine if CBRs play a role in the migration of the most invasive RB cells, Y79, we conducted Wound Healing assays. We observe a significant delay in migration (Dunnett's test,

$p<0.05$) in the Y79 cells upon the activation of CBRs with CP55,940 and 2-AG, which activate both CBRs, when compared to the untreated cells. To determine if CB2R is responsible for the delay of migration we used a specific antagonist for CB1R (SR 141716A) and a specific agonist of CB2R (JWH-133). We observe that cells exposed to the combination of SR 141716A and JWH-133 display a delay in migration. In contrast to the migration effect, CBR ligands CP55,940 and 2-AG did not affect Y79 cell proliferation. Overall, our results suggest a potential role of CBRs in the migration of RB cells. We propose that CB2R play a role in the migration rate of Y79 cells, however, ongoing studies are evaluating the role of CB1R. Successful outcomes will contribute to identify novel targets that prevent the migration of RB cells to the brain, and hence increase these patient population survival rate.

Disclosures: C.M. Vecchini-Rodriguez: None. **Y. Oquendo-Alvarado:** None. **F. Biaggi-Huyke:** None. **M. Portela-Vázquez:** None. **J. Flores-Otero:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.15/J12

Topic: D.07. Vision

Support: MOST 106-2311-B-002-033-MY3

Title: Light at night influences intestine transcriptome profile in mice

Authors: *I.-C. LEE, S.-K. CHEN;
NTU, Taipei City, Taiwan

Abstract: Environmental light affects mammalian circadian clock through ipRGCs in retina, and may also influence peripheral circadian oscillation and regulate several physiological hormone homeostasis. Previous studies showed that abnormal light at night time might cause obesity, insulin resistance and gut microbiota oscillation abnormality in mouse. However, the mechanism through which environmental light influences the gut microbiota and host metabolic mechanism remains unknown. In this study, we analyzed the transcriptome expression in small intestine from mice housed under dim light at night (dLAN) or normal light-dark cycle. We found that many genes which influence protein and fat absorption are enriched in dLAN group mice and different expression profile of immune-related genes between dLAN and normal group. Therefore, light exposure during the night time could modulate small intestine gene expression profile which may influence metabolic status of the host or gut microbiota.

Disclosures: I. Lee: None. **S. Chen:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

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Program #/Poster #: 575.16/J13

Topic: D.07. Vision

Support: CPRIT
Brain Research Foundation
T32EY007001

Title: LKB1 is required for cone photoreceptor nuclear positioning and function

Authors: *C. BURGER[1], F. LI[1], N. ALBRECHT[2], D. JIANG[1], M. A. SAMUEL[3]; [2]Neurosci., [3]Dept. of Neuroscience, Huffington Ctr. on Aging, [1]Baylor Col. of Med., Houston, TX

Abstract: Cone photoreceptors detect light and are responsible for color vision. These cells are unique in that they have a distinct polarized morphology where their nuclei are precisely aligned at the apical surface of the retina. However, little is known about the mechanisms involved in proper nuclear positioning or the impact of this organization on retina function. LKB1 is a serine/threonine kinase involved in cellular polarity. By deleting LKB1 specifically in cones ($LKB1^{Cones}$), we show that LKB1 is required for proper nuclear localization, while no changes to other cell types are observed. Electroretinography in one-month-old $LKB1^{Cones}$ mice reveal that altered cone nuclear localization reduces photopic but not scotopic retinal responses, indicating that visual processing in cones is reduced. However, by two months of age, scotopic vision also declines, suggesting that changes to cone structure and function progressively impact rod photoreceptor signaling. Together, these data suggest that LKB1 is a regulator of cone nuclear translocation and indicate that nuclear alignment is required for proper signaling in cones and for the preservation of both cone and rod function.

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Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

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Topic: D.07. Vision

Support: MEXT S1511027
Grants-in-Aid for Scientific Research (B) (

Title: Gene delivery to cone photoreceptors by subretinal injection of rAAV2/6 in the mouse retina

Authors: M. FUKUTOME[1], T. HORI[1], C. MAEJIMA[1], H. MATSUSHIMA[1], K. KOBAYASHI[1], S. KITAZAWA[1], R. KITAHARA[1], K. KITANO[1], K. KOBAYASHI[3], S. MORITOH[1], *C. KOIKE[2];
[2]Col. of Pharmaceut. Sci., [1]Ritsumeikan Univ., Kusatsu, Japan; [3]Natl. Inst. for Physiological Sci., Okazaki, Japan

Abstract: Adeno-associated virus (AAV) has been studied as a safe delivery tool for gene therapy of retinal blinding diseases such as Leber's congenital amaurosis (LCA). The tropism of recombinant AAV (rAAV) including its specificity and efficiency in targeting retinal cell types has been studied with native or engineered capsids, along with specific promoters. However, one of the rAAV serotypes, rAAV2/6, has not been well-studied based on a report of low infection efficiency in the retina. We investigated the tropism of several rAAVs by subretinal injection in the adult mouse and found that rAAV2/6 predominantly infected cone photoreceptors including the main spectral type. Our data suggest that subretinal injection with rAAV2/6 may provide both an efficacious and specific means of gene delivery to cone photoreceptors in murine retinas.

Disclosures: M. Fukutome: None. **T. Hori:** None. **C. Maejima:** None. **H. Matsushima:** None. **K. Kobayashi:** None. **S. Kitazawa:** None. **R. Kitahara:** None. **K. Kitano:** None. **K. Kobayashi:** None. **S. Moritoh:** None. **C. Koike:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.18/DP06/J15

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: D.07. Vision

Support: EY028633
MH105960

Title: Using cell atlases to investigate the evolution and development of retinal cell types in multiple vertebrate species

Authors: *Y.-R. PENG[1], W. YAN[1], K. SHEKHAR[2], M. LABOULAYE[1], M. YAMAGATA[1], Q. ZHANG[4], G. FENG[4], A. REGEV[3,5], J. R. SANES[1];
[1]Dept. of Mol. & Cell. Biology, Ctr. for Brain Sci., Harvard Univ., Cambridge, MA; [3]Howard Hughes Med. Inst., [2]Broad Inst. of MIT and Harvard, Cambridge, MA; [4]McGovern Inst. for Brain Res. and Dept. of Brain & Cognitive Sci., [5]Dept. of Biol., MIT, Cambridge, MA

Abstract: The vertebrate retina exhibits profound species-specific specializations superimposed on a conserved retinal plan comprising six cell classes: horizontal, bipolar, amacrine and retinal ganglion cells, photoreceptors and Müller glia. Species-specific regional specializations (e.g., area centralis or fovea) and functional capabilities (e.g., high acuity or chromatic vision) stem from the diversification of cell types within shared classes. We have used large-scale high throughput single-cell RNA-sequencing (scRNA-seq) to generate comprehensive cell atlases in two model systems, mice (Macosko et al., Cell, 2015; Shekhar et al., Cell, 2016) and macaques (Peng et al., Cell 2019). These cell atlases enabled us to examine cell types that are specific to the fovea, a high-acuity retinal region in primates, and to identify the degree to which cell types are common to the two species. With these results as a foundation, we are now generating retinal cell atlases from eight additional vertebrate species—human (*Homo sapiens*), marmoset (*Callithrix jacchus*), chicken (*Gallus gallus domesticus*), deer mouse (*Peromyscus maniculatus*), ferret (*Mustela putorius furo*), pig (*Sus scrofa domesticus*), zebrafish (*Danio rerio*), and sheep (*Ovis aries*). Analysis of these atlases is allowing us to tackle the largely unexplored issue of how cell types within classes evolve. In parallel, we are asking when regional specializations arise. To this end, we generated cell atlases of fovea and peripheral retina from neonatal marmosets. Comparison with the adult atlases showed that the majority of cell types are present in neonates, but there are significant differences in foveal gene expression between neonates and adults. Some of these differentially expressed genes may play a role in mediating the formation of structural and functional foveal specializations.

Disclosures: Y. Peng: None. **W. Yan:** None. **K. Shekhar:** None. **M. Laboulaye:** None. **M. Yamagata:** None. **Q. Zhang:** None. **G. Feng:** None. **A. Regev:** None. **J.R. Sanes:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.19/J16

Topic: D.07. Vision

Support: NIH

Title: Transcriptomic classification of retina cells from human and non-human primate

Authors: *W. YAN[1], Y.-R. PENG[1], T. VAN ZYL[2], Q. ZHANG[3], G. FENG[3], J. R. SANES[1]; [1]Dept. of Mol. and Cell. Biol., Harvard Univ., Cambridge, MA; [2]Glaucoma Service, Dept. of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Med. Sch., Cambridge, MA; [3]Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: The retina has been studied intensively in a variety of model organisms, leading to a growing understanding of the cells and circuits that underlie the initial steps in vision. Among mammals, however, only primates have a central specialized retinal region called the fovea, embedded in a slightly larger macula. The fovea underlies most high acuity and much chromatic vision, and is most vulnerable in age-related macular degeneration and other macular diseases. As a first step in understanding the molecular and cellular bases of structural and functional foveal specializations, we recently generated cell atlases of macaque fovea and peripheral retina (Peng, Shekhar *et al*., *Cell*, 2019). Here, we extended this work by generating atlases of human fovea and peripheral retina from over 75k single cell RNA-seq profiles collected from 5 human donors. Among the >50 neuronal types and 6 non-neuronal types in the human retina, most are shared between fovea and periphery, but some genes are enriched in one or the other region. For example, *FBXO15* and *FXYD6* are selectively expressed by foveal *DB4* bipolars and peripheral *DB3a* bipolars respectively. We then generated an atlas from a third commonly used primate model, marmoset. With >45k single cells collected from 2 adult marmosets, we identified >50 neuronal types and 5 non-neuronal types. Finally, we used these data sets to compare retinal cell types among the three primates and between primates and mice. We found that photoreceptor and bipolar types were largely conserved across species, but found species-specific differences among horizontal, amacrine and retinal ganglion cell types. Together these results reveal the specializations of primate fovea compared to the lower acuity peripheral retina and the differences between primate and rodent retina. More generally, the transcriptomic resources we provide establish molecular foundations for studies of human retinal disease and shed light on the evolution of retina.

Disclosures: W. Yan: None. **Y. Peng:** None. **T. van Zyl:** None. **Q. Zhang:** None. **G. Feng:** None. **J.R. Sanes:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

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Topic: D.07. Vision

Support: Intramural Research Training Award- NINDS NIH
NIH Grant EY 14358

Title: Alterations in photoreceptor signals due to thyroid hormone receptor beta mutations are present in larval and adult zebrafish

Authors: *C. DEVEAU[1], J. XIAODONG[2], T. YOSHIMATSU[3], S. SUZUKI[4], J. HEJTMANCIK[2], R. NELSON[1];
[1]NIH NINDS, Rockville, MD; [2]NIH NEI, Rockville, MD; [3]Univ. of Sussex, Sussex, United Kingdom; [4]Univ. of Washington, Seattle, WA

Abstract: Thyroid hormone receptor beta (thrb, trB2), the gene responsible for vertebrate red cone development, diminishes and eliminates responses to red cone wavelengths in larval zebrafish (5-12 days post fertilization). We hypothesize that this loss of functional thrb will extend through the retinal circuit, development and into behavior, specifically the optomotor response (OMR) and optokinetic response (OKR). We investigated this hypothesis with two thrb Crisper mutant strains: c. 184_188delTATGGinsGTTCCC (6BP+1) frameshift indel and an in frame c. 184_186delTAT single codon deletion (3BP).
Zebrafish at the larval stage (5-12 dpf) and adult stage (> 3 months dpf) spawning from two breeding pairs, mutant/het-mutant and two het-mutants, were the subjects of this study. Spectral PIII cone signals and ON-bipolar cell signals were recorded using ERG with a light stimulus protocol that ranged from 650nm to 330nm. Eyes were perfused with L-aspartic acid and CNQX to isolate the respective signals. For behavior, the PsychoPy stimulus was presented on a monitor with the larval fish placed directly on top. Antibodies labeling red cone opsin and were imaged with DAPI using a confocal microscope.
The loss of red response in the larval ON-bipolar cells was maintained as seen in cones in larvae. There is a significant loss of red response in the cones with additional significant alterations to the green, blue, and UV cones for the 6BP+1 mutated adult. Larval 6BP+1 mutants OMR and OKR tests showed a loss of red perception. Antibody stains showed no fluorescent red opsin labeled in the mutant while it was present in the heterozygotes and wild types, confirming the thrb:td Tomato transgene confocal images that showed no thrb activity and no presence of red cones.
After finding the eliminations and alterations of red cone ERG signals in larval zebrafish, we continued to find the same lack of long-wavelength cone response in the ON-bipolar cells and adult zebrafish. This shows that the altered signal is maintained through the next step of the circuit and there are no changes throughout development that compensate for the lack of thrb into adulthood. OMR and OKR behavior showed that the red light is not being perceived in the brain so the fish are red colorblind. The antibody stains confirmed that the red opsin is not formed when functional thrb is lost, as seen in additional vertebrates such as mice. Without functional thrb, zebrafish cannot form red cones, red opsin, or perceive red light.

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Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

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Program #/Poster #: 575.21/J18

Topic: D.07. Vision

Support: NIH R01 EY024016
McKnight Scholarship Award
Sloan Research Fellowship

Title: Neural mechanisms of contextual modulation in the retinal direction selective circuit

Authors: *X. HUANG[1], M. RANGEL[2], K. L. BRIGGMAN[2], W. WEI[3];
[1]Dept. of Neurobio., The Univ. of Chicago, Chicago, IL; [2]Computat. Neuroethology, Ctr. of Advanced European Studies and Res., Bonn, Germany; [3]Univ. of Chicago, Chicago, IL

Abstract: Contextual modulation of neuronal responses by surrounding environments is a fundamental attribute of sensory processing. In the mammalian retina, On-Off direction selective ganglion cells (DSGCs) are maximally activated by bright or dark contours moving in the preferred direction across their receptive field (RF) center. Contextual tuning of DSGCs has been previously reported in the rabbit retina (Chiao and Masland, 2003). However, this phenomenon is yet to be studied in the mouse, which is currently the prevalent model organism for retinal circuit analysis. Importantly, how synaptic circuits are engaged to modulate DSGC responses during more complex motion contexts is poorly understood.
Using two-photon targeted patch-clamp recording of genetically labeled posterior-preferring On-Off DSGCs (pDSGCs), we found that pDSGCs are sensitive to discontinuities of moving contours owing to contextually modulated cholinergic excitation from starburst amacrine cells (SACs). Using a combination of synapse-specific genetic manipulations, patch clamp electrophysiology and connectomic analysis, we identified distinct circuit motifs upstream of On and Off SACs that are required for the contextual modulation of pDSGC activity for bright and dark contrasts. The contextual tuning of DSGC Off responses requires GABAergic inputs from wide-field amacrine cells (WACs) onto SACs. By contrast, the weak contextual modulation of DSGC On responses is mediated by a "SAC - WAC - bipolar cell" circuit motif. Furthermore, our results reveal a class of WACs with straight, unbranching dendrites that function as "continuity detectors" of moving contours.
Together, these results demonstrate that divergent amacrine cell circuits implement contextual modulation of DSGC response in the On and Off pathways. Therefore, the extensive retinal network impinging on SACs and DSGCs shapes the information encoding by On-Off DSGCs beyond their direction selectivity during complex motion stimuli.
Reference:

Chiao, C., and Masland, R.H. (2003). Contextual tuning of direction-selective retinal ganglion cells. Nat. Neurosci. *6*, 1251-1252.

Disclosures: **X. Huang:** None. **K.L. Briggman:** None. **W. Wei:** None. **M. Rangel:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.22/J19

Topic: D.07. Vision

Support: MOST 107-2813-C-007-097-B

Title: Enhancement of information transfer on mouse retina by the addition of external noise

Authors: *A. HUNG[1], J. J.-S. WU[1], C.-K. CHAN[2], C.-C. CHIAO[1];
[1]Inst. of Systems Neurosci., Natl. Tsing-Hua Univ., Hsinchu, Taiwan; [2]Inst. of Physics, Academia Sinica, Taipei, Taiwan

Abstract: The addition of noise usually corrupts a system's sensitivity and reliability. However, the phenomenon stochastic resonance [1] (SR) indicates otherwise: adding noise to a certain degree improves visual sensitivity when the cue is obscure [2,3]. However, SR's underlying neural mechanisms remain elusive. Here we report our experimental results on the effects of noise on the encoding process of mouse retinal ganglion cells in a multi-electrode array system under whole field light stimulation. To have a more naturalistic stimulus, the stimulation is generated by a hidden Markov model while the added noises are zero-mean with uniform distribution. Mutual information (MI) between the stimulation and the response is measured at different noise levels to determine whether SR occurs in the retina. Our results suggest that some of the cell types indeed demonstrate stochastic facilitation - mutual information attains a maximum at intermediate levels of noise. This signifies that noise aids in signal detection at lower values, and corrupts the signal at higher values. Some cell types in the retina show monotonically decreasing trends in measured MI, which may correspond to the stimulation being supra-threshold for them. Others show irregular trends in measured MI, which might indicate even more complicated dynamics at work. Moreover, our results indicate that not only does the mutual information increases with noise but the information per spike as well! This means that stochastic facilitation is also energy efficient when improving the encoding process.
[1] Gammaitoni, Luca, et al. "Stochastic resonance." *Reviews of modern physics* 70.1 (1998): 223.
[2] Simonotto, Enrico, et al. "fMRI studies of visual cortical activity during noise stimulation." *Neurocomputing* 26
(1999): 511-516.

[3] Simonotto, Enrico, et al. "Visual perception of stochastic resonance." *Physical review letters* 78.6 (1997): 1186.

Disclosures: **A. Hung:** None. **J.J. Wu:** None. **C. Chan:** None. **C. Chiao:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.23/J20

Topic: D.07. Vision

Support: BBSRC BH163322
Newcastle University Faculty of Medical Sciences

Title: Neonatal retinal waves revisited: Evidence for a novel, transient population of hyper-connected cholinergic cellular clusters

Authors: ***E. SERNAGOR**, J. DE MONTIGNY, V. KRISHNAMOORTHY;
Inst. of Neurosci., Newcastle Univ., Newcastle upon Tyne, United Kingdom

Abstract: In the developing retina, spontaneous waves sweep across the layer of retinal ganglion cells (RGCs), the output cells of the retina. Experimental evidence indicates that retinal waves play a crucial role in guiding the refinement of visual connectivity. Wave dynamics undergo profound developmental changes. From initial gap junction communication during late gestation (Stage 1), they become controlled by directly interconnected cholinergic starburst amacrine cells (SACs), the only known retinal cholinergic cells (Stage 2 waves). Direct connections between SACs withdraw at P10 (in mouse). Waves become then driven by newly formed glutamatergic connections originating from bipolar cells (Stage 3 waves, P10-eye opening). Recent observations from our group are challenging the hypothesis that Stage 2 waves are driven by SACs. Using wide-field fluorescence microscopy (Zeiss ApoTome) to visualize retinal wholemounts stained with an antibody against Choline Acetyltransferase (ChAT, the enzyme that synthesizes acetylcholine), we found a novel transient population of cholinergic cells present from P2-9. These cells co-exist with SACs, but they are larger, residing only in the RGC layer and not in the inner nuclear layer. They form tight clusters in an annulus pattern around the optic disc at P2-3. Labelling cholinergic terminals with an antibody against Vesicular Acetylcholine Transporter (VAChT) reveals that they are more conspicuous near the cholinergic cell clusters, suggesting cholinergic neurotransmission in their vicinity. The annulus of cell clusters expands towards the periphery with development, until the clusters disappear at P10, coinciding with the disappearance of Stage 2 waves, which suggests that they may be involved in their generation. In support, using large-scale multielectrode array recordings from the entire retina, we found that wave origins follow a centrifugal pattern between P2-P10 as well, with gradually more waves

becoming initiated in the peripheral retina. Once waves become driven by glutamate, this center-to-periphery pattern disappears and wave origins tile the entire retina. We propose that these cells represent transient hubs of hyper-excitable neurons responsible for the generation of cholinergic waves, somewhat reminiscent of transient subplate neurons in the developing cortex, and super-connected GABAergic hub neurons in the developing hippocampus, suggesting a universal mechanism mediating hyper-excitability in developing CNS networks during the critical period for brain wiring.

Disclosures: **E. Sernagor:** None. **J. de Montigny:** None. **V. Krishnamoorthy:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

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Program #/Poster #: 575.24/J21

Topic: D.07. Vision

Support: R01EY013528
R01EY019498
P30EY003176

Title: Development of direction selectivity maps in the mouse retina

Authors: *A. TIRIAC, M. B. FELLER;
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Abstract: Detecting the directions in which objects move is critical for everyday behavior. In mice, directional motion detection begins in the retina where a subset of direction selective retinal ganglion cells (DSGCs) fire more action potentials in response to visual stimuli moving in one direction, called the preferred direction, than visual stimuli moving in the opposite direction, called the null direction. In adult mice, the preferred directions cluster along four directions that align along two optic flow axes—paths that visual stimuli trace across the retina as the animal moves through space (Sabbah et al., Nature 2017). We aim to determine whether visual experience plays a role in the clustering of preferred direction along the optic flow axes. Here, we used two-photon microscopy to image from large populations of RGCs and assess the direction selectivity map in multiple regions of the retina in normal- (12-hour light/dark cycle) and dark-reared mice. We also assessed the direction selectivity map of transgenic mice that express GFP under the Hb9 promoter, which labels DSGCs that prefer ventral motion (Hb9-DSGCs). Our results show that in normal-reared mice, the preferred directions of DSGCs changed as a function of their location on the retina, with the axes of preferred directions of DSGCs skewed in the more ventral parts of the retina, consistent with their alignment along the axes of optic flow. For example, the Hb9-DSGCs close to the optic nerve preferred ventral

motion whereas Hb9-DSGCs in peripheral ventronasal retina preferred ventral and temporal motion. Hb9-DSGCs from dark-reared mice exhibited similar direction selectivity maps as normal-reared mice, suggesting that the development of direction selectivity maps in this cell type does not depend on visual experience. We will present data assessing the impact of dark-rearing on the direction selectivity maps of other DSGCs to determine whether different DSGC subtypes are differentially impacted by visual experience. Support: **R01EY013528, R01EY019498, P30EY003176**

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

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.25/DP05/J22

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: D.07. Vision

Support: ERC starter 757732
I-CORE program 51/11
ISF 1396/15

Title: Temporal dynamics of inhibitory circuits shape the directional code of the retina

Authors: *L. ANKRI[1], E. EZRA-TSUR[1], M. RIVLIN-ETZION[2];
[1]Neurobio., [2]Dept. of Neurobio., Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Direction selective retinal ganglion cells (DSGCs) fire robustly in response to motion in one (preferred) direction, and poorly to motion in the opposite (null) direction. Starburst amacrine cells (SACs) underlie this computation via two mechanisms - they form asymmetric inhibitory connections onto DSGCs; and each of their processes is direction selective. Surprisingly, it has been shown that DSGCs can reverse their directional preference upon a short repetitive stimulation of drifting gratings. This reversal cannot be explained within the scope of the known mechanisms for retinal DS, which heavily rely on the circuit's anatomy. Here we used this reversal to shed new light on the mechanisms underlying the computation of motion. Using patch-clamp recordings, we found that processes of SACs lose their direction selectivity following repetitive stimulation. Instead, SACs' response phase changed, a shift that is reflected in the timing of inhibition to DSGCs, supporting the reversed computation by pulling the excitation-inhibition balance towards the null-direction. We determined SACs' center-surround organization and found that it changed following repetitive visual stimulation. Using a morphology-based simulation we demonstrated that this reorganization underlies the observed

shift in SACs' responses. Taken together, we revealed a novel way to dissect the retinal computation of motion direction to its elementary parts and thereby determine their role in the beautiful complexity hiding in this seemingly simple neural network.

Disclosures: L. Ankri: None. **E. Ezra-Tsur:** None. **M. Rivlin-Etzion:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.26/J23

Topic: D.07. Vision

Support: DFG EXC 307
DFG MU3792/3-1
Swiss National Science Foundation Ambizione (PZ00P_167989)

Title: Saccadic suppression in the retina and its underlying mechanisms

Authors: *S. IDREES[1], F. FRANKE[2], M. BAUMANN[1,3], Z. M. HAFED[1,3], T. A. MÜNCH[1,4]; [1]Werner Reichardt Ctr. for Integrative Neurosci., Tuebingen, Germany; [2]ETH Zürich, Basel, Switzerland; [3]Hertie Inst. for Clin. Brain Res., Tuebingen, Germany; [4]Inst. for Ophthalmic Res., Tuebingen, Germany

Abstract: Purpose: During natural viewing, image flow on the retina is determined primarily by the behavior of the observer. Eye movements during active visual exploration, such as saccades, are particularly dominating in this regard. Despite this, retinal image processing has in the past often been studied with isolated stimuli, ignoring the highly dynamic aspects of natural viewing. We recently showed that saccade-like image shifts suppress the responses to subsequent stimuli in the retina, and in a manner that is directly congruent with human perceptual effects of saccadic suppression (Idrees et. al., 2019). Here, we add detailed characterization of retinal ganglion cell (RGC) responses in the context of saccade-induced image shifts, and we also probe the mechanisms underlying these effects.
Methods: We used ex-vivo retinal electrophysiology and recorded from more than 1,000 retina ganglion cells (RGC's) in isolated mouse and pig retinae. We showed test visual stimuli at different times after background image translations mimicking saccade-induced retinal image shifts (Idrees et al., 2019). We varied background image statistics and test stimulus luminance, and we also investigated center-surround interactions and amacrine cell contributions to retinal saccadic suppression.
Results: Retinal responses to test stimuli, when presented in the context of saccades, were strongly suppressed in comparison to responses to the same stimuli presented in isolation. Such saccade-related retinal suppression occurred robustly across many different RGC cell types.

Suppression properties critically depended on the delay between saccade and test stimulus, as well as on the statistical properties of the background scene presented during the saccades. In ON RGCs the suppression lasted for up to 1s, whereas OFF RGCs tended to recover much faster. The suppression did not critically depend on particular saccade-like profile speeds, but was a result of general stimulus-stimulus interaction effects triggered by image displacements. A component of this suppression originated from wide-field amacrine cell mediated inhibition. Another component originated from the cell's receptive field center and might originate in the outer retina.
Conclusion: Saccadic suppression does occur robustly across many different RGC cell types and is a result of specific spatio-temporal retinal-circuit image processing, in which the saccade stimulus elicits activity in both local and global retinal circuits to suppress responses to the test stimulus.

Disclosures: S. Idrees: None. **F. Franke:** None. **M. Baumann:** None. **Z.M. Hafed:** None. **T.A. Münch:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.27/J24

Topic: D.07. Vision

Support: NIH DP2 EY026770-01

Title: Intrinsic properties shape a feature selectivity computation in a novel RGC

Authors: *S. WIENBAR, G. SCHWARTZ;
Northwestern Univ., Chicago, IL

Abstract: Neural computations arise through the integration of synaptic inputs and intrinsic cell properties. The purpose of this project was identify mechanisms by which intrinsic properties influence cell-type-specific computations in the retina. We identified a new retinal ganglion cell (RGC) type called the Bursty Suppressed-By-Contrast (bSbC) RGC. The bSbC is a morphologically and physiologically distinct cell type. Its key feature selectivity is that its tonic firing rate is decreased by both positive and negative contrast light stimuli. We measured synaptic currents and action potential waveforms in bSbC RGCs though whole-cell voltage, current, and dynamic clamp recordings in whole mount retinas. While the bSbC RGC receives similar synaptic inputs to those in the well-known OFF Sustained Alpha RGC, its feature selectivity is driven by its different intrinsic properties; bSbCs undergo depolarization block more readily than OFF Sustained Alphas. We have investigated the channel mechanisms underlying this key difference. While synaptic inputs in different retinal circuits are frequently

studied for their role in retinal computation, our work highlights the importance of intrinsic properties in RGCs.

Disclosures: S. Wienbar: None. **G. Schwartz:** None.

Poster

575. Cellular Mechanisms of Retinal Connectivity in Health and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 575.28/J25

Topic: D.07. Vision

Support: 5F31EY028022-02
R01EY013528

Title: Gap junction coupling shapes the encoding of light in the newborn retina

Authors: *F. CAVAL-HOLME, C. VOUFO, Y. ZHANG, M. B. FELLER;
Univ. of California Berkeley, Berkeley, CA

Abstract: Intrinsically photosensitive retinal ganglion cells (ipRGCs) are present early in development and mediate reflexive and behavioral light responses before conventional photoreceptors mature. During development, ipRGCS are extensively gap junction coupled both to other ipRGCs and to non-intrinsically photosensitive neurons. However, the role this gap junction coupling plays in mediating the light sensitivity of developing retinas is not known. Here we use two-photon calcium imaging in a mouse expressing GFP under the melanopsin promoter (Opn4::eGFP) to characterize the irradiance-response and temporal response functions of ipRGCs from postnatal day 6-9 mice. By combining unsupervised clustering algorithms with anatomical approaches, we identify at least 6 distinct functional groupings that mostly but not exclusively map onto the ipRGC subtypes identified in the adult. By pharmacologically uncoupling gap junction circuits, we show that gap junction coupling is required to generate light responses in M2-M6 ipRGCs. Conversely, enhancement of gap junction coupling increases the gain of light-responses in all ipRGCs. We find that the different subtypes of ipRGCs have distinct tracer-coupling patterns, with M1 ipRGCs exhibiting the least coupling and M4s exhibiting the most. Together these data indicate that, even though ipRGCs have a cell-autonomous intrinsic light response, gap junction coupling among these cells significantly contributes to the encoding of light intensity in the neonatal retina.

Disclosures: F. Caval-Holme: None. **C. Voufo:** None. **Y. Zhang:** None. **M.B. Feller:** None.

Poster

576. Visual System: Response Modulation and Adaptation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 576.01/J26

Topic: D.07. Vision

Support: Grant-in-Aid for Scientific Research(C) 17K01527

Title: Visual evoked magnetic fields to 8Hz repetitive pattern-reversal stimulation

Authors: *Y. GOTO[1], S. TOBIMATSU[2];
[1]Physiol., Sch. of Medicine, Intl. Univ. of Helth and Welfare, Narita, Japan; [2]Kyushu Univ, Grad Sch. Med. Sci., Fukuoka, Japan

Abstract: PURPOSE: P100m of transient (TR) visual evoked magnetic fields (VEFs) is originated in the primary visual cortex (V1). However, neural generator(s) of steady-state (SS) VEFs has not been fully elucidated. We investigated the sources of equivalent current dipoles (ECDs) in each response using 8Hz repetitive pattern-reversal stimulation with a whole-head 306-channel magnetoencephalography. METHODS: Ten healthy young adults were subjected to this study. A black and white checkerboard pattern (check size, 50 min; mean luminance, 30 cd/m^2; contrast, 97 %) was phase-reversed at a rate of 8 Hz (duration, 1 s; interstimulus interval, 1.5 s) to stimulate each right and left visual half-field (field size, 8 deg). A total of 100 responses were averaged. RESULTS: In this stimulus condition, TR-VEFs and SS-VEFs were simultaneously obtained in all subjects. In TR-VEFs, N75m and P100m were clearly evoked whereas N145m was not identified because of overlapping with SS-VEFs. The mean peak latency of P100m was 97.3 ms and its ECD was located in V1 around the calcarine fissure contralateral to the stimulated visual field. SS-VEFs were higher amplitude and quasi-sinusoidal responses compared with TR-VEFs and they were continuously observed from 150 ms after the stimulus onset to the end of stimulus offset. Fast Fourier analysis showed that second harmonic response (16 Hz) was the major component. In 8 of 10 subjects, the ECDs of SS-VEFs were widely spread in V1 contralateral to the stimulated visual field. Interestingly, sustained (SU)-VEF was observed in this stimulus condition. CONCLUSIONS: These results suggest that neural generators between TR- and SS-VEFs are differently located in V1. In addition, 8 Hz repetitive pattern-reversal stimulation can be a unique method to obtain TR-, SS- and SU-VEFs, simultaneously.

Disclosures: Y. Goto: None. **S. Tobimatsu:** None.

Poster

576. Visual System: Response Modulation and Adaptation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 576.02/J27

Topic: D.07. Vision

Title: Functional characteristics of stimulus driven resting state fMRI signals

Authors: *Y.-W. SUNG[1], S. OGAWA[2];
[1]Tohoku Fukushi Univ., Sendai, Japan; [2]Kansei Fukushi Res. Inst., Touhoku Fukushi Univ., Sendai-shi, Japan

Abstract: In the brain mapping study task-fMRI has been used to localize brain regions specifically reflecting a task-related function. On the other hand, resting-state fMRI (rsfMRI) is known to reflect some intrinsic brain function such as the default mode network rather than to reflect specific function. In previous studies, we measured typical rsfMRI signals with no stimulus or task, and stimulus-driven rsfMRI signals, and showed that the primary motor and visual areas could be localized by the comparison of typical rsfMRI and stimulus-driven rsfMRI signals but the locations were off the focal sites by task-fMRI. We, in this study, aimed to further examine characteristics in stimulus-driven rsfMRI signals evoked while participants were solving a puzzle and compared with the previous studies.
MRI measurements were conducted by a 3-Tesla MRI scanner (Skyra-fit; Siemens). From eight subjects, structural images (T1) and functional images were measured. In the resting-state fMRI session, subjects were asked to lie on the bed and not to wander their mind with their eyes open and to gently focus their eyes on the center of the visual field. The resting-state fMRI session was followed by task-fMRI session. In the task-fMRI session, a picture with nine dots were presented on the screen during an 8-min scan and subjects were asked to solve a puzzle, the solution of the nine dot puzzle.
We could find a brain region in BA4/6 that tended to have larger fractional amplitude of low frequency fluctuation (fALFF) for task-fMRI than for rsfMRI ($p = 0.053$, FWE corrected). However, we could not find any brain areas showing larger fALFF for rsfMRI. We also performed regional homogeneity (ReHo) analyses for the present data in addition to the previous studies of motor and visual tasks. ReHo values were larger in the primary motor and visual areas for rsfMRI signals ($p = 0.05$, FEW corrected). The brain areas shown larger ReHo values for task-fMRI during puzzle solving were parietal and middle occipital cortices.
Our results suggest that coherent neuronal activities result in the low frequency band signals at a resting state fMRI and the coherent neuronal activities are disturbed by the external stimulation input. Our results also indicate that the disturbance of the low frequency signals in a functional area by external stimulation is specific to its functional role. On the other hand, coherent neuronal activities observed for internal stimulation of solving a puzzle are different. The

differences in rsfMRI signals for those external and internal stimuli observed through fALFF and ReHo values can be clues for further elucidation of characteristics of rsfMRI signals.

Disclosures: **Y. Sung:** None. **S. Ogawa:** None.

Poster

576. Visual System: Response Modulation and Adaptation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

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Topic: D.07. Vision

Support: MEXT/JSPS KAKENHI JP 16K01965

Title: Contrast dependent spatial frequency tuning dynamics in the cat primary visual cortex

Authors: *H. TANAKA;
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Abstract: Previous studies on single cells in the primary visual cortex (V1) reported little effect of stimulus contrast on spatial tuning properties inside the receptive field. With regard to spatial frequency (SF) tuning, they showed that the preferred SF of cells hardly changed with stimulus contrast. These studies measured tuning properties using the cell's steady state responses. However, as it is well known, the preferred SF of V1 cells often changes with time. A proposed mechanism of these dynamics is the convergence of two separate thalamocortical pathways with different SF tuning and temporal characteristics. These pathways may also have different contrast dependence. Therefore, if we study SF tunings with high temporal precision, the preferred SFs may highly depend on stimulus contrast. To address this issue, we measured the time course of SF tunings of cat V1 cells under different contrast conditions. We recorded the activities of V1 cells in response to random sequences of flashed sinusoidal gratings of various orientations, SFs, and phases. Stimulus contrast of each sequence was constant and sequences of different contrasts were interleaved. The time courses of the SF tunings for each contrast were computed by applying a subspace reverse correlation technique. We obtained reliable SF tuning time courses for contrast 50%, 12.5%, and 6.25% from 117, 88, and 52 cells, respectively. We first examined whether the total amount of temporal change of the preferred SF during response time depended on contrast. We found that the shifts of preferred SF during response time became larger as the stimulus contrast increased (mean SF shift: 0.20, 0.30, and 0.39 octaves for contrast 6.25%, 12.5%, and 50%, respectively). Next, we compared the preferred SFs between different contrast conditions at three temporal phases. At response onset, preferred SF of the cells does not differ with stimulus contrast. On the other hand, at response peak and offset, the preferred SF is often higher when the stimulus contrast is higher. The present results show that the preferred SF

of cells in V1 highly depends on stimulus contrast, and this dependence dynamically develops during response time.

Disclosures: H. Tanaka: None.

Poster

576. Visual System: Response Modulation and Adaptation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 576.04/J29

Topic: D.07. Vision

Title: Visual oddball paradigm reveals feature non-specific prediction errors in V1 of a mouse model of fragile X syndrome

Authors: *A. PAK, S. T. KISSINGER, A. A. CHUBYKIN;
Dept. of Biol. Sci., Purdue Univ., West Lafayette, IN

Abstract: Proper functioning in a noisy world requires specific and timely adjustment of the animal's internal world representation in response to dynamically changing sensory inputs. There is an emerging idea that this process might be impaired in autism. Recent findings support this idea by providing evidence for altered information processing in early sensory areas. Given that feature-specific prediction errors (PE) are crucial for effective adjustment of animal's internal model, we investigated the visual feature tuning of prediction errors in Fmr1 KO mouse model of Fragile X syndrome, a leading genetic cause of the autism. We first showed that there are a decreased habituation and surprise adaptation in the oddball paradigm in *Fmr1* KO mice using pupillometry recordings. We then used silicon probe recordings in the primary visual cortex (V1) along with the modified oddball paradigm and revealed differential laminar processing and feature-specificity of prediction errors in *Fmr1* KO animals. Specifically, we observed a feature-specific "tuning" of PE in WT animals but not in mutant mice. Our results suggest that neural populations in Fmr1 KO mice do not report PE in a specific manner, which would undermine effective adjustment of the animal's internal model following sensory experience.

Disclosures: A. Pak: None. **S.T. Kissinger:** None. **A.A. Chubykin:** None.

Poster

576. Visual System: Response Modulation and Adaptation

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Topic: D.07. Vision

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National Centre for Research and Development grant REVIS ERA-NET NEURON/08/2012 987 (WJW)

Title: A periorbital pulse current stimulation preceding upcoming visual stimulation causes macroscopic changes in visual information processing in healthy humans - An EEG study

Authors: *P. DZWINIEL[1], M. ŁABĘCKI[2], I. RACIBORSKA[1], M. ŻEBROWSKA[1], W. J. WALESZCZYK[1];
[1]Nencki Inst. of Exptl. Biol. PAS, Warsaw, Poland; [2]Univ. of Warsaw, Warsaw, Poland

Abstract: *Aim:* To explore how a periorbital pulse current stimulation (pPCS) will affect visual information processing in healthy humans.
Methods: Computer simulations of the induced electric field were performed prior to the study for the planned pPCS setting. Next, 32 healthy volunteers (16 females) in age of 25.7 ± 3.7 were divided randomly into two gender- and age-equal groups - placebo and experimental. Participants watched checkerboard pattern reversals (CPRs) presented on the computer screen in a darkened room. CPR was performed alone (placebo group) or preceded directly with pPCS (experimental group) of different duration (12.5, 25, 50 and 100 ms) and amplitude (100 and 200 μA). Inter-CPR interval was 2.25 ± 0.25 s (0.4 - 0.5 Hz). Simultaneously, EEG signal was recorded and analysed in Python. Amplitudes and latencies of the visual evoked potential (VEP) N1, P1 and N2 components were analysed, as well as the scalp potential distribution, power of the chosen frequency bands and Shannon entropy measures.
Results: Computer simulations indicated strongest electric field on the skin around stimulation electrode edges and corners. Induced electric field was around 10 times stronger in the eyeballs, than in the pre-frontal grey and white matter. During the experiment, despite of the current pulse characteristics, pPCS caused uniform decrease of the VEP's N1-P1 and P1-N2 peak-to-peak amplitudes in the posterior scalp regions. Peak-to-peak amplitude changes were related to N1 and N2 component's amplitude modulation rather than affecting P1 component's amplitude which remained unchanged. Described changes were co-morbid with the overall decrease of the potential in the posterior and increase in the anterior scalp regions. Latencies of the components remain intact. Power in all considered frequency bands dropped in response to pPCS, whereas the strongest pPCS effects were observed in participants who had relatively higher power in all considered frequency bands prior the stimulation. Those participants had also highest and most stable entropy dropout persisting few minutes after pPCS ends. In other participants entropy dropout was also present but vanished after pPCS ends.
Conclusions: We presented an electrical stimulation able to induce complex changes in visual information processing in healthy humans.

Disclosures: P. Dzwiniel: None. **M. ŁabĘcki:** None. **I. Raciborska:** None. **M. Żebrowska:** None. **W.J. Waleszczyk:** None.

Poster

576. Visual System: Response Modulation and Adaptation

Location: Hall A

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Program #/Poster #: 576.06/J31

Topic: D.07. Vision

Support: NIH EY025102

Title: Cross-orientation suppression in mouse visual cortex

Authors: *D. J. BARBERA, N. J. PRIEBE;
The Univ. of Texas at Austin, Austin, TX

Abstract: Neurons in the primary visual cortex (V1) exhibit a number of nonlinear response properties to sensory stimuli. One example of a nonlinear response in visual cortex is cross-orientation suppression, when an stimulus oriented orthogonally to the preferred orientation (a mask) suppresses the response to the preferred orientation despite failing to evoke a response on its own. The mouse visual cortex has been shown to exhibit many of the same properties seen in other mammals, such as orientation tuning. Certain features, however, appear to be altered in mouse V1 compared to other species. For example in cats and primates orientation selectivity is invariant to the contrast of the stimulus whereas in the mouse orientation selectivity is not invariant to contrast (Ya-tang et al. 2012). We sought to determine whether neurons in mouse visual cortex exhibits the robust cross-orientation suppression seen in primates and carnivores (Morrone et al. 1982, Carandini et al. 1997, Priebe and Ferster, 2006). We performed in-vivo whole cell recordings from simple cells in mouse V1. Drifting sine wave gratings were presented at the preferred and orthogonal orientation at four different contrasts (0%, 16%, 32%, 48%). These stimuli were then presented simultaneously at all contrast combinations as a plaid stimulus. We observe robust cross-orientation suppression, with some cells exhibiting suppression at the magnitude seen in other species (ex. 85% spike reduction, 75% membrane potential reduction). Although most cells exhibited suppressed responses to the two stimuli, a subset of neurons increased their responses when the preferred and orthogonal orientations were presented, but in a sublinear fashion. We quantify the interaction between the preferred and orthogonal stimuli by comparing the sum of responses to each of the stimuli alone to the responses when they are presented simultaneously. Across our population we found that responses to a plaid stimulus are strongly sublinear (mean reduction for 32% test, 48% mask = 26.31%). These data demonstrate that nonlinear cross-orientation interactions are a common feature of the mammalian visual cortex.

Disclosures: D.J. Barbera: None. **N.J. Priebe:** None.

Poster

576. Visual System: Response Modulation and Adaptation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 576.07/J32

Topic: D.07. Vision

Support: Whitehall Foundation #20121221
NSF CRCNS #1308159
NIH R00 MH104259

Title: Skewed distribution of response reliability in mouse V1 across different types of visual stimuli

Authors: *J. XIA[1], P. O'NEILL[2], M. GOARD[3], R. WESSEL[1];
[1]Physics, Washington Univ. In St. Louis, Saint Louis, MO; [2]New York Univ., New York, NY; [3]Molecular, Cell. and Developmental Biol. / Psychological & Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Neural responses in cortical circuits vary considerably across repeated presentation of identical sensory stimuli. The apparent irreproducibility of stimulus-modulated cortical activity raises the question to what extent the across-trial variability differs among neurons and depends on the statistics of the visual stimuli. To address this question, we performed two-photon Calcium imaging of excitatory neurons in the primary visual cortex of awake, head-fixed mice during visual stimulation with repeated identical natural movie clips or drifting gratings. We quantified the stimulus-modulated neural activity and between-trial variability for a given neuron in terms of the "response reliability", which is defined as the correlation coefficient between the inferred firing rates from pairs of trials of identical stimulus presentation, averaged across all trial pairs. We found that response reliabilities followed a similar skewed distribution among neurons for both natural movies and drifting gratings, with most neurons having a low response reliability. Which network properties mediate the skewed distribution of response reliabilities? To investigate this question, we built a deterministic model network, consisting of 4000 excitatory and 1000 inhibitory point neurons with random sparse connectivity and external inputs of different amplitude to neurons in the network. The external inputs ("stimulus") are Poisson spike trains that were unique for each neuron, but identical ("frozen") across 20 repeated presentations. There is no inter-trial interval between neighboring trials, so the overall network activity was unique at each stimulus onset. This model investigation yields two important results. First, because of the chaotic nature of this deterministic balanced network and the unique initial condition for each stimulus presentation, the responses of individual neurons were highly variable across trials. Second, the distribution of external input amplitudes across neurons, instead of external input rates, affected the skewness of the reliability distribution. In conclusion,

we found that the response reliability of neurons in mouse V1 follows skewed distribution across different types of visual stimuli. Using a parsimonious deterministic model, we proposed that this may arise from chaotic system with different initial conditions even in the absence of noise.

Disclosures: J. Xia: None. **P. O'Neill:** None. **M. Goard:** None. **R. Wessel:** None.

Poster

576. Visual System: Response Modulation and Adaptation

Location: Hall A

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Topic: D.07. Vision

Support: ERC Starting Independent Researcher grant
DFG NI 1718/1-1
DFG EXC 307

Title: Serotonergic modulation of functional connectivity in V1 of awake macaques

Authors: *L. SEILLIER, K. KAWAGUCHI, H. NIENBORG;
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Abstract: Neural activity in the sensory cortex is modulated by behavioral state, which can affect the strength of the neuronal response as well as the state of the local network. Such modulation involves - in part - the action of neuromodulators such as noradrenaline, acetylcholine and serotonin. We previously reported that in the primary visual cortex (V1) of awake macaques, serotonin (5HT) reduces the spiking activity by decreasing response gain without changing neuronal selectivity (Seillier, Lorenz et al., 2017). The effect of serotonin on the local network state is however not understood. To gain insights into the role of serotonin in modulating the local network state, we simultaneously recorded single unit activity (70 units) and local field potentials (LFP) in V1 of macaque monkeys performing a standard fixation task while we presented them with briefly flashed grating stimuli inside the neurons' receptive fields. To examine the modulatory effect on the local network state we applied serotonin (10mM; pH=3.5) or pH-matched saline as a control via iontophoresis. We observed that serotonin ($p < 0.001$, $n = 53$), but not saline ($p = 0.94$, $n = 17$), decreased the power of the LFP, especially in the low frequency (<10 Hz) range. To examine the dependence of the spiking activity on the local network activity as measured by the LFP, we used two metrics. First, we quantified the amplitude of the spike-triggered LFP (stLFP), which has previously been used to infer functional connectivity. Since this metric depends on the power of the LFP, we also used a model-based approach to infer functional connectivity. For each unit we quantified how well the spiking activity could be predicted by the simultaneously recorded LFP using a factored spike-triggered Gaussian mixture model (STM, Theis et al., 2016). Applying serotonin decreased the amplitude

of the stLFP ($p<0.001$) and rendered the spikes less predictable from the LFP ($p<0.001$), suggesting that it decreased the local functional connectivity. Such changes did not occur for the pH-matched saline control condition and could not be accounted for by the observed changes in firing rate. Taken together, we found that the serotonergic effects on the local network state were reduced low-frequency power of the LFP as well as decreased local functional connectivity in V1 of awake macaques. Interestingly, these effects on the local network state paralleled those previously reported for spatial attention (Chalk et al., 2010), raising the possibility of a serotonergic involvement in spatial attention at the level of visual processing.

Disclosures: L. Seillier: None. **K. Kawaguchi:** None. **H. Nienborg:** None.

Poster

576. Visual System: Response Modulation and Adaptation

Location: Hall A

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Program #/Poster #: 576.09/J34

Topic: D.07. Vision

Support: NIH EY029999
NIH EY022122

Title: Combined visual and patterned optogenetic stimulation of ferret visual cortex reveals that cortical circuits may work in the supralinear stabilized network regime

Authors: *S. WANG[1], K. D. MILLER[2], S. D. VAN HOOSER[1];
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Abstract: A recently proposed theory, the *supralinear stabilized network (SSN)*, has shed light on how canonical computations may be implemented in neural circuits. The SSN shows that, given supralinear neuronal input/output functions, network stabilization requires that recurrent input largely cancel or "loosely balance" feedforward input. This leads to sublinear summation of responses to multiple stimuli. However, for weak stimuli, little or no stabilization is needed and response summation becomes linear or supralinear. Across multiple visual cortical areas, responses to presentation of multiple stimuli are typically closer to the average than the sum of the responses to the individual stimuli, that is, response summation is sublinear (except for very weak stimuli). In most cases, it is not clear whether the sublinear summation is created by the local cortical circuit or is already present in the inputs to that circuit. Combining visual and nonspecific optogenetic stimuli, previous studies found sublinear summation in monkey V1 and linear summation in mouse V1. Here we directly test a cortical component to the sublinearity by using patterned optogenetic stimuli to drive different sets of cortical neurons, or combined visual and optogenetic stimuli. Both methods should provide independently driven inputs to cortex and

allow isolation of the cortical circuit's summation properties. Preliminary results showed that simultaneous optogenetic stimulation targeting independent orientation columns produced sublinear response summation. Combined visual and patterned optogenetic stimulation also elicited sublinear responses. We also found that even though optogenetic inputs were local to specific orientation columns, the resulting neural responses did not respect orientation column boundaries. More importantly, the optogenetic stimulation of inhibitory cells revealed inhibition-stabilization-network type of responses, along with other distinct types of responses from inhibitory cells. These results show that the cortex integrated inputs sublinearly and support the hypothesis that sensory cortex operates in the SSN regime, though incorporation of multiple inhibitory cell types into the SSN model is needed to explain the various types of inhibitory cells' responses.

Disclosures: S. Wang: None. **K.D. Miller:** None. **S.D. Van Hooser:** None.

Poster

576. Visual System: Response Modulation and Adaptation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 576.10/J35

Topic: D.07. Vision

Support: NIH R01EY024678 (SK)
Intelligence Advanced Research Projects Activity (IARPA) via Department of Interior/Interior Business Center (DoI/IBCContract D16PC00007 (TSL and SK)

Title: Impact of experience on tuning diversity and natural scene discriminability in primary visual cortex

Authors: P. L. STAN[1], J. E. KAUTTONEN[2], B. JEON[3], T. FUCHS[2], S. M. CHASE[3], T. LEE[4], ***S. J. KUHLMAN**[2];
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Abstract: Optimal encoding of visual scenes requires early-life visual experience. One strategy to determine how experience enhances vision is to identify the specific response features that are modulated by experience to improve natural scene encoding. Our goal was to determine whether experience improves encoding of natural scenes by refining Gabor-like response properties versus directly increasing sensitivity to natural scene features in animals reared under different sensory conditions. We performed large field of view calcium imaging of excitatory neurons in primary visual cortex (V1) in awake standard- and dark-reared mice, as well as mice with delayed-visual experience. The ability of functionally defined neurons to discriminate similar

and dissimilar natural scenes was assessed. We found standard rearing experience improves the encoding of natural scenes in V1 by shifting neural preference away from Gabor-like simple edges towards more complex features present in natural scenes. The net impact of standard experience was a counter-intuitive decrease in neural responses to simple edges. Animals exposed to light after being deprived of vision during postnatal development failed to accurately encode similar natural scenes. Rather than refining the Gabor-like distribution of tuning in V1, our results indicate that early experience improves scene discrimination by enhancing sensitivity to features specifically present in natural scenes.
Examination of the Gabor-like distribution revealed that experience re-shaped the population distribution of orientation preferences such that cardinal axes were over-represented, as expected. We also detected a modest net sharpening of orientation tuning across the population. However, in contrast to the shift towards complex natural scene features, refinement of the Gabor-like distribution was not predictive of discrimination performance on an animal-by-animal basis. Our results support a model in which experience-dependent development of natural scene encoding in V1 is dissociable from that of refining the representation of simple edges and does not rely on increased sensitivity to gratings of high spatial frequencies.

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Poster

576. Visual System: Response Modulation and Adaptation

Location: Hall A

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Program #/Poster #: 576.11/J36

Topic: D.07. Vision

Support: NIH Grant EY025438

Title: Synaptic mechanisms underlying rapid adaptation in mouse visual cortex

Authors: *J. Y. LI, L. L. GLICKFELD;
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Abstract: Adaptation is a fundamental feature of visual processing that enables the nervous system to adjust to features of our surrounding environment. Previous studies have largely used stimuli presented for tens of seconds to identify mechanisms underlying adaptation in V1. However, the statistics of natural scenes and the time scale of saccadic eye movements suggest that in most animals, visual input is constantly changing at much higher rates. Indeed, in previously published work, our lab has shown that neurons in V1 can adapt to a stimulus presented for 100 ms (Jin et al., 2019). Thus, we sought to identify mechanisms contributing to adaptation in V1 at naturalistic time scales. To do this, we performed *in vivo* whole-cell

recordings in primary visual cortex of awake mice and measured stimulus-evoked EPSCs and IPSCs in putative layer 2/3 pyramidal neurons. We compared currents evoked by pairs of brief 100 ms static gratings separated by inter-stimulus intervals ranging from 250 ms to 4 s. Consistent with studies of rapid adaptation in somatosensory and auditory cortices, we find that brief stimulus presentation leads to a reduction in stimulus-evoked excitatory and inhibitory inputs (n=11 cells). Interestingly, we observe slightly less adaptation of inhibition than excitation, opposite from what is seen in those other cortical areas, potentially prolonging the time course of adaptation. Generally, these inputs recover on a similar time course to the spike output of these neurons, which suggests that the lasting suppression of responses in V1 is primarily influenced by the suppression of the inputs that cells receive. This is in contrast to a previously identified mechanism of slow contrast adaptation in V1 where suppression of spike output is largely mediated by a tonic hyperpolarization. Our data indicate that suppression of stimulus-evoked excitation and inhibition is conserved across sensory cortical areas for similar time scales of adaptation and that within a single sensory area, different time scales of adaptation could engage distinct mechanisms to suppress spike output. Future experiments will assess the degree to which synaptic depression or network mechanisms could contribute to these changes in synaptic input.

Disclosures: **J.Y. Li:** None. **L.L. Glickfeld:** None.

Poster

576. Visual System: Response Modulation and Adaptation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 576.12/J37

Topic: D.07. Vision

Support: R01 EY023037

Title: Cellular representation of visual recognition memory in the mouse primary visual cortex

Authors: ***T. KIM**[1], M. T. HARNETT[2], M. F. BEAR[1];
[1]Picower Inst. for Learning and Memory, [2]Mcgovern Inst. for Brain Res., MIT, Cambridge, MA

Abstract: Brief daily exposure to a phase-reversing grating stimulus increases the magnitude of associated visual-evoked potentials (VEPs) in mouse V1 layer 4, a phenomenon termed stimulus-selective response potentiation (SRP). SRP is induced in V1 by mechanisms shared with canonical long-term potentiation (LTP) and is accompanied by behavioral habituation to the familiar stimulus. Both SRP and the behavioral readout of visual recognition memory are sensitive to molecular manipulations restricted to V1. In the present study, we investigated the cellular activity changes associated with the induction and expression of SRP using longitudinal calcium imaging of layer 4 excitatory neurons in V1. Using two-photon microscopic calcium

imaging, we found no significant net change in the population of active neurons during the familiar (learned) stimulus presentation. However, endoscopic calcium imaging revealed a robust reduction of calcium responses elicited by phase-reversals of the familiar visual stimulus and a strong within-session habituation. Despite this dramatic plasticity of responses to phase-reversing gratings, we found no changes in the response to unfamiliar drifting grating stimuli of the same orientation, underscoring the exquisite selectivity of SRP. Combined with previous work, our findings suggest that potentiation of short-latency visually evoked potentials (VEPs) to familiar visual stimuli reflects increased feed-forward activation of V1 but likely recruits feedback inhibition to suppress sustained cellular responses in layer 4 neurons.

Disclosures: T. Kim: None. **M.T. Harnett:** None. **M.F. Bear:** None.

Poster

576. Visual System: Response Modulation and Adaptation

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Topic: D.07. Vision

Support: European Union's Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreements No.785907 (Human Brain Project SGA2) to CAB and UO
FLAG-ERA JTC 2015 project CANON (co-financed by the Netherlands Organization for Scientific Research -NWO) to CAB and UO

Title: Cross-species analysis of mismatch negativity responses in primary visual cortex of mice and ferrets

Authors: *T. SIKKENS, L. M. F. KLAVER, M. A. MULLER, C. M. A. PENNARTZ, C. A. BOSMAN, U. OLCESE;
Cognitive and Systems Neurosci. Group, Univ. of Amsterdam, Amsterdam, Netherlands

Abstract: Mismatch negativity (MMN) is a brain's response to violations of a rule, which is established by regularities in the sensory environment. Following the predictive coding framework, these regularities allow the brain to construct predictions on sensory inputs, where unpredicted sensory changes elicit error or mismatch signals. MMN is typically studied in humans using an oddball paradigm, in which a specific stimulus is being presented repeatedly (standard) but is sometimes changed for a different stimulus (deviant). The MMN response consists of two components: 1) one that can be explained purely by stimulus specific adaptation (SSA), a process caused by the repeated presentation of the same input to the (sensory) system, and 2) a true deviance detection (DD). Previous studies in mice have shown that SSA and DD operate in different time windows and may involve distinct cortical networks. Although mice are

an increasingly common animal model in visual neuroscience, their visual system is distinct from other mammals such as carnivores and primates. It is unknown whether responses to visual mismatch stimuli differ between mice and other mammals. To address this issue we compared mismatch responses in mice and ferrets, whose visual system more closely resembles that of humans.
We performed electrophysiological recordings in primary visual cortex (V1) of head-fixed mice and ferrets using 32 channel laminar probes. During recordings, passively viewing animals were presented with a visual oddball paradigm where the orientation of a presented stimulus changes from standard to deviant. We identified how local fields potentials and single units respond to the different stimuli. We also examined how these responses adapt to stimulus change or stimulus repetition and how these responses compare between mice and ferrets.
We find clear MMN responses in both mouse (n = 8 animals) and ferret (n = 3 animals) visual cortex. Moreover, response parameters such as the timing and amplitude of event related potentials are similar between mice and ferrets. Both species show distinct epochs in which SSA and DD occur, with SSA occurring in earlier (35-120 ms) and DD in later (120-240 ms) time windows. This is consistent with previous reports in mice. Ongoing analysis focuses on similarity of laminar activity profiles and neuronal firing patterns in the two species. These results provide novel insight into the (dis)similarities of cortical mismatch responses in different mammalian species.

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Poster

576. Visual System: Response Modulation and Adaptation

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Program #/Poster #: 576.14/J39

Topic: D.07. Vision

Support: NIH RO1 EY024912
NIH P50 MH103204

Title: Contribution of receptive field center and surround to repetition suppression in macaque visual area V2

Authors: *N. P. WILLIAMS, C. R. OLSON;
Ctr. for the Neural Basis of Cognition, Biol. Sci. Dept., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Monkey inferotemporal cortex (ITC) neurons respond with declining strength to repeated presentations of a large and complex natural image. This phenomenon - repetition suppression - has often been assumed to arise at the level of ITC because ITC neurons possess

the large receptive fields and sophisticated stimulus selectivity necessary for recognizing the image as a repetition. However, we recently discovered that neurons in V2 exhibit repetition suppression under conditions identical to those employed in studies of ITC (Williams and Olson, 2018, Neuroscience Meeting Planner, Program No. 397.08). This raises the question: How do V2 neurons, with classical receptive fields encompassing only a small fraction of the image, recognize it as a repetition? One possibility is that they are sensitive to repetition of image content not only in the classical receptive field but also in the receptive field surround. To assess this possibility, we monitored neuronal responses to sequential displays in which we controlled independently the repetition of elements in the classical receptive field and in the surround. Each stimulus consisted of a disk scaled to and centered on the classical receptive field and an adjoining annulus with an outer diameter of 8°. The disks and annuli were taken from different natural scenes. The typical receptive field had a diameter of 2° and was located at 5° eccentricity in the lower contralateral visual field. The display on each trial consisted of a prime, a delay and a probe, each 300 ms in duration. Across trials, we independently varied the relation of the probe to the prime with respect to identity of the center component (same or different) and the surround component (same or different). Upon analyzing data from 46 neurons (23 in monkey O and 23 in monkey R), we found that repetition of the central disk was sufficient to produce repetition suppression but that suppression was enhanced by simultaneous repetition of the annulus. Suppression arising from repetition of the annulus occurred in a relatively late phase of the response, beginning around 100 ms after stimulus onset, in accordance with the idea that it might have been mediated by horizontal connections in V2 and/or feedback from downstream areas of higher order. The contribution of the surround to repetition suppression cannot be explained in terms of adaptation as characterized in classical grating-based experiments. Repetition of surround content in the current paradigm leads to reduced response strength whereas repetition of surround content in grating-based adaptation experiments leads to enhanced response strength (Wissig and Kohn, 2012, J.Neurophysiol. 107: 3370-3384).

Disclosures: **N.P. Williams:** None. **C.R. Olson:** None.

Poster

576. Visual System: Response Modulation and Adaptation

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Program #/Poster #: 576.15/J40

Topic: D.07. Vision

Support: RBIQ
FRSQ
RRSV

Title: Cholinergic enhancement of visual conditioning on cortical activity mapping

Authors: *G. LALIBERTÉ, E. VAUCHER;
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Abstract: Visual conditioning can refine the response and connectivity of neurons in the visual cortex and higher associative areas. The cholinergic system could play a role in this tuning, given its important modulatory influence in attention. Our goal is to determine the effect of the cholinergic potentiation on a one-week daily visual conditioning. This was assessed by studying changes on cortical visual responses using wide-field calcium imaging in awake adult (P60-90) transgenic mice. C57BL6 Thy1-GCaMP6s mice were used to assess the neuronal activity in the superficial layers of the primary visual cortex (V1), some secondaries visual areas (PM, RL, AM, A, AL, LM) and the retrosplenial cortex (RS). Cortical activity, latency of the peak response, and size of cortical activation were measured at rest and in response to conditioned or non-conditioned stimuli. The conditioning consisted of drifting gratings, oriented at 30° with 100% contrast (0.03 cpd, 1 Hz), presented daily to head-fixed mice for 10 minutes for a week. The response to monocular stimulation at 3 different contrasts (50, 75 and 100%) and 2 different orientations (30° and 90°, 0.03 cpd) were compared before and after visual conditioning. To evaluate the influence of the cholinergic system, donepezil (0,3mg/kg), a cholinesterase inhibitor, or saline was injected prior to each conditioning session. Naive animals elicited similar cortical responses in terms of strength and contrast sensitivity for the 2 orientations presented (30° and 90°). In the V1 of the DPZ group, results showed a significant decrease in evoked neuronal activity (43%) and latency of peak response (18%) for the conditioned stimulus. Inversely, the latency of peak response was increased for the non-conditioned orientation at lower contrast (50 and 75%). The PM region of the DPZ group showed a decrease of 46% in neuronal activity for the trained orientation compared to the pre-conditioning values. Similarly, the DPZ group showed a decrease in contrast sensitivity for multiple areas of the cortical visual pathway (V1, RS, A, A, and AL). Although we expected a DPZ-induced potentiation of the conditioned responses, based on previous studies in layer 4 of V1, the effect measured here in layer 2-3 rather shows a reduced amplitude and spread of the responses. This could be explained by the interactions of the cholinergic system with local microcircuits, particularly GABAergic neurons, that differ across layers.

Disclosures: G. Laliberté: None. **E. Vaucher:** None.

Poster

576. Visual System: Response Modulation and Adaptation

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 576.16/J41

Topic: D.07. Vision

Support: the Templeton Foundation Grant No. 21569

Title: Spatiotemporal dynamics of brightness coding in human visual cortex revealed by the temporal context effect

Authors: *H. ZHOU[1], M. DAVIDSON[2], P. KOK[3], L. MCCURDY[4], F. P. DE LANGE[5], H. LAU[6], K. SANDBERG[7];
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Abstract: Human visual perception is modulated by both temporal and spatial contexts. One type of modulation is apparent in the temporal context effect (TCE): In the presence of a constant luminance patch (a long flash), the perceived brightness of a short flash increases monotonically with onset asynchrony. The aim of current study was to delineate the neural correlates of this illusory effect, particularly focusing on its dynamic neural representation among visual cortical areas. We reconstructed sources of magnetoencephalographic (MEG) data recorded from observers (6 male and 9 female human adults) experiencing the TCE. Together with retinotopic mapping, signals from different occipital lobe areas were extracted to investigate whether different visual areas have differential representation of the onset vs. offset synchronized short flashes. From the data, TCE related responses were observed in LO and V4 in the time window of 200-300 ms, while neuronal responses to physical luminances were observed in the early time window of 100-150 ms across early visual cortex, such as V1 and V2, also in V4 and VO. Based on these findings, we suggest that two distinct processes might be involved in brightness coding: one bottom-up process which is energy driven and responds fast, and another process which may be broadly characterized as top-down or lateral, is context driven, and responds slower. For both processes, we found that V4 might play a critical role in dynamically integrating luminances into brightness perception, a finding that is consistent with the view of V4 as a bottom-up and top-down integration complex.

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Poster

576. Visual System: Response Modulation and Adaptation

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Topic: D.07. Vision

Support: JSPS KAKENHI Grant Number JP15K21078

Title: Following neural response against 15Hz blinking light stimuli in goldfish's optic-tectum

Authors: *A. FUNASE[1], Y. SUZUKI[1], S.-E. FUJIWARA[2], S. MIKI[3], I. TAKUMI[1], Y. HIRATA[4];
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Abstract: [Purpose] Our final goal is to the brain function of the Steady-state visual evoked potential (SSVEP). In this study, we focus on the relationship between neural activities and a visual stimulus for the SSVEP. We describe neural activity in the optic-tectum when we show a blinking light stimulus (blinking frequency: 15 [Hz] and 1 [Hz]) to goldfishes. We discuss the following neural response against blinking light stimuli.[Method] We set a white LED in front of the eye so that the eye presented the blinking stimulus. The action potential is recorded in the dark room. the blinking white LED is presented to a goldfish for 60[sec]. The blinking frequency is 1 [Hz] and 15 [Hz]. Action potentials of two goldfishes are recorded in the optic-tectum and action potentials are obtained on 16 positions. 46 units are obtained by the spike sorting. We make a histogram of firing rate (Bin size: 5 [msec]). Separated units are categorized into three categories (on-response unit, off-response unit, and on- and off-response unit). The on-response unit is the unit which has firing rate over 2 SD(standard deviation) only during the lighted time. The off-response unit is the unit which has a firing rate over 2 SD only during the non-lighted time. The on/off-response unit is the unit which has firing rate over 2 SD during the lighted time and during the non-light time. The NULL-response unit is the unit which does not have a firing rate over 2 SD during the lighted time and during the non-light time.[Results and Discussion] We obtained units related to presenting a blinking light stimulus. In 1 [Hz] blinking stimulus, 5 on-response units are obtained, 10 off-response units are obtained, and 31 on/off-response units are obtained. In 15 [Hz] blinking stimulus, 8 on-response units are obtained, 20 off-response units are obtained, and 18 NULL-response units are obtained. 31 on/off-response units in 1 [Hz] blinking stimulus changed into 6 on-response units, 17 off-response units, and 8 NULL-response units in 15 [Hz] blinking stimulus. From these results, neurons in optic-tectum have the following neural response against 15 [Hz] blinking light stimuli and most on/off-response units in 1 [Hz] blinking stimulus change into off-response units in 15 [Hz] blinking stimulus.

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Poster

576. Visual System: Response Modulation and Adaptation

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Topic: D.07. Vision

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Wellcome Trust

Title: Monocular and binocular components of contrast gain control in primate V1

Authors: L. PALMIERI, *B. G. C. CUMMING;
Natl. Eye Institute, NIH, Bethesda, MD

Abstract: We studied the effect of interocular contrast differences on the disparity selectivity of neurons recorded extracellularly from V1 of awake fixating monkeys. We presented random dot stereograms at different disparities under four contrast conditions: 1) High contrast (>99%) in both eyes (HH) 2) Low Contrast (20%) in both eyes (LL) 3) High contrast in the dominant eye, low contrast in the non-dominant eye (HL) 4) the reverse (LH). In the binocular energy model with no contrast gain control, conditions LH and HL reduce the extent of disparity modulation by a factor of 5 (proportional to the contrast). However, the response to binocularly uncorrelated patterns (baseline) is only halved, so the signal to noise ratio becomes poorer. If the monocular gain is increased by a factor of 5 (exactly compensating for the contrast reduction), the disparity tuning curve is identical to that for HH. Changes in gain control after binocular summation affect baseline and modulation equally. We exploit the fact that monocular and binocular gain changes have different effects on baseline and modulation depth to estimate changes in monocular and binocular gains. We estimate the slope and offset the relationship between the HH and LH tuning curves (type II regression) and find the values of monocular and binocular gains in the model that reproduce these. As already reported in the cat (Truchard et al, 2000), we find that increases in monocular gain are larger than binocular gain (paired t-test, $p < 0.01$, $n = 34$ samples from 17 cells). We also find a correlation between monocular gain changes for the dominant and nondominant eye (Pearson correlation = 0.54, $p < 0.05$). There is considerable heterogeneity in the strength of monocular contrast gain control between neurons. The correlation of gain modulation strength between the two eyes identifies a new property that appears to be matched across eyes in binocular neurons. Although correlated, monocular contrast gain changes were significantly larger in the non-dominant eye that the dominant eye. This result raises that intriguing possibility that ocularity measures reflect not just the relative strength of excitatory drive from the two eyes, but also reflect the strength of contrast normalization driven from each eye, with the ‘non-dominant’ eye characterized by a stronger contrast normalization. In human observers, contrast differences (HL or LH) reduce stereoacuity relative to LL. Two features or our data can explain this. First, changes in monocular gain only partially compensate for the contrast changes. Secondly, there is often a significant increase in binocular gain. Therefore, a simple mechanism may explain this paradoxical phenomenon.

Disclosures: L. Palmieri: None. **B.G.C. Cumming:** None.

Poster

576. Visual System: Response Modulation and Adaptation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 576.19/J44

Topic: D.07. Vision

Support: NIH Grant NEI EY023371
NSF Grant IOS-1457024
NSF Grant CAREER-1652617

Title: A model of efficient coding for motion without ambiguity in cortical area MT

Authors: N. A. LINGAREDDY[1], B. LIU[3], L. C. OSBORNE[4], *S. E. PALMER[2];
[1]Computer Sci., [2]Univ. of Chicago, Chicago, IL; [3]Neurosci. Dept., Duke Universtiy, Durham, NC; [4]Neurobio., Duke Univ., Durham, NC

Abstract: Sensory adaptation can shift the response properties of neurons so that efficient coding for the full range of inputs is maintained. Adaptive changes have been observed in the firing rates and the gain of neurons in response to changes in stimulus properties such as the mean and variance. These adaptation mechanisms in visual areas like the retina operate over a range of timescales. Recent experiments from Liu and Osborne have shown that neurons in the middle temporal visual area of the primate cortex (area MT) respond to fast and slow input fluctuations by independent mechanisms - they modulate their firing rate without changing their response gain (the change in firing rate per change in direction) and vice versa. We use a conductance-based integrate-and-fire model to explore the mechanistic underpinnings of these results. By adding stimulus-dependent firing-rate adaptation to a network model, we can show that the response gain rescales without changing the mean response rate. Adding spike-rate adaptation to the model can help set the mean input noise levels that are required to attain such rescaling of the gain without fine-tuning. This simple model also reproduces observed asymmetric changes in MT responses when the input signal changes from high to low variance versus low to high. Tuning curve shapes also change in response to constant stimulation as a function of motion direction. Our model may also help explain these tuning shift, which have also been observed in other visual areas, such as V1.

Disclosures: S.E. Palmer: None. **N.A. Lingareddy:** None. **B. Liu:** None. **L.C. Osborne:** None.

Poster

576. Visual System: Response Modulation and Adaptation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 576.20/J45

Topic: D.07. Vision

Support: NIH Grant EY023371
NSF Grant IOS1457024

Title: Efficiency without ambiguity: An adaptive sensory code in cortical area MT

Authors: B. LIU, ***L. C. OSBORNE**;
Neurobio., Duke Univ., Durham, NC

Abstract: A sensory neuron's response to its inputs depends on recent history. Adaptive changes in input-output functions increase coding efficiency, but they also appear to create an ambiguous mapping between stimulus and response. Here we show that cortical sensory neurons maintain both an efficient and unambiguous stimulus representation by encoding fast and slow timescale stimulus changes via independent information channels. We recorded visual motion selective neurons in area MT responding to coherent optic flow. Dot patterns had a constant speed, and direction that fluctuated stochastically at a timescale shorter than the neural integration time (20ms) around a mean direction that changed on a longer timescale (>100ms). We configured the stimuli such that the mean drive to the neuron did not change as a function of variance level in order to disambiguate the responses to different stimulus features. We find that the variance of fast stimulus fluctuations is encoded efficiently through rapid multiplicative rescaling of response gain, without changes in firing rate. In contrast, firing rate dynamics are insensitive to short time scale motion fluctuations (stimulus variance), but do encode information about the mean stimulus value. Fast and slow adaptation processes add linearly to determine the instantaneous neural response. Independent information channels allow neurons to optimize sensitivity to fast stimulus fluctuations without creating ambiguity about the mean over longer periods. We present a mechanistic model of spiking probability based on feed-forward excitatory drive and balanced excitatory and inhibitory recurrent inputs to account for the data, demonstrating how the brain can encode, and decode, sensory information efficiently and unambiguously.

Disclosures: B. Liu: None. **L.C. Osborne:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.01/J46

Topic: D.07. Vision

Support: CIHR

Title: Pulvinar mediates the oscillatory transmission across low to high hierarchical cortical areas

Authors: *N. CORTES[1], B. SOUZA[2], C. F. CASANOVA[1];
[1]Univ. de Montréal, Montréal, QC, Canada; [2]Anatomie, Univ. du Québec à Trois Rivières, Québec, QC, Canada

Abstract: Cortical activity across the visual hierarchy has different oscillatory ranges. While 25-90 Hz gamma band from supragranular layers influences the feedforward processing, 6-13 Hz alpha band from infragranular layers travels in the feedback direction. However, we have limited understanding of how this cortical communication depends on transthalamic pathways, in particular from the primary visual cortex (V1) to other levels of the visual cortical hierarchy. Here, we investigated how the cortical oscillatory coupling across V1 and area 21a depends on transthalamic pathways by inactivating pharmacologically the pulvinar in cats. Extracellular responses to full-field 100% contrast gratings were recorded in cortical areas 17 and 21a, from anesthetized cats using linear probes before, during and after GABA injection in the pulvinar. Local field potentials, from low-pass filtering of raw recordings, were analyzed with Wavelet and Granger causality tools to determine the oscillatory coupling between cortical layers. Cortical oscillatory activity was enhanced during pulvinar inactivation. In area 17, alpha and gamma bands significantly increased in layers IV, V, and IV. In area 21a, all layers, except layer I, enhanced their oscillatory activity, especially in layer IV with gamma oscillations. Granger causality showed that the pulvinar inactivation caused an enhancement of feedforward gamma waves from area 17 (layer III) to area 21a (layer IV). For the feedback coupling, alpha waves rose from area 21a (layer V) to area 17 (layers III, V, and VI). Our findings suggest that, during visual stimulation, the pulvinar mediates the feedforward gamma band from areas 17 (layer III) to 21a (layer IV). Furthermore, the pulvinar regulates the feedback alpha band from layer V in area 21a to layers II, V, and VI in area 17. Together, these findings provide a possible mechanism underlying feedforward and feedback oscillatory processing throughout the visual cortical hierarchy.

Disclosures: **N. Cortes:** None. **B. Souza:** None. **C.F. Casanova:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.02/K1

Topic: D.07. Vision

Support: NIH NRSA F31 Grant EY028853-01
NIH Grant EY022577
NIH Grant MH063912

Title: Dynamic functional influence of corticothalamic pathways on first- and higher-order visual thalamus

Authors: *M. A. KIRCHGESSNER[1,2], A. D. FRANKLIN[3,1], E. M. CALLAWAY[1,2];
[1]Salk Inst. for Biol. Studies, La Jolla, CA; [2]Neurosciences Grad. Program, [3]UC San Diego, La Jolla, CA

Abstract: The nature of corticothalamic feedback is a topic of significant interest but little consensus. While previous optogenetic studies in mice have shown that layer 6 corticothalamic (L6CT) neurons in V1 have a net-inhibitory influence over first-order visual thalamus dLGN (Olsen et al., 2012; Denman & Contreras, 2015), slice experiments in the somatosensory system have demonstrated that this can switch to net-facilitation when driven by a 10Hz train (Crandall et al., 2015). Whether these frequency-dependent effects are also discernible in the visual system *in vivo* has not been tested. Moreover, how L6CTs influence higher-order thalamic nuclei, such as the rodent lateral posterior (LP) nucleus, *in vivo* is completely unexplored. Here, we utilize optogenetics in Ntsr1-Cre transgenic mice to selectively manipulate L6CTs in V1 while recording single-unit activity with microelectrode arrays in LP and dLGN as well as the inhibitory thalamic reticular nucleus (TRN) of awake mice viewing drifting gratings. First, we find that sustained L6CT photostimulation with channelrhodopsin largely suppresses visually-evoked and spontaneous activity in dLGN (as has been shown before), and similar inhibition is also observed in LP. However, optogenetic activation of L6CT neurons at 10Hz facilitates activity in both dLGN and LP; this provides the first demonstration of dynamic, frequency-dependent L6CT pathways *in vivo.* Additional experiments probing the mechanism of these effects support the interpretation that L6CTs' influences over their visual thalamic targets are mediated by a balance of direct, facilitating excitation and indirect, depressing inhibition from TRN. Optogenetic inactivation experiments further indicate that these dynamically opposing pathways subserve a fundamentally "modulatory" role for L6CTs in both dLGN and LP. Ongoing studies are probing how layer 5 corticothalamic (L5CT) projections influence LP and whether they exhibit similar or complementary frequency-dependent characteristics. Overall, this work illustrates the dynamic nature of corticothalamic pathways *in vivo* and how their circuitry

allows for tremendous flexibility and a wide range of influence that may promote adaptability to different contextual and behavioral constraints.

Disclosures: M.A. Kirchgessner: None. **A.D. Franklin:** None. **E.M. Callaway:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.03/K2

Topic: D.07. Vision

Support: NSERC
FRQS (Quebec)

Title: Morphology of the projection of the visual cortex to the claustrum in the mouse: A single axon study

Authors: *E.-M. FRIGON, J. ROY, D. BOIRE;
Univ. Du Quebec A Trois-Rivieres, Dept. d'anatomie, Trois-Rivieres, QC, Canada

Abstract: The claustrum is a subcortical telencephalic structure present in all mammals. It is widely and reciprocally interconnected with the entire cerebral cortex. Stimuli from all sensory modalities elicits responses in claustrum neurons and some studies report multimodal responses in the claustrum. It has been proposed that the claustrum is a site of multisensory integration and involved in the generation of conscious percepts. This led to the proposal that sensory representations would overlap. The claustrum in mice exhibits a clear dorsoventral organisation of sensory cortical projections. There is also a significant overlap of sensory domains. Presently, there are no study of the cortical projections to the claustrum at the single axon level. Iontophoretic injections of *Phaseolus vulgaris* leucoagglutinin were performed in the primary visual cortex of adult C57BL/6J mice. A triple immunohistochemistry of Phaseolus, myelin binding protein and neuronal specific NeuN has been done to reconstruct individual axons of the projections from the primary visual cortex to the claustrum using Neurolucida 360 (MBF Biosciences).
These projections were shown in the ipsi- and contralateral claustrum. They were found in the central region along the dorsoventral axis of the claustrum. Individual axons entered the claustrum from caudal levels and traveled for significant distances within the claustrum. Axons were poorly branched along this trajectory expect in some areas where more significant branching was observed. Some collaterals of the main axon branched out, traveled more ventrally and returned to a linear rostral directed trajectory. This suggests that axonal branches of the visual projection to the claustrum leave the visual domain to branch out into parallel domains of other sensory modalities. The local arborisations might suggest smaller modules within the

longitudinal organization of the claustrum. Moreover, the absence of myelin throughout the structure is observed.

Disclosures: **E. Frigon:** None. **J. Roy:** None. **D. Boire:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.04/K3

Topic: D.07. Vision

Support: CIHR grant MOP-119498

Title: On-afferent inhibition underlies stronger V1 responses to dark

Authors: *D. ST-AMAND[1], *C. L. BAKER[2];
[1]McGill Vision Res., McGill Univ., Montreal, QC, Canada; [2]Ophthalmology, McGill Vision Res. Unit, Montreal, QC, Canada

Abstract: The primary visual cortex (V1) receives excitation and inhibition from two distinct retinogeniculate pathways, processing lightness (ON) and darkness (OFF). V1 neurons are more strongly driven by dark than by light stimuli (Jin et al, 2008; Yeh et al, 2010; Kremkov et al, 2013), but it has been unclear to what extent this is due to excitation from the OFF pathway or inhibition from the ON pathway. The goal of this study is to disambiguate excitation and inhibition from both pathways on a large sample of single neurons, by training customized machine learning algorithms to predict their responses to complex stimuli. We record single-unit responses of V1 neurons to natural images, in anesthetized and paralyzed cats, using spike-sorting (Swindale & Spacek, 2014) of signals from multi-channel polytrodes. We then employ a biologically inspired convolutional neural network which separately processes stimuli that are locally above (ON) and below (OFF) the mean luminance. Rectified responses of parameterized 2D Gaussian filters are utilized to mimic lateral geniculate nucleus (LGN) neurons. Excitatory and inhibitory inputs from these ON and OFF pathways combine in a weighted summation, to generate the predicted cortical neuron response. Parameters of this model are optimized in TensorFlow, to best predict a training dataset, with separate holdback datasets for validation (early-stopping) and testing performance. Analysis of 74 simple-type cells shows responses are more strongly driven by dark than by light stimuli, consistent with previous studies (Yeh et al, 2010; Kremkov et al, 2013). Since layer 4 of primary visual cortex receives more input from the OFF than from the ON pathway (Jin et al., 2008), one might have expected this “dark-dominance” to arise from excitation via the OFF pathway. Surprisingly, we instead find the dark-dominance to be driven by relatively greater inhibition from the ON pathway. In addition, we find excitation and inhibition from the OFF pathway to be, on average, approximately balanced.

Inferring the inputs from ON and OFF pathways to primary visual neurons using machine learning provides an opportunity to ask new questions about excitatory and inhibitory integration in cortical neurons.

Disclosures: D. St-Amand: None. **C.L. Baker:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.05/K4

Topic: D.07. Vision

Support: Canada Foundation for Innovation

Title: Spatiochromatic processing in adults who had childhood unilateral amblyopia

Authors: M. A. KLASSEN[1], H. D. J. HATHARASINGHAGE[2], A. R. CRAIG[1], C. S. CHISHOLM[1], C. BEADLE[1], ***M. F. WESNER**[3];
[1]Psychology, [2]Biol., [3]Lakehead Univ., Thunder Bay, ON, Canada

Abstract: Unilateral amblyopia is a visual developmental disorder characterized by a monocular decrease in visual performance usually associated with signal processing miscorrelations between the affected and the non-affected, fellow eye. Generally, it is believed that higher-ordered visual pathway operations in the CNS suppress the less effective ocular signals in favour of the better functioning fellow eye. The extent of dysregulation as it relates to the pathway hierarchy, however, is poorly understood (e.g., Wong, 2014). For example, studies have identified impairments in visual acuity, perimetry, form, face, color, and motion perception, yet these specific functional investigations often overlook a more extensive, global dysregulation that can include cortical compensation for lower-level pathway deterioration (Hamm et al., 2014). To examine possible hierarchical changes in adult amblyopes, we psychophysically measured perimetric thresholds of the retinal cones and the spatiochromatic, post-retinal contrast sensitivities (CS) of the parvocellular (PC) and the koniocellular (KC) streams for both the dominant (DE) and non-dominant (NDE) eye. Traditional automated perimetry assessed the sensitivities of the long- (L) and middle- (M) wavelength cones; Short-wavelength automated perimetry assessed the more disease vulnerable short-wavelength (S) cone sensitivities. Spatiochromatic CS was determined using isoluminant, heterochromatic gabors of varying spatial frequencies along "red-green" (R/G) or "blue-yellow" (B/Y) opponent CIE axes to achieve maximal PC or KC responsivities, respectively. Of the 30 participants (age 18-42; M = 23.7, SD = 6.2), 20 were Controls (14 female) and 10 were child-diagnosed unilateral amblyopes (8 female). Participants were screened for acute or chronic vision disorders, near visual acuity and color vision deficits. DE and NDE sensitivity differences across central (0-6°) and peripheral

(10-22°) zones were found. Most notable were with the Amblyopes who showed substantially higher L- and M-cone DE sensitivities, but higher S-cone NDE sensitivities, particularly at the temporal retinal zones. Interestingly, post-retinal CS showed the largest shifts with presentations of the B/Y gabors where the amblyopic DE showed a >1 log unit gain over the NDE and over both eyes of the Controls. Finally, the DE of Amblyopes had higher CS than Control DEs. We discuss these findings in terms of retinal circulation patterns, KC gain compensations and interocular transfer effects. Our findings support a more global, feedforward and feedback dysregulatory influence in adults who have experienced pediatric unilateral amblyopia.

Disclosures: M.F. Wesner: None. **M.A. Klassen:** None. **H.D.J. Hatharasinghage:** None. **A.R. Craig:** None. **C.S. Chisholm:** None. **C. Beadle:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.06/K5

Topic: D.07. Vision

Support: T32 NS007473
F32 EY029556
R01EY013613
U54 HD090255
R01 NS095959

Title: Late dark rearing disrupts axis selectivity in the mouse thalamus and primary visual cortex

Authors: *C.-E. STEPHANY[1], J. D. REGGIANI[2], N. PICARD[1], M. FAGIOLINI[1], C. CHEN[1]; [1]Neurol., F.M. Kirby Neurobio. Center, Boston Children's Hosp., Boston, MA; [2]Harvard University, Program in Neurosci., Boston, MA

Abstract: Critical periods are brief windows during development when circuits in the brain can be altered by experience. In the visual system, monocular deprivation during the critical period in primary visual cortex (V1) alters the circuitry underlying ocular dominance. Recently, the Chen lab has defined a thalamic critical period when visual deprivation by dark rearing between postnatal day (P) 20-P30 (Late Dark Rearing; LDR) triggers a recruitment of weak retinal inputs onto neurons in the dorsal lateral geniculate nucleus (dLGN). The timing of cortical and thalamic critical periods overlaps, but how LDR affects visual feature selectivity in these structures is unknown. Here, we employed extracellular electrophysiology to measure changes in receptive field properties in both the dLGN and V1 in response to LDR.
In the dLGN, we found that increased retinal convergence by LDR did not affect receptive field size, but was associated with a decrease in axis selectivity and linearity. This supports the idea

that the refinement of retinal inputs enhances feature selectivity in post-synaptic dLGN neurons. In V1, both the spontaneous and evoked firing rates of putative inhibitory neurons were higher in response to LDR compared to normally reared (NR) controls, but remained unchanged in putative pyramidal neurons (Pyr). Thus, paradoxically, the median axis selectivity of Pyr across V1 increased with LDR and a laminar analysis revealed that the largest increase was in the subgranular layers (L5/6). We next tested whether disrupted feature selectivity in V1 in response to LDR is transient or persistent by returning mice to normal housing for 4-6 weeks after LDR (LDR+recovery) and subsequently recording at P60-P70. While firing rates in LDR+recovery mice returned to baseline, the median axis selectivity in Pyr was significantly lower when compared to NR controls. These data demonstrate that the dLGN and V1 respond differently to LDR and are consistent with our working hypothesis that changes in cortical activity feeds back to the dLGN to disrupt retinogeniculate convergence, ultimately reducing axis selectivity in both dLGN and V1. Future work will test this hypothesis by examining the temporal sequence of circuit changes in the two structures in response to LDR.

Disclosures: C. Stephany: None. **J.D. Reggiani:** None. **N. Picard:** None. **M. Fagiolini:** None. **C. Chen:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

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Program #/Poster #: 577.07/K6

Topic: D.07. Vision

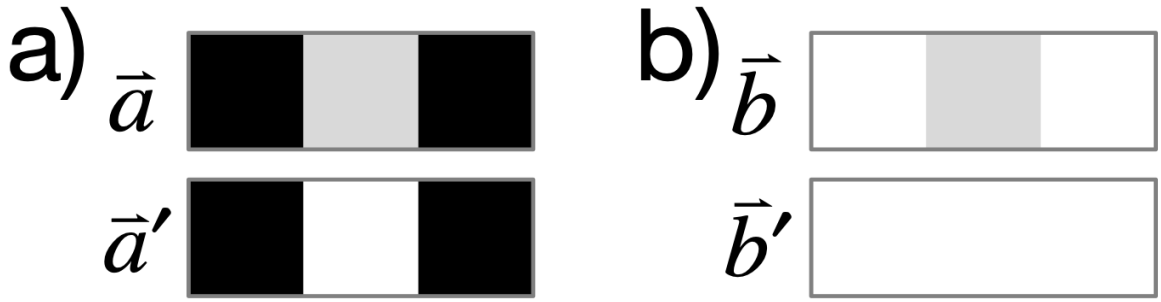
Support: ONR N00014-16-1-2359
ONR N00014-15-1-2132

Title: Perceptual similarity arises from center-surround interactions

Authors: E. F. W. BOWEN, E. CHILDERS, A. RODRIGUEZ, ***R. GRANGER**;
Dartmouth, Hanover, NH

Abstract: When do two things look alike? Below are closeups of three adjacent pixels. The intensity changes from top to bottom images in a) are identical to those in b); i.e., the Euclidean vector distance from a to a' is the same as from b to b'. Yet human perceivers universally report that a and a'are more similar to each other than b and b'. What measure, other than Euclidean distance, corresponds to these reported perceptual distances?
Evidence from our lab and others shows that Euclidean distance between two comparable images is consistently a poor estimator of human similarity judgments. Widely-used "image quality assessment" methods such as "structural similarity" (SSIM) outperform Euclidean measures, but it is not entirely clear which characteristics of these measures confer their predictive power.

We formulate a model directly from the size and dendritic projection patterns of center and surround neurons in the early visual path, generating a simple difference-of-Gaussian computation. We provide new empirical evidence that this center-surround organization underlies these psychophysical judgments. Forty-nine subjects (35F, ages 18-22) compared original and degraded versions of images, scoring them from 0 (least similar) to 100 (identical to original). Surprisingly, the biological center-surround model predicts human similarity evaluations as well as SSIM, despite being simpler and directly derived from dendritic architectures. Ongoing studies suggest further prominent roles for center-surround formulations in several psychophysical phenomena.



Disclosures: **E.F.W. Bowen:** None. **E. Childers:** None. **A. Rodriguez:** None. **R. Granger:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.08/K7

Topic: D.07. Vision

Support: The JPB Foundation

Title: Identifying neural circuits underlying visually evoked entrainment

Authors: ***C. ADAIKKAN**[1], K. ABDELAAL[1], M. MURDOCK[1], A. J. HUANG[3], H. A. SULLIVAN[2], I. WICKERSHAM[2], T. J. MCHUGH[3], L.-H. TSAI[1];
[1]Picower Inst. for Learning and Memory, [2]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [3]RIKEN Ctr. for Brain Sci., Wako, Japan

Abstract: Entrainment is an established neural response phenomenon in which patterned sensory stimuli generate neural oscillations with an evoked frequency equal to the frequency of the stimulation. Visually evoked entrainment has been documented in humans and cats, highlighting

the evolutionary conservation of entrainment, but the underlying mechanism of entrainment remain poorly understood. We recently described gamma entrainment in mice, and found profound neuroprotective effects of gamma entrainment on molecular and behavioral phenotypes in mouse models of neurodegeneration. In this study, we examine the cellular and circuit mechanisms of entrainment. Using high-density electrophysiological recordings with silicon linear probes in awake freely moving mice, we find that visual flicker up to 50 Hz faithfully generates entrainment of multiunit activity and local field potential (LFP) in the lateral geniculate nucleus (LGN) and in primary visual cortex (V1). Current source density (CSD) analyses reveal stimulus frequency and layer specific modulation of entrainment with prominent and weaker LGN recipient layers in V1 showing well-delineated sink-source relationship. Selectively decoupling parvalbumin (PV) expressing interneurons in V1 using viral mediated expression of tetanus toxin light chain abolished sensory evoked entrainment at the level of multiunit spiking, spiking of putative excitatory neurons, local filed potential, and CSD in V1. By exploiting rabies virus tracing and simultaneous linear probe recording in V1 and LGN, we are now examining monosynaptic inputs of LGN to PV interneurons in V1 during visually evoked entrainment. Together, our data suggest that synaptic contributions of PV interneurons in V1 is indispensable for sensory evoked entrainment of range frequencies including theta (5 Hz, 8 Hz and 10 Hz) and gamma (30 Hz, 34 Hz, 36 Hz, 38 Hz, 40 Hz, 42 Hz, 44 Hz and 50 Hz). Our data also suggest that harmonic LFP and spiking responses in the V1 is governed by the synaptic activities of PV interneurons locally in the V1.

Disclosures: C. Adaikkan: None. **K. Abdelaal:** None. **M. Murdock:** None. **A.J. Huang:** None. **H.A. Sullivan:** None. **I. Wickersham:** None. **T.J. McHugh:** None. **L. Tsai:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.09/K8

Topic: D.07. Vision

Support: NINDS, 5R01NS104949

Title: Mapping functional thalamocortical connections in the mouse visual system

Authors: *J. ZHUANG, S. CHATTERJEE, R. LARSEN, K. TAKASAKI, N. OUELLETTE, B. MACLENNAN, J. WATERS, C. REID;
Allen Inst. for Brain Sci., Seattle, WA

Abstract: A prominent feature of visual information processing in mammalian brains is a hierarchical representation. In the early stage of this hierarchical system, the retina, the lateral geniculate nucleus (LGN) and primary visual cortex (V1) represent progressively more complex

and abstract features of the visual environment. Previous work in carnivores has shown that the projections from LGN to V1 are highly organized with precise functional specificity. In recent years, the mouse visual system is becoming a powerful model for functional studies due to the experimental tractability and availability of genetic tools. Despite some similarities, the visual system of the mouse has multiple structural and functional features that are distinct from what is found in carnivores and primates. For example, in mice, a large proportion of V1-projecting LGN axons are direction selective (DS) and LGN axons project to not only layer 4 but also all superficial layers in V1. It has been proposed that DS LGN axons preferentially project to superficial layers (similar to W pathway in cats and koniocellular pathway in primates) while those with concentric receptive fields mainly project to layer 4 (similar to X/Y pathways in cats and parvocellular/magnocellular pathways in primates). However, attempts to test this hypothesis have showed contradictory results partly due to the lack of LGN labeling specificity. Here by combining the genetic and stereotaxic targeting, we have achieved expression of calcium indicator in LGN neurons with unprecedented specificity. Using volumetric axon calcium imaging, we systematically mapped the response properties of LGN axons/boutons in V1 from layer 1 through layer 4. Our preliminary results show similar levels of DS afferent input across these layers, in contradiction to the hypothesis of strict functional segregation.

Disclosures: **J. Zhuang:** None. **S. Chatterjee:** None. **R. Larsen:** None. **K. Takasaki:** None. **N. Ouellette:** None. **B. MacLennan:** None. **J. Waters:** None. **C. Reid:** None.

Poster

577. Visual Pathways: To and From the Cortex

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Program #/Poster #: 577.10/K9

Topic: D.07. Vision

Support: Science and Technology Development Fund (STDF) Grant 5168
COMSTECH-TWAS Joint Research Grants Program Grant 17-029

Title: Encoding models of visual and electrical stimuli in rat lateral geniculate nucleus: A deep learning approach

Authors: E. MOUNIR[1], B. ABDULLAH[1], H. M. K. MAHDI[1], ***S. ELDAWLATLY**[1,2];
[1]Computer and Systems Engin., Ain Shams Univ., Cairo, Egypt; [2]German Univ. in Cairo, Cairo, Egypt

Abstract: Visual prostheses hold hope of vision restoration for millions with retinal degenerative diseases. The main principal of visual prosthesis is to integrate an electrical stimulation system into functional sites of the visual system, bypassing the damaged site, hence restoring vision. One promising type of visual prostheses targets the thalamic Lateral Geniculate Nucleus (LGN).

Such prosthesis is useful when the retina is completely damaged or when the optic nerve is not functional. One challenge in developing thalamic visual prostheses as well as other prostheses is understanding how stimulus information is encoded in the underlying neuronal population. In this work, we introduce a deep learning approach to model the encoding of both visual and electrical stimuli in rat LGN. We recorded the activity of right LGN neurons in 15 anesthetized female Albino rats *in vivo* using multi-electrode arrays during visual and electrical stimulations. For visual stimulation, a screen was placed tangent to the left eye divided into 4 x 8 pixels. We examined two types of visual stimulation patterns: single-pixel and checkerboard patterns. In both cases, each pattern is repeated for 100 trials. For electrical stimulation, we used a pulse train pattern consisting of 5 biphasic pulses applied 50 times per stimulation channel. An average of 13 and 8.6 neurons per rat were identified for visual and electrical stimulations, respectively. Firing rates of recorded neurons were computed with bins of size 10ms and 50ms. Extracted firing rates and the corresponding stimulation patterns were used to train a deep Convolutional Neural Network (CNN) model using 80% of the data. In this CNN, the stimulus at any time instant in addition to the stimulus history are provided to the network along with the firing history of the recorded neurons. We then used the model to predict the firing rates of the recorded neurons in the remaining 20% of the data. Our results demonstrate significant similarity between actual and predicted firing rates in both visual and electrical stimulation paradigms. The mean correlation between the predicted and actual firing rates across all rats for the visual encoding was 0.63 (maximum was 0.9) and 0.75 (maximum was 0.93) for 10ms and 50ms firing rate windows, respectively. For the electrical encoding, the mean correlation was 0.22 (maximum was 0.42) and 0.59 (maximum was 0.69) for 10ms and 50ms firing rate windows, respectively. Our results demonstrate the efficacy of using deep CNNs in predicting the response of LGN neurons to visual and electrical stimulation. These models could be further integrated to tune electrical stimulation patterns for thalamic visual prostheses.

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Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.11/K10

Topic: D.07. Vision

Support: Japan Society for the Promotion of Science (JSPS) KAKENHI (JP17H04684)

Title: Using macromolecular tissue volume mapping to parcellate magno and parvo subdivisions in the human lateral geniculate nucleus

Authors: *H. OISHI[1,2], H. TAKEMURA[1,2], K. AMANO[1,2];
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Abstract: Lateral geniculate nucleus (LGN) consists of magnocellular (M) and parvocellular (P) subdivisions, which are known to have different response selectivity for visual stimuli. More specifically, M cells are more sensitive to luminance contrast while P cells are more sensitive to color contrast. Identification of these subdivisions using non-invasive neuroimaging is essential for establishing a method to assess functions, developments and impairments of the LGN subdivisions and subsequent visual streams in living humans. However, it has been difficult to identify LGN subdivision using structural neuroimaging partly due to inhomogeneity in conventional T1-weighted image.
Based on the fact that the subdivisions have different anatomical properties, here we tested to utilize macromolecular tissue volume (MTV) mapping (Mezer et al., 2013), which provides quantitative maps corrected for image inhomogeneities, to identify human LGN subdivisions. We first identified the location of the entire LGN using high-resolution proton density-weighted (PD) image ($0.75 \times 0.75 \times 1$ mm^3) from four healthy participants. We then collected MTV data (0.8 mm^3 isotropic voxels) and registered to the PD image. We classified 20% of voxels with the lowest MTV to the putative M-group and the remaining 80% of voxels to putative P-group. This classification is based on a previous study showing that the area size of P-group is roughly four times larger than that of M-group (Andrews et al., 1997). As a result, we found that estimated M- and P-group voxels are clearly separated and are located ventromedially and dorsolaterally, respectively, in all participants. These patterns were consistent with LGN anatomy for human and primates (Selemon and Begovic, 2007). This result suggests that MTV mapping provides a stable parcellation for LGN subdivisions.
MTV separation has some advantages as compared with fMRI-based mapping (Denison et al., 2014) because fMRI experiment requires precise visual stimulation with repeated number of measurements, which may not be suitable for the clinical population with retinal disorders. Since MTV-based parcellation does not require any visual stimulation, this method will be useful to study human LGN subdivisions with respect to retinal disorders, developments or visual functions.

Disclosures: H. Oishi: None. **H. Takemura:** None. **K. Amano:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.12/K11

Topic: D.07. Vision

Support: NIH Grant EY024946
NIH Grant EY028905

Title: Rules of connectivity limiting promiscuous relations between LGN concentric neurons and retinotopically aligned fast-spike interneurons in rabbit V1

Authors: Y. BERESHPLOVA[1], X. HEI[1], J. ALONSO[2], ***H. A. SWADLOW**[1];
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Abstract: The specificity of thalamocortical (TC) connectivity differs for different classes of sensory cortical neurons. TC connectivity onto simple cells of V1, for example, is highly specific, and is governed by multiple rules of connectivity, based largely on congruity of pre- and postsynaptic spatiotemporal receptive field properties (Alonso et al., 2000; Sedigh-Sarvestani et al., 2017, Lien and Scanziani, 2018). Such specificity results in a relatively small proportion of retinotopically aligned LGN neurons synapsing onto each simple cell. By contrast, the connection probability between a sensory TC neuron and an aligned cortical fast-spike interneuron is much higher. Thus, connection probabilities of ~ 2/3 are observed between ventrobasal TC neurons and putative fast-spike interneurons (SINs) in the aligned S1 barrel of rabbits and rats (Swadlow and Gusev, 2002; Bruno and Simons, 2002). Here we examined synaptic connectivity between LGN concentric neurons (by far, the most numerous cell type in rabbit LGN) and retinotopically aligned fast-spike interneurons in layer 4, and we explore reasons for the small proportion of exceptions to the rule of full promiscuity between these populations. We used extracellular cross-correlation methods, combined with spike-triggered LFP/CSD analysis to examine connectivity. We found (a) connection probabilities of ~ 75% between aligned LGN/SIN pairs, and (b) that the remaining (~25%) aligned but unconnected cases could not be explained by a mismatching of receptive field properties. These unconnected cases could, however, be accounted for by one of two factors. The first concerns differences among LGN neurons in the “strength” of the synaptic impact that they generated near the V1 SIN under study. This strength is measured by the amplitude of the spike-triggered LFP elicited by spikes of the LGN neuron. Thus, even when alignment is perfect, an LGN axon can generate no spike-triggered LFPs in the aligned column. Also, an LGN axon may generate a strong impact at some depths, but a weak impact near the L4 SIN under study. In all such cases, we found no connectivity between LGN neuron and L4 SIN. The second factor concerns the postsynaptic L4 SIN, and differences in the extent to which these cells respond to any monosynaptic drive from the LGN. This measure is gained by their responses to electrical stimulation of the thalamus. Notably, the effects of these two (pre- and postsynaptic) measurable factors account for ~ 90% of the exceptions from complete promiscuity in the connectivity between LGN concentric neurons and retinotopically aligned L4 SINs of V1.

Disclosures: Y. Bereshplova: None. **X. Hei:** None. **J. Alonso:** None. **H.A. Swadlow:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

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Topic: D.07. Vision

Support: NIH Grant EY024946
NIH Grant EY028905

Title: Activation of a visual cortical column by a directionally selective thalamocortical neuron

Authors: *Y. I. BERESHPOLOVA[1], C. R. STOELZEL[1], C. SU[1], J. ALONSO[2], H. A. SWADLOW[1];
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Abstract: The retina of rabbits and rodents has neurons that signal the motion direction of a visual stimulus. These direction selective signals are transferred to the visual cortex (V1) via directionally selective (DS) neurons in the lateral geniculate nucleus (LGN). Notably, the function and synaptic impact in V1 of these LGN DS signals are unknown. Using the method of single-axon spike-triggered LFP/current source-density analysis, we measured the synaptic impact generated by individual LGN DS neurons in area V1 of awake rabbits, and compared them to the impact generated by individual LGN concentric neurons. We show that LGN DS neurons make fast and strong connections in layers 4 and 6, and that their postsynaptic effects are similar to those made by LGN concentric neurons, the main thalamic drivers of V1. By contrast, the synaptic impact of LGN DS neurons on superficial cortical layers was not detectable. We also found that both LGN DS neurons and concentric neurons powerfully (and similarly) drive putative fast-spiking neurons of layers 4 and 6. This powerful DS thalamic input could provide a mechanism for fast and strong feed-forward inhibition to sharpen cortical sensory tuning around the four cardinal directions of motion signaled by LGN DS cells. These results suggest that LGN DS neurons activate a cortical column primarily by targeting the main input layers of the cortex and that the role of DS input to superficial cortical layers is likely to be modulatory.

Disclosures: Y.I. Bereshpolova: None. **C.R. Stoelzel:** None. **C. Su:** None. **J. Alonso:** None. **H.A. Swadlow:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.14/K13

Topic: D.07. Vision

Title: Primary visual cortex representing central, near peripheral, and far peripheral vision are differentially functionally connected, and these differences follow patterns of known brain networks

Authors: *P. DEMIRAYAK, S. SIMS, U. PANDEY, K. VISSCHER;
Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: In primary visual cortex (V1) central and peripheral vision are specialized for different functions. Due to this specialization, interactions between central, near peripheral and far peripheral regions of V1 and other cortical areas are expected to be different. Previous work from our lab found differential functional connection profiles for different eccentricities of vision, and these patterns followed patterns of known brain networks (Griffis et al., 2017). This earlier work had showed strongly significant effects in only 20 participants, and participants were fixating during minute-long breaks between tasks. We sought to replicate this previous work in a larger sample, and also extend the findings to free viewing during rest. Our resting state analyses were done on 3T preprocessed MRI data from the Human Connectome Project (HCP) database. Data used for the primary analyses were acquired from 782 healthy right-handed participants (22-36; M/F=335/447). Additional preprocessing analyses were performed on the residual BOLD data to reduce spurious variance not associated with neural activity. Regions of interests (ROIs) on central, near and far periphery of V1 were defined for seed-to-voxel analyses based on Freesurfer's retinotopy template developed by Benson et al. (2014) within Freesurfer 6.0 segmented gray matter boundaries. Cingulo-opercular, fronto-parietal and default mode networks were identified as seed ROI for seed-to-seed analyses based on Yeo et al. (2011) reference resting state networks. For both seed-to-voxel and seed-to-seed analyses time series from each seed ROI was extracted and its correlations with either all voxels or other seed ROIs were calculated in Matlab. Our results showed that central, near peripheral and far peripheral sectors of primary visual cortex have different connectivity patterns with non-visual areas. Components of the fronto-parietal control network are tightly functionally connected with central and near peripheral sectors of V1, components of cingulo-opercular control network are tightly connected with near peripheral sectors of V1, components of default mode network are connected with central and far sectors of V1. These results replicated and extended to a broader context, our previous data (Griffis et al., 2017) by suggesting that visual input that is processed by different sectors of primary visual cortex are prioritized by different large-scale resting state networks. Overall, our findings contribute to the understanding of functional processing of visual

information in the healthy young brain and they might serve as a template to compare with abnormal brain functioning.

Disclosures: P. Demirayak: None. **S. Sims:** None. **U. Pandey:** None. **K. Visscher:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.15/K14

Topic: D.07. Vision

Title: Retinotopic patterns of structural connectivity between V1 and functional networks

Authors: *S. A. SIMS[1], U. PANDEY[1], S. CEDOTAL[1], J. L. ROBINSON[2], K. M. VISSCHER[3]; [1]Univ. of Alabama At Birmingham, Birmingham, AL; [2]Psychology, Auburn Univ., Auburn University, AL; [3]Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Vision is important for our everyday life, but we use our central vision differently than our peripheral vision. For example, we use central vision to read and peripheral vision when surveying a landscape. Different functions of central and peripheral vision suggest that information from central vision may be processed differently from that in peripheral vision. A previous functional connectivity study from our lab suggested reliable differences in connections between centrally- and peripherally-representing visual cortex, and those differences follow well-established networks. Central-representing cortex was preferentially connected to the fronto-parietal (FP) network, mid-peripheral was generally more connected to the cingulo-opercular (CO) network, and far-peripheral was more connected to the default mode network (DMN). This led to the question of whether these connections reflect differing structural tracts or if they reflect multisynaptic connections. In this study, we used diffusion MRI of 786 subjects from the Human Connectome Project (ages=22-36; M/F=335/451). We performed probabilistic tractography on anatomically defined target regions of interest in V1, corresponding to central, mid-peripheral, and far-peripheral visual eccentricities and seed regions of the FP network, CO network, and DMN. Differences in cortical termination track probabilities were then analyzed on the surface. Difference maps comparing tract probability for far-peripheral vs. central V1 regions showed the FP network and the DMN were more connected to far-peripheral V1 than central V1. The CO network was more connected to mid than central V1 and in comparison of mid to far V1, the network subdivided so that portions were more connected to mid and others more connected to far V1. These results suggest eccentricity-based regions are differentially structurally connected to cortical, functional networks. In the comparison of eccentricity based regions we found resemblance of structural connectivity to functional connectivity network patterns found in previous work. Results imply that some of the differences in functional connectivity previously observed and recently replicated derive from direct connections

observable through diffusion imaging, but some of these connections cannot be observed through diffusion imaging and may derive from multisynaptic connections. Studying the differential structural connections of portions of V1 contributes to our understanding of the way the human brain processes visual information and forms a baseline for understanding any modifications in processing that might occur with training or experience.

Disclosures: S.A. Sims: None. **U. Pandey:** None. **S. Cedotal:** None. **K.M. Visscher:** None. **J.L. Robinson:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.16/K15

Topic: D.07. Vision

Support: NIH Grant GM109086

Title: Distinct cellular and network responses to thalamo-cortical versus cortico-cortical L1 inputs in non-primary neocortex

Authors: *C. MURPHY, B. M. KRAUSE, M. I. BANKS;
Dept. of Anesthesiol., Univ. of Wisconsin, Madison, WI

Abstract: Processing of sensory information occurs in cortical networks via the integration of feedforward and feedback signals. Because both matrix thalamocortical (TC) and feedback corticocortical (CC) afferents terminate in cortical layer 1, post-synaptic targets in layer 1 are particularly relevant for integration of these signals and propagation of information through the cortical hierarchy. However, characterization of the synaptic and network response properties of distinct inputs to layer 1 has been limited, especially in non-primary areas. Here, we use murine brain slices to describe cellular and network responses to independent activation of feedback CC and matrix TC inputs to layer 1 of non-primary neocortex. We injected channelrhodopsin into either posterior thalamus or cingulate cortex to isolate TC or CC projections to posterior parietal cortex and extrastriate visual cortex, respectively. We optogenetically activated axon terminals in layer 1. We recorded evoked extracellular responses across the cortical column to measure induced network activity (bursts). We also performed intracellular recordings to measure responses of post-synaptic pyramidal cells, somatostatin-positive inhibitory cells, and parvalbumin-positive inhibitory cells to activation of CC and TC inputs to layer 1. Despite overlap of their terminal fields in layer 1, TC and CC inputs induced unique activation profiles in non-primary cortex. Bursts of coordinated spiking activity, most often restricted to the deep layers, were evoked by activation of TC inputs to layer 1; however, bursts were very rarely observed following activation of CC inputs to layer 1. Whole-cell recordings suggest that this

result may be subserved by differences in response properties of post-synaptic targets between each pathway. For example, pyramidal cells were more strongly activated by TC inputs than CC inputs. Conversely, dendrite-targeting somatostatin-positive inhibitory cells were rarely activated by TC inputs, but exhibited strong, short latency activation by feedback CC inputs. These data support a model in which TC projections enable network activation and information propagation, while feedback CC projections serve a regulatory role.

Disclosures: C. Murphy: None. **B.M. Krause:** None. **M.I. Banks:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.17/K16

Topic: D.07. Vision

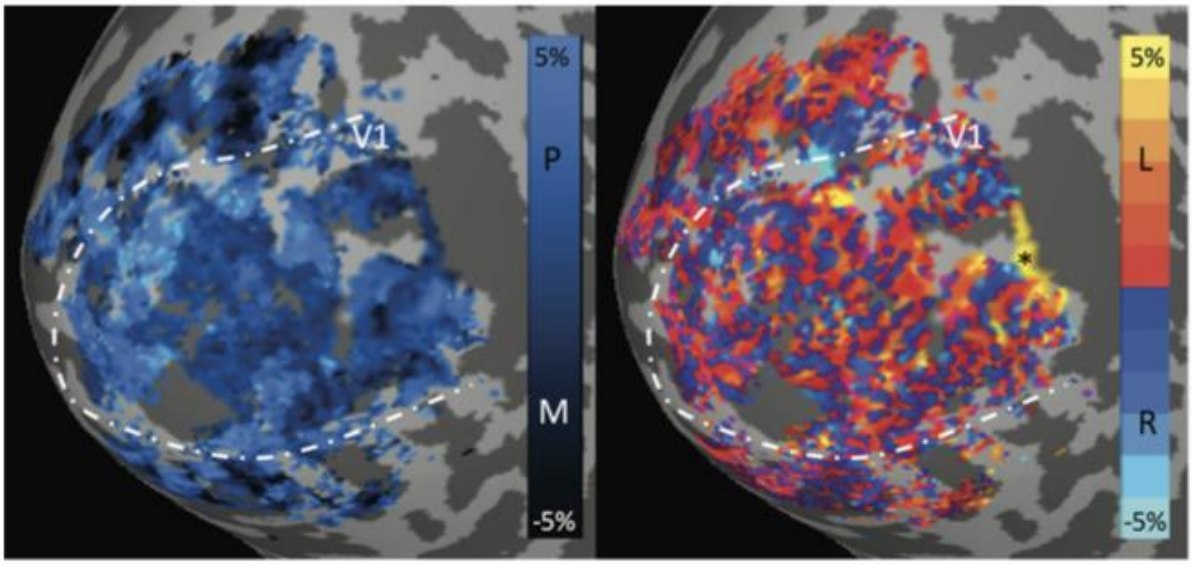
Support: NIH R01 MH111447
S10 RR026783, WM KECK Foundation

Title: Structural measures of magno- and parvocellular projections in visual cortex using ultra-high field fMRI

Authors: *K. T. NAVARRO[1], K. B. WELDON[2], M. J. SANCHEZ[3], K. E. M. TREGILLUS[1], S. A. ENGEL[4], C. A. OLMAN[1];
[1]Psychology, [2]Ctr. for Magnetic Resonance Res., [3]Psychiatry, Univ. of Minnesota, Minneapolis, MN; [4]Psychology, Univ. of Minnesota Dept. of Psychology, Minneapolis, MN

Abstract: Magnocellular and parvocellular streams are important features of the primate visual system. These streams project from the retina to V1 and have been shown to process different aspects of visual stimuli. Recent access to high-resolution neuroimaging has facilitated the exploration at mesoscopic scales in human visual cortex. Here, we investigate potential differences in the structure of magnocellular and parvocellular responses within and across layers of V1 and V2. We used 7T fMRI to observe selective activation of these streams in seven subjects across two scanning sessions. Achromatic, low spatial and high temporal frequency checkerboards targeted the magnocellular stream. Chromatic, high spatial and low temporal frequency checkerboards targeted the parvocellular stream. These stimuli were displayed dichoptically for further analysis of eye selectivity, ocular dominance columns, and presence of the blind spot. This work resulted in four findings: First, responses driven by parvocellular-targeted stimuli resulted in a laminar profile biased towards superficial layers of V1, as compared to magnocellular responses. Second, we found selective activation of the parvocellular stream in foveal V1 when compared to peripheral V1, corroborating data from nonhuman primates (NHP). Third, we found thick, repeating color-selective bands of activation stemming

from the V1 border into V2 and V3 (Fig 1). These bands are analogous to color-selective stripes found in both NHP and human extrastriate cortex, although our data suggest notable differences in the size of these bands across V2. Our bands are on a larger scale compared to NHP findings. Lastly, the depth profile of ocular dominance, computed by comparing left vs right eye responses, differed from the profile of parvocellular vs magnocellular response. Ocular dominance signals were weakest in superficial layers of the cortex (Fig 1). Together, our findings provide insight into how the magnocellular and parvocellular streams are structured in human cortex and how eye selectivity varies depending on the depth of cortical layers.



Disclosures: **K.T. Navarro:** None. **K.B. Weldon:** None. **M.J. Sanchez:** None. **K.E.M. Tregillus:** None. **S.A. Engel:** None. **C.A. Olman:** None.

Poster

577. Visual Pathways: To and From the Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 577.18/K17

Topic: D.07. Vision

Support: NIH Grant R35NS097287

Title: What degree of global synchrony exists in noradrenergic and cholinergic axons across mouse cortex?

Authors: *L. N. COLLINS, E. D. VICKERS, D. A. MCCORMICK;
Inst. of Neurosci., Univ. of Oregon, Eugene, OR

Abstract: The neuromodulators acetylcholine (ACh) and norepinephrine (NE) regulate excitation and inhibition of cortical circuits via long-range projections from nuclei in the basal forebrain and locus coeruleus, respectively, to broad regions of cortex. Both are strongly implicated in modulation of arousal state based on electrophysiological, pharmacological, and, more recently, calcium imaging experiments which demonstrate that activity of these systems correlates strongly with changes in behavioral state. However, it is unknown whether neuromodulation by NE and ACh is synchronized across wide areas of cortex. Therefore, it is unclear whether NE and ACh signalling differentially modulate cortical excitability across cortical regions. Moreover, it is not known whether any such synchronization that exists across cortical regions is maintained both during spontaneous and sensory stimulus-evoked activity. To begin to answer these questions, the present work examines activity of large numbers of individual cholinergic and noradrenergic axons across multiple regions of cortex simultaneously. Using a combination of viral tracers and transgenic GCaMP6s mouse lines we have been able to replicate previous demonstrations that activity of these axons strongly correlates with arousal measures, such as pupil diameter, whisking activity, and locomotion. We have expanded upon this body of knowledge by exploring the synchronization of activity between axons in disparate cortical regions using mesoscopic 2-photon imaging, allowing investigation of the activity of individual axons over a large field of view at high spatial and temporal resolution. Current results suggest a strong correlation between both noradrenergic and cholinergic axons up to at least 3 mm apart and distributed throughout motor, somatosensory, and visual cortices. In addition, preliminary analyses suggest that NE provides a global neuromodulatory signal throughout the cortex that is tied closely with arousal state of the animal. Ongoing work is focused on recording from regions as far as 5 mm apart in noradrenergic and cholinergic fibers in the cortex and relating their activity to behavior to determine the extent to which NE and ACh provide global, synchronized neuromodulation throughout the mouse neocortex during both spontaneous firing and visual stimulus presentation.

Disclosures: **L.N. Collins:** None. **E.D. Vickers:** None. **D.A. McCormick:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.01/K18

Topic: D.09. Multisensory Integration

Title: An electroencephalography investigation of the effects of attention on crossmodal temporal acuity

Authors: *C. BABARINSA, Z. KEELEY, K. HIRABAYASHI, S. PAPADAKIS, Z. BARNES-SCOTT, R. JAFFE, L. D. KWAKYE;
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Abstract: The ability to accurately integrate sensory information from our environment, a concept known as multisensory integration, is an integral mechanism in information processing that allows us to create a coherent perception of the world around us. The accuracy of this integration is heavily reliant on our ability to precisely distinguish timing differences between unisensory stimuli (crossmodal temporal acuity). Our previous research investigated whether attention alters crossmodal temporal acuity using a crossmodal temporal order judgment (CTOJ) task in which participants were asked to report if a flash or beep occurring at different time intervals appeared first while concurrently completing a visual or auditory distractor task. We found that increasing the perceptual load of the distractor task led to sharp declines in participants' crossmodal temporal acuity. The current study uses electroencephalography (EEG) to understand the neural mechanisms that lead to decreased crossmodal temporal acuity. Participants completed a CTOJ task as described above while EEG activity was recorded 64 scalp electrodes. We found that increasing auditory load led to differences in ERP amplitude approximately 300-1000 ms post onset of the first CTOJ stimulus. In contrast, when increasing visual load, differences in ERP amplitude were found 100-200 ms after the onset of the visual stimulus regardless of which stimulus was presented first. These results indicate that visual and auditory distractors may influence crossmodal temporal acuity through differing mechanisms although the behavioral effects of the two distractor tasks were highly similar.

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Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.02/K19

Topic: D.09. Multisensory Integration

Title: Bayesian causal inference modeling of attentional effects on the temporal binding window of multisensory integration

Authors: *V. L. FISHER[1], M. JACKSON[2], C. NAVE[2], O. JUNG-BEEMAN[2], L. D. KWAKYE[2];
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Abstract: In order to understand the world around us, we combine information across the different senses, deficits in this integration have been implicated in various neurological

disorders. This multisensory integration is highly dependent on the temporal relationship between unisensory events and our brain's ability to discern small timing differences between stimuli (crossmodal temporal acuity). Our previous research found that increasing both visual and auditory perceptual load led to sharp declines in participants' crossmodal temporal acuity. Previous research in other labs has demonstrated that the brain integrates multisensory information in a Bayes' optimal way and that the integration of temporally disparate audiovisual stimuli can be modeled using Bayesian causal inference modeling. The present study investigates the influence of visual and auditory perceptual load on the integration of simple stimuli using Bayesian modeling. Participants completed a simultaneity judgment (SJ) task during which they determined whether temporally offset flash-beep stimuli occurred (a)synchronously. Participants completed the SJ task alone (distractor free; DF), in the presence of task-irrelevant visual or auditory distractors (no load; NL), and while completing a concurrent visual or auditory distractor task (high load; HL). Data was modeled using the causal inference model derived in Magnotti et al. 2013, which is based on Bayesian statistics. Our preliminary data show an increase in the temporal binding window with increasing visual and auditory load, confirming our previous studies. Sensory noise consistently increased with increasing visual and auditory load; however, increasing perceptual load led to increases in prior for auditory distractors but decreases in prior for visual distractors. These preliminary findings indicate that attention alters both low-level (sensory noise) and high-level (priors) processing of simple multisensory stimuli and are distractor modality dependent. This supports our previously observed effects of attention on multisensory temporal processing and their applicability to the more general population.

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Poster

578. Multi-Sensory Integration

Location: Hall A

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Program #/Poster #: 578.03/K20

Topic: D.09. Multisensory Integration

Support: F32DC015391
R01DC015780
R01MH111439

Title: Visual modulation of neuronal firing in the macaque auditory core

Authors: J. J. ORCZYK[1], C. E. SCHROEDER[2], *Y. KAJIKAWA[1];
[1]Nathan Kline Inst., Orangeburg, NY; [2]Nathan Kline Inst. - Translational Neurosci. Div., Columbia Univ. Col. of Physicians and Surgeons, Orangeburg, NY

Abstract: Previous studies have identified modulation of auditory cortical activity by visual inputs using fMRI, scalp EEG, and intracortical electrophysiological recordings in several mammalian species. Intracortical electrophysiological measures include single unit or multiunit activity (MUA) as well as local field potentials. However, most findings regarding modulation of auditory cortical activity by visual stimuli are based on local field potentials. We have also found strong field potential responses to conspecific faces in the auditory cortex of macaque monkeys performing an audiovisual task. However, the generators of visual field potentials in auditory cortex were localized to face recognition areas located in the inferior temporal cortex several millimeters away from auditory cortex. It would thus appear that visual-evoked changes in auditory cortical field potentials are mostly attributable to far-field effects. However, the existence of far-field effects does not necessarily preclude the possibility of local effects of visual inputs on auditory cortical activity even if the local effect on field potentials is masked by the far-field effect. In the current study, we addressed local responses in MUA in the macaque auditory cortex. Visual stimuli were ineffective in driving neuronal firing in the majority of sites. However, brief MUA responses occurring ~100 ms after visual onset were observed at depths below granular layer in a small subset of auditory cortical loci. Additionally, weak inhibition of MUA was observed after 100 ms at many sites. The visual field potentials did not differ between those expressing deep brief MUA responses and/or weak MUA inhibition. These results suggest that one type of visual modulation of auditory cortical responses occurs through a weak suppression of auditory cortical responses, consistent with findings from prior intracortical recordings in human surgical epilepsy patients.

Disclosures: J.J. Orczyk: None. **C.E. Schroeder:** None. **Y. Kajikawa:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.04/K21

Topic: D.09. Multisensory Integration

Title: Audiovisual integration in anterior fundus face patch of macaque monkeys

Authors: *A. P. KHANDHADIA[1], A. P. MURPHY[1], L. M. ROMANSKI[2], J. K. BIZLEY[3], D. A. LEOPOLD[1];
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Abstract: The macaque superior temporal sulcus (STS) is a major area of convergence of socially relevant stimuli, for example integrating visual and auditory signals. In the visual domain, the STS contains several face patches, which are defined as brain regions more responsive to images of faces than non-face objects. Within these patches, the influence of

auditory information on neural responses is largely unknown, for example during the issuance of an acoustic vocalization. In this experiment, we assessed the responses of single neurons of the anterior fundus face patch (AF) to audiovisual clips of macaque vocalizations, focusing on the spatial sensitivity of AF neurons to the acoustic and visual components. The results indicate a high proportion of visual responses in AF cells to dynamic facial expressions are modulated by the accompanying auditory vocalizations. Such modulation often showed strong stimulus specificity and could be expressed as either enhancement or suppression of the spike rate for different stimuli. A relatively small subset of cells responded to the auditory vocal stimuli alone. We further explored the selectivity of these cells to the spatial properties of audiovisual integration. In one experiment, we presented the same audiovisual clips to the macaques while spatially separating the audio component of the stimuli from the visual shifting it 45 degrees to the left or right but maintaining central visual presentation. Under these conditions, the extent of visual enhancement or suppression depended on both the spatial position and spatial congruence of the visual and auditory components, with suppression most common when the audio stimulus was presented to the contralateral hemifield of the recorded hemisphere. In a second preliminary experiment, we altered head- and eye-centered coordinate systems by turning the animal's head +-45 degrees so it faced the position of the sound sources and requiring the animal to view the centrally presented face with eccentric gaze. Under these conditions, the response suppression was largely abolished. Overall, these results indicate that AF neurons incorporate auditory signals to shape spiking responses to observed socially relevant facial behaviors and these responses depend on the spatial position and congruence of auditory and visual components.

Disclosures: A.P. Khandhadia: None. **A.P. Murphy:** None. **D.A. Leopold:** None. **J.K. Bizley:** None. **L.M. Romanski:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.05/K22

Topic: D.09. Multisensory Integration

Support: NIH NS 101325

Title: Neural basis of stereognosis in somatosensory system

Authors: *E. V. OKOROKOVA[1], C. M. GREENSPON[2], Q. HE[3], S. J. BENSMAIA[3]; [2]Dept. of Organismal Biol. & Anat., [3]Dept. of Organismal Biol. and Anat., [1]Univ. of Chicago, Chicago, IL

Abstract: When we grasp an object, we acquire information about its three-dimensional structure, which relies on integration of proprioceptive and tactile signals. Cutaneous cues

provide information about the local spatial features of the object - the curvature and texture of a surface, the orientation of edges - whereas proprioceptive signals about the conformation of the hand and the relative positions of these features in space. These two streams of information are then combined to yield a three-dimensional percept of the object, a phenomenon called stereognosis. However, little is known about how signals from these two disparate sensory modalities are integrated to give rise to stereognosis and support our ability to effortlessly identify objects and dexterously manipulate them. To address this question, we have developed an experimental apparatus that allows us to generate objects varying in size and shape for the monkey to grasp while we track its hand movements and measure the forces it exerts on the object at each point of contact. We will simultaneously record neural activity in somatosensory cortex of macaques and seek to characterize the response properties of neurons during active interactions with objects. In particular, we are interested in later stages of processing (including areas 2 and S2), where proprioceptive and cutaneous information is integrated and, as such, are likely to mediate stereognosis.

Disclosures: E.V. Okorokova: None. **C.M. Greenspon:** None. **Q. He:** None. **S.J. Bensmaia:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.06/K23

Topic: D.09. Multisensory Integration

Title: Vision automatically exerts online and offline influences on tactile spatial perception

Authors: Y. R. WANI, S. CONVENTO, ***J. M. YAU**;
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Abstract: Vision and touch interact in spatial perception. How vision exerts online influences on tactile spatial perception is well-appreciated, but far less is known about how vision modulates tactile perception offline. Here, we investigated how visual cues exert both online and offline biases in tactile spatial perception. In a series of experiments, participants performed a 4-alternative forced-choice tactile detection task in which they reported the perception of taps on the left hand, right hand, both hands, or no touch (LRBN task). Participants initially performed the LRBN task in the absence of visual cues. Subsequently, participants performed the LRBN task in blocks comprising non-informative visual cues that were presented near the left and right hands. To explore the effect of distractor salience on the visuotactile spatial interactions, we varied the brightness of the visual cues such that visual stimuli associated with one hand were consistently brighter than visual stimuli associated with the other hand. We found that participants performed the tactile detection task in an unbiased manner in the absence of visual

distractors. Visual cues biased online tactile performance in a brightness-dependent manner, despite an instruction to ignore vision. Moreover, during task blocks comprising visual cues, tactile performance was biased toward the side of the brighter visual cues even on trials in which no visual cues were presented. Using a modeling framework based on signal detection theory, we compared a number of alternative models to recapitulate the behavioral results and to link the visual influences on touch to sensitivity and criterion changes. Our collective results reveal the obligatory and systematic influences of vision on both online and offline tactile spatial perception. Thus, the nervous system appears to automatically leverage multiple sensory modalities to build and calibrate representations for tactile spatial perception.

Disclosures: **Y.R. Wani:** None. **S. Convento:** None. **J.M. Yau:** None.

Poster

578. Multi-Sensory Integration

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Program #/Poster #: 578.07/K24

Topic: D.09. Multisensory Integration

Support: FRM Grant ECO20170637482

Title: Olfacto-tactile interactions in mice whisker somatosensory areas S1 and S2

Authors: *A. RENARD, E. HARRELL, B. BATHELLIER;
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Abstract: Perception is a multisensory phenomenon, however, the mechanisms allowing the integration of information coming from different senses remain poorly understood. A few recent studies in mice showed that multimodal interactions are ubiquitous even at the level of the primary sensory areas. Yet, there is still no report precisely describing the impact of cross-modal interactions on the representations of combinations of stimuli occurring in a passive context or during associative learning. In this study, we establish the existence of multimodal olfacto-tactile interactions in the mouse primary and secondary whisker cortical areas (wS1 and wS2). We performed 2-photon calcium imaging in layer 2/3 complemented with extracellular electrophysiological recordings in layer 5, in awake mice during the synchronized presentation of texture gratings and odors. Whiskers were tracked using high-speed videography and movements were precisely quantified.
We find that 28% of the wS1 responsive cells and 20% of the wS2 responsive cells are significantly modulated when an odor is paired with the grating presentation or presented alone, with a variety of enhanced and suppressed response types. These modulations were found to be non-additive for 15% of them and are not attributable to differences in whisking behavior. This result was confirmed with a close to maximal performance of SVM classifiers in separating the

bimodal from the unimodal trials, with a better prediction in area wS2.
This result shows the existence of an olfactory modulation in the whisker somatosensory cortex of awake mice in a passive stimulation context.

Disclosures: **A. Renard:** None. **E. Harrell:** None. **B. Bathellier:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.08/K25

Topic: D.09. Multisensory Integration

Support: NIH Grant DC016297

Title: Alpha and beta band brain activity tracks the temporal correlation between auditory and visual stimuli

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Abstract: Stimulus features that correspond to a common event in the environment are correlated over time and space. For example, mouth movements of a speaker are correlated with the amplitude envelope of the accompanying speech. The brain uses these correlations to bind these features within and across sensory systems which, in the case of multisensory binding, results in enhancements in speech comprehension and selective attention in multi-speaker situations. Though this much is known, little is known about the underlying mechanism by which the brain generates its representation of that correlation. In the current experiment, we recorded high-density electroencephalography (EEG) while presenting participants with continuous streams of auditory and visual stimuli which were amplitude modulated at frequencies from 3-8 Hz. Consistent with previous research, we found that the envelopes of the two streams were simultaneously tracked in EEG phase, and to a lesser extent EEG power. The audiovisual streams were generated independently such that the long-term correlation between their envelopes was zero but across smaller time scales (0.1 to 1 s), correlation fluctuated uniquely across time for each time scale. We first asked at what time scale EEG activity follows stimulus correlation. For most participants, EEG power (but not phase) best reflected correlation computed over the previous 500-800 ms. When examining activity across frequency bands, we found peaks in two bands, alpha and beta, where EEG power tracked stimulus correlation. Scalp topography of this activity revealed decreasing alpha power in parietal electrodes - consistent with the role of attentional suppression - and increasing beta power in frontal electrodes with increasing correlation. The relationship between attention and multisensory integration has been

a topic of interest, especially in the context of temporally dynamic stimuli. Further analysis will shed light on the influence of attentional engagement with the stimuli and the neural tracking of their correlation. These results begin to unravel how brain networks interact to compute and utilize the correlational structure of our environment to give rise to coherent perception.

Disclosures: **A.R. Nidiffer:** None. **E.C. Lalor:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.09/K26

Topic: D.09. Multisensory Integration

Title: Crossing the hands in cross-modal contexts affects the spatial cognition: Evidence from EEG

Authors: *A. BOLLINI, C. CAMPUS, M. GORI;
Unit for Visually Impaired People (U-VIP), Inst. Italiano Di Tecnologia (IIT), Genoa, Italy

Abstract: In daily life, to interact with the environment surrounding us, we have to combine information coming from different sensory modalities considering the spatial locations of events. The location of the stimulus can affect task performance even it has no relevance for the task, as in the case of the Simon effect. Indeed, in the Simon task, the participants are faster and more accurate when the position of the target and the response match than when their locations are in two opposite positions. A large body of the literature showed that each sensorial modality encodes spatial information according to a specific frame of reference, e.g. hearing and vision are based on external coordinates while touching on internal coordinates. One way to induce a conflict between the two reference frames is to cross the hands over the body midline. In this case, there is an incongruence between the internal (body-referred) and the external coordinates. Here, to investigate the frame of reference across different sensory modalities, we tested participants with unimodal and cross-modal versions of auditory-tactile Simon task, manipulating the hand's posture. We recorded EEG activity during the task in order to determinate the neural activity representing the direction of spatial cognition in the various scenario and therefore the dominant reference frame. We then focus on behavioral outcome, combining accuracy and reaction times in the Inverse Efficiency Score (IES), and EEG activity, measuring both ERPs and Time-Frequency representations.
Results show both behavioral and neurophysiological differences between the cross-modal and unimodal scenarios, both in the auditory and tactile version of Simon task. In particular, it seems that while in the unisensory auditory task participants followed the external, in the alternating cross-modal modality task, the Simon effect disappears in the auditory modality. Moreover, there was a great drop in performance in the cross-modal tasks, due to sensory-switch costs. This

resulted in greater IES and in a general increase of amplitude in the neural activity compared with performance and activity in unimodal tasks, probably reflecting a greater cognitive load. We also found modulations related to the hand's posture, which affected the behavioral performance and the EEG activity, in particular in the domain of N1 component, known as related also with spatial cognition processes.
These results show how in cross-modal contexts the weights associated with a spatial frame and a sensory modality change dynamically to adapt to the demands of the task.

Disclosures: **A. Bollini:** None. **C. Campus:** None. **M. Gori:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.10/K27

Topic: D.09. Multisensory Integration

Support: NSERC

Title: Decoding anticipatory action plans using EEG event-related potentials

Authors: ***T. C. CHEUNG**, L. L. GUO, A. FROST, C. PEREIRA, M. NIEMEIER; Psychology, Univ. of Toronto Scarborough, Toronto, ON, Canada

Abstract: Feedforward models allow for precise sensorimotor control by anticipating action outcomes. For example, hand movements may be anticipated in the dynamic crossed-hand illusion where the temporal order of tactile stimulations of the left and right hand are more likely to be confused when the hands are crossed as opposed to uncrossed as well as when hands are about to cross (Hermosillo et al., 2011). Study 1, conducted among psychology undergraduates (age: mean=19.26 years old, S.D.=1.29; male: 41.9%), consisted of two stimulus onset asynchronies (SOAs: 0ms and 150ms) between the auditory start-to-move signal and the first of two vibrotactile stimulations (100ms apart) on one of the two index fingers. Results suggested that stationary uncrossed and crossed conditions had the lowest and highest error rates respectively. In addition, planning to move the hands from uncrossed to crossed position increased the former error rate, and planning the otherwise decreased the latter. Two-way ANOVAs showed significant hand position (crossed/uncrossed) and movement planning (stationary/movement) interaction, with $F(1,28) = 7.62$, $p = .01$, partial eta sq. = .214. The results confirmed that anticipated arm movements influenced perceived hand positions.
Study 2 used EEG to map the influence of anticipated arm movements in time by using the spatial and temporal features of ERPs of aligned SOAs (0ms, 125ms, 250ms) after the start-to-move signal. Instead of using the TOJ task, a flashing light located adjacent to either middle finger was used for the SOA manipulations. Support Vector Machine (SVM) were trained

comparing the ERPs between the crossing versus uncrossing conditions at 3 different SOAs. We predicted that comparing with the ready-to-move signal time point, influence of the anticipated movement would become more salient in the time windows closer to the movement onset (i.e., SOA = 250ms), thus boosting the classification accuracy between the two movement conditions. In support to the hypothesis we observed that for SOA=250ms classification accuracies were over 75%, whereas they declined for SOAs of 125ms and were at chance level for SOA=0ms. Our data reveal electrophysiological correlates of forward models in action planning.

Disclosures: T.C. Cheung: None. **L.L. Guo:** None. **A. Frost:** None. **C. Pereira:** None. **M. Niemeier:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.11/K28

Topic: D.06. Auditory & Vestibular Systems

Support: NIH Grant DC017532

Title: Relationship between saccade-related eardrum oscillations and clinical measures of middle ear impedance

Authors: *C. KING[1], R. LANDRUM[1], D. MURPHY[1], S. SCHLEBUSCH[1], D. KAYLIE[1], C. A. SHERA[2], J. GROH[1];
[1]Duke Univ., Durham, NC; [2]USC, Los Angeles, CA

Abstract: Integration of auditory and visual information is necessary in order to make sense of the world around us. How and where this integration occurs within the brain is not known. Our laboratory has identified a phenomenon where, in the absence of auditory stimuli, both eardrums begin synchronous, low-frequency oscillations just prior to saccadic eye movements. These eye movement-related eardrum oscillations (EMREO) change in amplitude and phase with changes in saccade magnitude and direction. This discovery suggests that connections between the visual and auditory systems likely begin as early as the auditory periphery (Gruters, Murphy et al, PNAS 2018). Ongoing work in non-human primates can provide insights into potential anatomical mechanisms (Schlebusch et al, Advances and Perspectives in Auditory Neuroscience conference 2018; Schlebusch et al, Society for Neuroscience conference, 2019) and examining the response in different human clinical populations can also further our understanding of the underlying mechanisms and potential utility of these oscillations.
To further characterize this phenomenon in humans and assess the feasibility for use in future clinical research, we examine the relationship between traditional measures of middle-ear function (e.g., compliance) and characteristic features of the EMREO. Normal hearing subjects

participated in visual tracking tasks, divided into one-hour sessions across several days. Subjects were seated, facing a monitor, and stable head position was maintained using a chinrest. Microphones placed in both ear canals recorded the oscillations. Eye movements were tracked with a video eye tracker. Analysis shows a reliably recorded EMREO in approximately 5 minutes of recording time, suggesting potential value in future clinical research. Middle-ear tympanometric measurements were obtained prior to each recording session, allowing the investigation of the relationship between variations in middle-ear measurements and the structure of the EMREO. The impact of altered visual or auditory input on the response is examined.

Disclosures: C. King: None. **R. Landrum:** None. **D. Murphy:** None. **S. Schlebusch:** None. **D. Kaylie:** None. **J. Groh:** None. **C.A. Shera:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.12/K29

Topic: D.06. Auditory & Vestibular Systems

Title: Eye movement is linearly encoded by eardrum motion: The decipherable EMREO

Authors: *D. L. K. MURPHY[1], C. D. KING[1], R. LANDRUM[1], S. SCHLEBUSCH[1], C. A. SHERA[2], J. M. GROH[1];
[1]Duke Univ., Durham, NC; [2]USC, Los Angeles, CA

Abstract: After every eye movement, the brain must realign the visual and auditory reference frames in order to co-locate sights and sounds. Exactly where, when, and how such visual-auditory spatial integrations occur is not fully understood. We recently discovered that the eardrum oscillates beginning a few milliseconds before saccades and continuing until well into ensuing periods of fixation (Gruters, Murphy et al PNAS 2018). Information about at least the horizontal direction and length of saccades appear to be reflected in the phase and magnitude of these eye movement-related eardrum oscillations (EMREO).
Here, we sought to assess the full spatial characteristics of this signal for saccade parameters in both vertical and horizontal dimensions. Concurrently we sought to validate that independent estimations of vertical and horizontal saccade parameter contributions can be linearly combined to predict EMREO waveforms for saccades in all directions – a fundamental assumption of current analyses.
We found that EMREOs depend on both horizontal and vertical saccade components, varying predominantly with eye displacement, but modulated by absolute (initial or final) position as well. In toto, EMREO appear to represent combinations of these saccade parameters such that any saccade corresponds to a specific eardrum oscillation that contains a linear combination of the vertical and horizontal saccade parameters. Regressions in both the time and frequency

domain create a fuller picture of the spatial information contained in EMREO. These results demonstrate that detailed information about the relationship between visual and auditory reference frames is present in the earliest stage of the auditory pathway. They also demonstrate that this information is mapped linearly and can therefore be recovered with a small set of basis components.
Future work delving into the relationship between EMREO and the transduction of incoming sounds will be needed to ascertain their effects on the processing of auditory spatial locations in relation to the visual scene. While the frequency and magnitude of EMREO suggest that they may be related to middle ear muscle contractions, the underlying mechanisms that generate them are unknown.

Disclosures: D.L.K. Murphy: None. **C.D. King:** None. **R. Landrum:** None. **S. Schlebusch:** None. **C.A. Shera:** None. **J.M. Groh:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.13/K30

Topic: D.06. Auditory & Vestibular Systems

Support: R01 DC017532

Title: Changes in saccade-related eardrum oscillations after surgical denervation of the stapedius muscle

Authors: *S. N. SCHLEBUSCH[1], M. W. COOPER[1], D. M. KAYLIE[1], D. L. K. MURPHY[1], C. D. KING[1], C. A. SHERA[2], J. M. GROH[1];
[1]Duke Univ., Durham, NC; [2]USC, Los Angeles, CA

Abstract: The connection between the visual and auditory systems plays an important, integrative role in perceiving surrounding stimuli correctly. We have recently reported an oscillation of the eardrum time-locked with the onset of a saccade and in the absence of incoming sound that suggests this connection may begin as early as the auditory periphery. These eye movement-related eardrum oscillations (EMREOs) covary in phase and amplitude with the direction and magnitude of a synchronous saccade (Gruters, Murphy et al. PNAS 2018). However, the acting anatomical features and their joint contributions to this eardrum oscillation-possibly including the stapedius, tensor tympani, and outer hair cells - are still unknown. We first sought to determine the interactions between the stapedius muscle and the eardrum during saccade activity, an important initial step towards understanding both the mechanisms within the middle and inner ear that cause the EMREO and the function of the EMREO.
We recorded EMREOs in one rhesus monkey during a spontaneous saccade task before and after

denervating and transsecting the stapedius muscle of one ear. The monkey was head-restrained in a dark room, and eye movements were tracked with a video eye tracker (1000 Hz sampling rate) while eardrum oscillations were recorded using microphones placed in the ear canals of both ears. We report pre-surgery that we can see a well-characterized, highly reproducible EMREO in both the left and right ear, and that the horizontal component of a saccade has significant input to an accompanying EMREO, as expected from previous work. We then performed surgical transsections of the facial nerve and stapedius muscle on the right side, thus completely denervating the stapedius as well as disconnecting it from the stapes bone of the middle ear. We retested the monkey during and after a four-month recovery period with the same pre-surgery recording methods. After surgical intervention of the stapedius muscle, characteristic EMREOs are not immediately apparent in the operated ear and regression analyses show that the input of the horizontal component of a saccade to an accompanying EMREO is significantly diminished (by about 30%), but not absent. The control ear maintains its pre-surgery, highly reproducible EMREO. Trial-wise analysis in the frequency domain suggests post-surgery changes in the frequency of oscillations of the eardrum in the operated ear and/or phase synchronization with respect to eye movement. Together, these findings suggest that there may be multiple contributors to the EMREO in a complex mechanism within the ear, and that the stapedius muscle is one of these contributors.

Disclosures: **S.N. Schlebusch:** None. **M.W. Cooper:** None. **D.M. Kaylie:** None. **D.L.K. Murphy:** None. **C.D. King:** None. **C.A. Shera:** None. **J.M. Groh:** None.

Poster

578. Multi-Sensory Integration

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Topic: D.09. Multisensory Integration

Support: University of Buenos Aires (UBACyT 20020130300008BA)
CONICET (PIP2014 GI 11220130100729CO01)
ANPCyT (PICT 20121578)

Title: Stimulus salience and spatial correspondence determine enhancement or depression of multisensory integration in fish

Authors: N. MARTORELL[1,2], M. PERARA[1,2], ***V. MEDAN**[1,2];
[1]Univ. of Buenos Aires, Buenos Aires, Argentina; [2]IFIBYNE-CONICET, Buenos Aires, Argentina

Abstract: Most animals combine multiple sources of information to form a coherent percept of the world for adaptive behavioral decisions. The underlying mechanisms of such interactions are

far from clear. Here we ask: (i) What are the parameters of a combination of stimuli which determine if integration occurs, and (ii) How is response latency modified by multisensory integration? We answer these questions analyzing the C-start escapes of goldfish (Carassius auratus) in response to auditory pips and visual looming stimuli.
We first described the response probability and response latency to 6 levels of unimodal auditory or visual stimuli of increasing strength. Varying the volume of auditory stimuli and the contrast of visual looms allowed us to obtain unimodal stimuli ranging from low to high salience (<10% to >70% response probability). To determine which combinations produced multisensory integration, we created a multimodal stimuli matrix combining these 6 auditory and 6 visual stimuli. Experiments in 60 animals showed that the strongest multisensory enhancement occurs when both stimuli have minimum salience while it disappears as salience increases.
We next described how integration changes when spatial correspondence between the auditory and visual components is altered. For low salience combinations, we observed multisensory enhancement when both components came from the same direction, multisensory depression when they were 90° apart and no integration at 180° separation. For higher salience combinations, integration was non-significant regardless of spatial separation.
Finally, we analyzed C-start response latency for auditory or visual stimuli with respect to the auditory pip onset or the end of the looming expansion respectively. As expected, brief (5 ms) auditory pips evoked responses with a narrow latency distribution (median = 12.5 ms, 25-75th percentile = 8 to 17 ms, N = 56) compared to longer lasting (4000 ms) visual looms (median = -29 ms, 25-75th percentile = -166 to 30 ms, N = 67). Interestingly, when we presented an auditory pip 116 ms before the end of the loom expansion, the multimodal responses were centered around the auditory latency distribution and showed the same range (median = 12.5 ms, 25 to 75th percentile = 8 to 17 ms, N = 215).Overall we found multisensory enhancement of weak but spatially congruent audio-visual stimuli whose response latency was determined by the auditory stimulus. Ongoing experiments are testing the temporal dependence of these audio-visual stimuli to determine to which extent the auditory stimulus dictates response latency.

Disclosures: **N. Martorell:** None. **M. Perara:** None. **V. Medan:** None.

Poster

578. Multi-Sensory Integration

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Topic: D.09. Multisensory Integration

Support: University of Buenos Aires (UBACyT 20020130300008BA)
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ANPCyT (PICT 20121578)

Title: Auditory-visual multisensory enhancement in a vertebrate command neuron

Authors: *S. OTERO CORONEL[1,3], V. MEDAN[2,3];
[1]Sch. of Med., [2]Sch. of Exact and Natural Sci., Univ. of Buenos Aires, Buenos Aires, Argentina; [3]Inst. of Physiology, Mol. Biol. and Neurosci., CONICET - Univ. of Buenos Aires, Buenos Aires, Argentina

Abstract: Different sensory systems provide animals with valuable information that allows them to identify possible threats and react accordingly. In fish, the Mauthner cell receives inputs from the visual and auditory systems and commands the C-start escape response. By combining optic tectum and auditory stimulation with in vivo intracellular recordings of the Mauthner cell in goldfish (*Carassius auratus*), here we show that multimodal stimuli produce higher responses than their unimodal counterparts. We also address how the linearity of the multisensory enhancement depends on the temporal order of the unimodal stimuli, as well as the duration and frequency of the tectal stimulus.

Multimodal responses to a sound pip before (-50 ms), simultaneously or after (50 ms) a single 1 ms-tectal pulse are higher than those evoked by the best unimodal stimulus. To obtain a multisensory linearity index (MLI) we divided the peak multimodal response by the sum of the peak unimodal responses. We found that when presenting a sound pip 50 ms before a single tectal pulse, the mean (± SEM) MLI was 0.84 ± 0.02, N=23 and significantly lower than when presenting the sound pip simultaneously (0.91 ± 0.02, N=23, p=0.04) or 50 ms after tectal stimulation (0.92 ± 0.02, N=12, p=0.04).

Increasing the duration (1 to 200 ms) of a 60 Hz tectal train produced higher unimodal responses. However, a sound pip presented at the end of the tectal train produces multimodal responses that are equally effective for all train durations. Accordingly, the MLI for a pip after a single 1 ms-tectal pulse was significantly higher (0.91 ± 0.02, N=23) than for the longest tectal train (200 ms: 0.67 ± 0.05, N=13, $p<0.001$).

Similarly, increasing the frequency of a 100 ms tectal train yielded higher unimodal peaks but failed to improve the multimodal response when combined with a sound pip at the end of the train. As a result, a multimodal stimulus with a tectal train of 30 Hz rendered a higher MLI (0.79 ± 0.03, N=15) than with a 200 Hz train (0.67 ± 0.04, N=12, p=0.04).

Altogether, we found that multisensory enhancement in the Mauthner cell represents a unique example of the inverse effectiveness principle implemented at the single cell level. The linearity of the multimodal enhancement is maximal when a low intensity (i.e. brief or low frequency) tectal stimulus is presented with or shortly after a sound. Behavioral experiments from our lab further support the importance of multisensory integration of low-intensity audio-visual stimuli in the context of the escape response.

Disclosures: **S. Otero Coronel:** None. **V. Medan:** None.

Poster

578. Multi-Sensory Integration

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Topic: D.09. Multisensory Integration

Support: R01NS107383

Title: Functional magnetic resonance response shape and the inhibitory system

Authors: D. AKSENOV, L. LI, M. MILLER, ***A. M. WYRWICZ**;
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Abstract: Functional magnetic resonance imaging (fMRI) relies upon blood oxygenation level dependent (BOLD) signal changes for mapping brain activation in humans and animals. The shape of the BOLD fMRI signal can vary considerably even across structures of the same sensory pathway. To explore the relationship between BOLD signal shape and the local level of inhibition, we compared the temporal behavior of the stimulus-evoked BOLD response in the primary cortical and subcortical regions of the visual and somatosensory whisker systems. In order to test the hypothesis that region specific changes were driven by local differences in GABAergic inhibition, BOLD and electrophysiological data were acquired under normal and pharmacologically-modulated levels of neuronal spontaneous activity in the awake rabbit. Functional MR imaging experiments were performed on a 9.4T Bruker BioSpec imaging spectrometer. Imaging data were acquired from four consecutive slices using single-shot gradient-echo EPI pulse sequence (TR=2s and TE=11ms). The stimulus consisted of a 50 Hz vibration delivered to the whiskers on the left side by means of a nylon band coupled to an oscillating magnetic coil and monitored in real time by an infrared sensor to ensure consistent amplitude and frequency of the vibration. The visual stimulation consisted of a 2x2 array of green LEDs flashing at 8 Hz delivered to the left eye. Neuronal activity, including single units and local field potentials, was recorded with non-ferrous wires attached to a chronically implanted microdrive. Data were analyzed after removal of blocks of gradient interference. Data were acquired before and after localized injection of the GABA-agonist muscimol in the whisker barrel cortex (WBC). Our results show that during sensory visual or whisker stimulation, the BOLD responses in the thalamic lateral geniculate nucleus and ventral posteromedial nucleus correlated well with one another, whereas the responses in WBC and visual cortex (V1) showed significant differences in shape and duration. Our electrophysiological data showed that the stimulus-evoked neuronal responses more closely resembled the BOLD response in V1 than in WBC. Moreover, analysis of the average baseline neuronal activity revealed a much lower level of activity in V1 than in WBC. Based on these findings, we sought to test the dependence of the BOLD signal shape on the level of baseline inhibition, as opposed to evoked neuronal response.

Disclosures: **D. Aksenov:** None. **L. Li:** None. **M. Miller:** None. **A.M. Wyrwicz:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.17/K34

Topic: D.09. Multisensory Integration

Title: Transcriptional analysis of circadian correlations among dopamine, dopaminergic receptors and clocks genes in spinal cord of rat

Authors: *C. PIÑA LEYVA[1,2], B. FLORÁN GARDUÑO[1], L. RODRÍGUEZ SOSA[3], I. JIMÉNEZ ESTRADA[1], J. GONZÁLEZ BARRIOS[2];
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Abstract: In the spinal cord the dopaminergic receptors control locomotor activity and nociceptive functions. Some brain experiments have shown the clock genes are controlled by the dopamine receptors, but in the spinal cord remained unknown what components are present and how are controlled the circadian functions. We examined the circadian behavior and the transcriptional correlation of the dopamine receptors with the clock genes along the spinal cord. We evaluated the mRNA of the dopamine receptors and clock genes by using RT-qPCR (TaqMan assay) and HPLC to evaluate the concentrations of dopamine content in the rat spinal cord. The dopamine circadian behavior was highest in the lumbar and least in the thoracic region. DR3 and DR4 had the greatest circadian expression while DR2 and DR5 showed the least circadian expression in each region evaluated. The clock genes Bmal, Per1 and Cry2 exhibited the mayor expression in cervical, thoracic and lumbar. The positive correlations were: DR1 with Per2 and Per3, DR2 with Rev-erbα, DR4 with Rorα and Cry1, DR5 with Rev-erbα and Per2 and the negative correlations were: DR1 with Clock and Cry2, DR2 with Per1, Clock and Cry2, DR3 with Per1, Clock and Cry2, DR4 with Cry2 and DR5 with Per1, Clock and Cry2. Our results show that dopamine, dopaminergic receptors and the clock genes are organized throughout the spinal cord. All dopaminergic receptors expressed in the spinal cord are involucrate with the transcriptional regulation of the clock genes in order to keep the rhythmicity control of spinal cord functions.

Rhythmic parameters of dopaminergic receptors and clock genes in spinal cord

Gene name	Parameter	Cervical	Thoracic	Lumbar
DR1	Mesor	1.06	1.2	0.61
	Amplitude	0.34	0.22	0.17
	Acrophase	0.86	21.3	23.7
DR2	Mesor	0.8	0.89	0.74
	Amplitude	0.2	0.25	0.51
	Acrophase	4.36	16.04	0.85
DR3	Mesor	1.03	1.29	2.24
	Amplitude	0.12	0.11	0.97
	Acrophase	11.3	17.4	1.4
DR4	Mesor	1.49	1.52	1.52
	Amplitude	0.24	0.43	0.62
	Acrophase	3.02	23.8	21.7
DR5	Mesor	0.96	0.85	0.94
	Amplitude	0.19	0.03	0.78
	Acrophase	4.08	14.02	0.36
Bmal	Mesor	1.9	0.37	5.84
	Amplitude	1.31	0.31	1.99
	Acrophase	5.58	7.64	23.51
Cry1	Mesor	1.42	0.96	0.71
	Amplitude	0.43	0.0505	0.55
	Acrophase	18.72	16.76	23.13
Cry2	Mesor	4.5	0.84	3.49
	Amplitude	4.31	0.12	1.01
	Acrophase	1.84	14.54	11.07
Per1	Mesor	1.33	3.21	4.01
	Amplitude	0.19	1.12	3.2
	Acrophase	10.82	2.1	18.9
Per2	Mesor	1.65	1.37	1.58
	Amplitude	0.43	0.21	1.71
	Acrophase	17.11	21.4	22.36
Per3	Mesor	1.38	1.08	0.85
	Amplitude	0.48	0.22	0.33
	Acrophase	16.4	18	23.57
Rorα	Mesor	1.42	0.9	1.76
	Amplitude	0.0479	0.12	1.17
	Acrophase	15.08	22.53	21.8
Rorβ	Mesor	1.37	1.24	1.22
	Amplitude	0.56	0.63	0.73
	Acrophase	6.9	3.62	23.25

Disclosures: C. Piña Leyva: None. **B. Florán Garduño:** None. **L. Rodríguez Sosa:** None. **I. Jiménez Estrada:** None. **J. González Barrios:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.18/K35

Topic: D.09. Multisensory Integration

Support: JBC
SENC

Title: Implications of firing rate changes in the claustrum during classical conditioning

Authors: *M. REUS-GARCIA[1], N. PERETZ-RIVLIN[2], G. ATLAN[2], A. CITRI[2], A. GRUART[1], J. DELGADO-GARCIA[1];
[1]Div. of Neurosci., Pablo de Olavide Univ., Seville, Spain; [2]The Hebrew Univ., Jerusalem, Israel

Abstract: The claustrum (CL) has been the subject of different theoretical studies addressing its putative role in integrative neural functions, including consciousness. Anatomical studies have revealed that the CL is a sheet-like neural structure located between the putamen and the insular cortex. CL neurons are originated from the insula. The CL sends projections and receive afferents from all cortical regions. Although it is assumed that CL neurons could be involved in cognitive processes and in the integration of different sensory-motor modalities, CL functions studied in alert behaving animals remain unknown. In a previous work, it was shown that associative learning modifies the activity of CL neurons. Here, we have recorded in behaving rabbits claustral single units during the acquisition of a classical eyeblink conditioning task. For conditioning, we used a delay paradigm: a tone as conditioned stimulus (CS) followed by an air puff as unconditioned stimulus (US) that co-terminated with it. Conditioned (CRs) and unconditioned (URs) responses were determined from the rectified electromyographic (rEMG) activity of the orbicularis oculi muscle. Neurons were recorded across habituation and conditioning sessions using 16 channels proves with the aim of reaching the whole length of the CL. Recorded cells were identified by their synaptic and/or antidromic activation from medial prefrontal (mPFC) or motor (M1C) cortices of both sides. Preliminary results obtained using the software Kilosort showed that CL neurons were activated during sessions of paired CS-US presentations in early stages of the learning task. In contrast, CL neurons decreased their firing rates during the last conditioning sessions, i.e., when CRs reached asymptotic values.

Disclosures: M. Reus-Garcia: None. **N. Peretz-Rivlin:** None. **G. Atlan:** None. **A. Citri:** None. **A. Gruart:** None. **J. Delgado-Garcia:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.19/K36

Topic: D.09. Multisensory Integration

Support: NIH Grant P20GM10340

Title: Atypical afferents of the thalamic reticular nucleus

Authors: *B. D. RICHARDSON[1,2], E. J. HANSEN[1];
[1]WWAMI Med. Educ., [2]Biol. Engin., Univ. of Idaho, Moscow, ID

Abstract: Accurate coding and filtering of sensory information depends on the sensory thalamocortical circuit where the thalamic reticular nucleus influences thalamocortical neuron coding and activity. However, an understanding of afferents that may be regulating the thalamic reticular nucleus is incomplete. Brain regions that integrate multi-modal sensory information to form internal predictions or determine emotional state may impact sensory thalamic neuron regulation of information flow to cortex. To identify potential atypical afferents to the thalamic reticular nucleus that may modulate their activity, a retrograde adeno-associated virus (AAVrg-Chronos-GFP) was injected into the thalamic reticular nucleus of male and female C57bl/6 mice. After 20 days of recovery, mice were euthanized and coronal tissue sections were immunohistochemically stained for GFP and markers for specific cell types. Using fluorescence microscopy, retrograde-labeled neurons that have been well established as presynaptic to thalamic reticular neurons were identified, including neurons in the sensory cortices and thalamus. In addition, anatomical data from these retrograde viral tract-tracing studies suggest that cerebellar nuclei and amygdala also directly project to the thalamic reticular nucleus. Specifically, neuronal cell bodies in the ventral dentate, dorsolateral interpositus, and basolateral amygdala expressed GFP following AAVrg injections into thalamic reticular nucleus. These connections between cerebellum/amygdala and thalamic reticular nucleus may be important conduits for the relay of multi-modal sensory information or emotional context in regulating selection of and attention to specific stimuli and their features. While there is clear anatomical evidence for these connections, the function of cerebellar and amygdala projections to thalamic reticular nucleus and subsequent influence on auditory thalamic neurons is widely unknown. These data provide a foundation for identifying the functional impact of cerebellar and/or amygdalar projections to the thalamic reticular nucleus in a mouse model. Efforts to further develop the anatomical distribution and identify the functional impact of afferent projections from cerebellar nuclei and basolateral amygdala are ongoing.

Disclosures: B.D. Richardson: None. **E.J. Hansen:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.20/K37

Topic: D.09. Multisensory Integration

Support: NIH Grant DE027844

Title: Multisensory integration related to dentition in the neocortex of the naked mole-rat (Heterocephalus glaber)

Authors: *N. J. M. HITE[1], J. NIE[2], D. K. SARKO[3];
[1]Physiol., [3]Dept. of Anat., [2]Southern Illinois University, Sch. of Med., Carbondale, IL

Abstract: Multisensory studies focused on (or simply including) dentition are nearly absent, despite the fact that multisensory integration is essential to critical daily functions such as chewing and speech that rely on dental and craniofacial structures. In the current study, we assessed how tactile inputs from the teeth are combined with inputs from additional sensory modalities in the naked mole-rat, a species with highly specialized and well-developed dentition. Single-unit, *in vivo* electrophysiological mapping of the neocortex was performed in anesthetized naked mole-rats. Electrophysiological recordings examined multisensory neuronal responses, particularly targeting border zones between modality-specific cortical areas based on previous studies in laboratory rats. This cortical mapping compared neuronal responses to single-modality (e.g., somatosensory) stimuli alone vs. neuronal responses to multisensory stimulus combinations (i.e., more than one sensory modality, such as somatosensory + auditory). We presented auditory (A), visual (V), and tactile (T) stimuli in the following combinations to study multisensory integration regarding tactile stimulation of the incisor: A, V, T, AV, AT, VT, AVT. We hypothesized that auditory and visual stimuli would modulate the dominant mechanoreceptive inputs from the naked mole-rat's well-innervated and specialized dentition. We expected that multisensory stimulus conditions would generate stronger neuronal responses (i.e., increased firing rates and shorter latencies to response) compared to responses to unisensory stimuli alone. Altogether, these studies provide insight into the neural substrates facilitating dental sensory perception, and the critical role that additional sensory modalities might play.

Disclosures: **N.J.M. Hite:** None. **J. Nie:** None. **D.K. Sarko:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

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Program #/Poster #: 578.21/K38

Topic: D.09. Multisensory Integration

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Klingenstein-Simons Fellowship to SPB

Title: *In vivo* recordings of opto-tagged S1-projecting claustrocortical neurons in a cross-modal detection task

Authors: *M. CHEVÉE, E. F. FINKEL, D. H. O'CONNOR, S. P. BROWN;
The Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: The claustrum, a, thin, elongated subcortical nucleus located between the cortex and the striatum, forms extensive reciprocal connections with cortex. Claustrocortical (ClaC) neurons have been proposed to suppress cortical responses to distracting stimuli by modulating the gain of specific target regions (Jackson et al. 2018, Atlan et al. 2018, Narikiyo et al. 2018), which suggests that the claustrum integrates top-down information with sensory signals. *In vivo* recordings have revealed sensory responses in claustrum neurons. However, both *in vivo* and *in vitro* studies provide little evidence for multisensory integration (Olson and Graybiel 1980, Sherk and LeVay 1981, Remedios et al. 2010, 2014, Kim et al. 2016). How top-down signals and sensory information interact to influence the activity of ClaC neurons is poorly understood.
To address this question, we hypothesized that ClaC neurons respond to sensory stimuli differently based on context and on the cortical region they target. We trained mice to perform a cross-modal detection task and recorded from ClaC neurons that specifically project to the whisker associated somatosensory cortex. Mice were presented with interleaved whisker and visual stimuli and were trained to respond to one modality while ignoring the other. The modality rewarded alternated in blocks of trials multiple times within an experimental session. This approach allowed us to observe the response of ClaC neurons to sensory stimuli in distinct contexts defined by the task rules, motor signals and reward.
We found that ClaC neurons were strongly modulated by the task. Responses lasted up to 3 seconds, spanning the sensory, motor and reward phases of a trial. The neurons integrated the rules, as responses were stronger for the rewarded modality than for the unrewarded modality. Furthermore, we found that the response triggered in a trial was suppressed during licking. These findings provide new insights into how sensorimotor signals are represented in claustrocortical circuits and how these patterns of activity may influence cortical sensory processing.

Disclosures: M. Chevée: None. **E.F. Finkel:** None. **D.H. O'Connor:** None. **S.P. Brown:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.22/K39

Topic: D.09. Multisensory Integration

Support: CIHR

Title: Multisensory responses in primary auditory cortex of the cat

Authors: *C. BOUCHER[1], X. BAO[1], Y. MERRIKHI[1], M. MEREDITH[2], S. G. LOMBER[1]; [1]Dept. of Physiol., McGill Univ., Montreal, QC, Canada; [2]Dept. of Anat. and Neurobio., Virginia Commonwealth Univ., Richmond, VA

Abstract: Core auditory cortex of the cat is comprised of primary auditory cortex (A1) and the anterior auditory field (AAF). Neurons in both fields respond strongly to acoustic stimuli and are tonotopically organized. In hearing animals, a small number of cells in AAF respond to tactile stimulation. Following early-onset hearing loss, a much larger proportion of neurons in AAF become responsive to tactile and/or visual stimulation, indicating that crossmodal sensory reorganization is robust in this core auditory area. Unfortunately, results from similar studies conducted in A1 of the cat are not as clear. In hearing cats, most studies do not show multisensory responses in A1 (Stewart & Starr, 1970; Rebillard et al., 1977; Kral et al., 2003). Furthermore, only one study has documented crossmodal plasticity in A1 following perinatal hearing loss (Rebillard et al., 1977), while others have not (Stewart & Starr, 1970; Kral et al., 2003). A methodological consideration of these studies involves the type of anesthetic used. In this study, hearing animals were lightly anesthetized with ketamine. We recorded audiovisual responses from A1 (i.e., unisensory auditory, unisensory visual, subthreshold multisensory or bimodal) and we examined the visual characteristics to which A1 maximally responds. Multisensory stimuli were developed by pairing a pure tone stimulus with a flash stimulus at various stimulus onset asynchronies, and the visual stimuli presented include gratings, flashes, dots, and checkerboards. A linear multielectrode array recorded multi-unit activity and local field potentials across cortical layers. Contrary to previous work using other anesthetics, we identified unisensory auditory, unisensory visual, bimodal, and subthreshold multisensory multi-unit activity in A1. We also found neurons where auditory-visual interactions either suppressed or enhanced neuronal activity. Additionally, visual stimulation can modulate the neural response to auditory inputs depending on the stimulus onset asynchrony. Taken together, it is possible to identify visually responsive neurons in A1 of the cat. These results will serve as baseline data for a future study, examining the degree to which this cortical area undergoes crossmodal plasticity following early-onset hearing loss.

Disclosures: C. Boucher: None. **X. Bao:** None. **Y. Merrikhi:** None. **M. Meredith:** None. **S.G. Lomber:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.23/K40

Topic: D.09. Multisensory Integration

Title: Cortico-cortical representation induced by conditioning in primary of auditory, visual, somatosensory cortices

Authors: *G. TASAKA[1], Y. IDE[1], M. TAKAHASHI[1], N. NAKAJIMA[2], T. AIHARA[3]; [1]Tamagawa Univ., Machida,Tokyo, Japan; [2]Tamagawa Univ., Machida, Japan; [3]Tamagawa Univ., Tokyo, Japan

Abstract: Recently, many studies for plastic changes of cortico-cortical network were reported. Some of them were induced by association of sensory information. Sensory cortices are defined by responses to physical stimuli in specific modalities. Recently, however, human neuroimaging studies have shown auditory cortex activation without sound. In our previous study, plastic changes induced a fear conditioning by pairing a pure tone with an electric foot-shock (US) were measured in the auditory cortex and somatosensory cortex of a guinea pig, using optical recording with voltage sensitive dye. As the result, auditory information could be retrieved on the basis of an electric foot-shock alone. It showed that somatosensory and auditory cortices were associatively activated by a single modality of sensory information. However, the association mechanism of cortical signals elicited with the conditioning is still unclear. In this study, to investigate the influence of conditioning on cortical activity, the second-order conditioning with three sensory stimuli (light, tone, foot-shock) was additionally performed to first order conditioning paradigm in previous study. On the first day, blood flow was monitored during the tone-shock or light-shock conditioning; as a result, conditioning responses was observed. On the second day, paring of light and tone was repeated so that conditional responses to both light and tone were observed after the conditioning. Next, three cortical activities, in auditory cortex (ACx), visual cortex (V1), and somatosensory cortex (S1, S2), for each sensory stimuli were simultaneously measured using the optical imaging with voltage sensitive dye. As a result, we found that each stimulus (light, sound, foot-shock) alone, through second-order conditioning, could activate three cortices in absence of the others stimuli. These results suggest that two different modalities could be retrieved across each sensory cortex by one modality of sensory information after the conditioning. It is considered as a formation mechanism of cortico-cortical representation for some information modalities.

Disclosures: G. Tasaka: None. **Y. Ide:** None. **M. Takahashi:** None. **N. Nakajima:** None. **T. Aihara:** None.

Poster

578. Multi-Sensory Integration

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 578.24/L1

Topic: D.09. Multisensory Integration

Support: DARPA HR00111990034

Title: Brain miniaturization: Comparisons of the neuroarchitectures of brains in the honey bee and stingless bees

Authors: *I. T. SINAKEVITCH, S. NIVERTY, N. CHAWLA, B. H. SMITH;
Arizona State Univ., Tempe, AZ

Abstract: *Apis mellifera* is a model insect for the study of olfactory and spatial learning. A honey bee must navigate and orient over large distances for feeding and reproduction, which is critical for survival. It has highly structured visual and olfactory neuropils that send input to an elaborate area of the brain called the 'mushroom body', which integrates different sensory modalities and is vital for learning and memory. The architecture of the honey bee mushroom body has been well established, and it consists of two cup-like calyces each composed of two identical halves. Calyces receive inputs related to olfactory, visual, mechanosensory and reward processing, and it is thought that the mushroom body is important for spatial learning. Stingless bees have the smallest brains but perform similar behavioral tasks as a honey bee. We have investigated the structural differences in the honey bee and stingless bees mushroom bodies. We used immunocytochemistry with a synaptic neuropil marker (anti-synapsin), a mushroom body marker, anti-DC0, and a nucleus marker DAPI to compare the olfactory neuropils in honey bee and stingless bees. Images were collected from sections under a confocal laser scanning microscope. Digitized images were analyzed using a 3D visualization software AMIRA to produce a 3D model of the antennal lobes and mushroom bodies. We found that the stingless bee mushroom body has a similar general structure as the honey bee: a large mushroom body with two cup-like calyces and medial and vertical lobes located in the protocerebrum. However we also found differences in the synaptic neuropilar structure in the calyx and lobe. The stingless bee has a less columnar structure in the area where pedunculus subdivides in the vertical and medial lobes. Specifically, the smallest stingless bees have two columns of Kenyon cell axons in each mushroom body. This ranges to three columns in the biggest stingless bees compared to six in the honey bee. The difference in the Kenyon cell composition in the columns might reflect a difference in the organization of visual and olfactory inputs in the calyx, and thus they reflect the spatial/olfactory integration of the mushroom body in these bees. The honey bee has a large collar (visual input) and smaller olfactory input. The stingless bee with three columns in pedunculus has more substantial lip (olfactory) volume in the calyx compared with the volume of the collar (visual). We speculate that the number of the columnar Kenyon cells are reduced in the smallest stingless bee, which also has a sizeable antennal lobe and relatively smaller compound eyes.

Disclosures: I.T. Sinakevitch: None. **S. Niverty:** None. **N. Chawla:** None. **B.H. Smith:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.01/L2

Topic: E.02. Cerebellum

Support: NIH 1R01MH093727

Title: Plasticity of ponto-cerebellar circuits generates a prospective error signal in climbing fibers

Authors: *S. OHMAE, J. F. MEDINA;
Dept. of Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Climbing fibers play the role of teachers during motor learning, by sending two types of error signals to the cerebellum: a retrospective error signal driven by sensory feedback after an unexpected event occurs, and a prospective error signal of unknown origin that provides the cerebellum with a prediction of the upcoming sensory event before it occurs. Here, we use eyeblink conditioning in mice to demonstrate that the prospective signal of climbing fibers has a motor-related component (motor-CF), which is causally linked to the predictive defensive action generated by the mouse in anticipation of an aversive airpuff stimulus to the eye. Furthermore, we used simultaneous recording and targeted electrical and optogenetic stimulation to identify a ponto-cerebellar pathway that is sufficient and necessary for generating the prospective motor-CF signal. Altogether, our results reveal a hardwired recurrent circuit that allows the cerebellum to activate its own climbing fiber input and essentially become its own teacher.

Disclosures: S. Ohmae: None. **J.F. Medina:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.02/L3

Topic: E.02. Cerebellum

Support: NIH 1R01MH093727

Title: The cerebellum and prefrontal cortex cooperate to perform a cognitive timing task in mice

Authors: *G. J. WOJACZYNSKI, J. J. SIEGEL, J. F. MEDINA;
Dept. of Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Decades of research have firmly established the cerebellum as critical for associating external stimuli with adaptive motor responses, i.e. sensorimotor adaptation. Whether the cerebellum plays a similar role for cognitively driven motor behavior is currently unknown. In a novel task, we trained mice to produce an adaptive motor response to an internally generated representation of an omitted stimulus within a sequence. Here, we demonstrate through recording and optogenetic experiments that the medial prefrontal cortex encodes a cognitive signal representing the omitted stimulus, while the cerebellum mediates the adaptive motor response. Our results reveal a functional link between the prefrontal cortex and cerebellum during cognitively driven behavior, providing the foundation for further research into understanding how this link may be impaired in a variety of neurological and neuropsychiatric disorders.

Disclosures: G.J. Wojaczynski: None. **J.J. Siegel:** None. **J.F. Medina:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.03/L4

Topic: E.02. Cerebellum

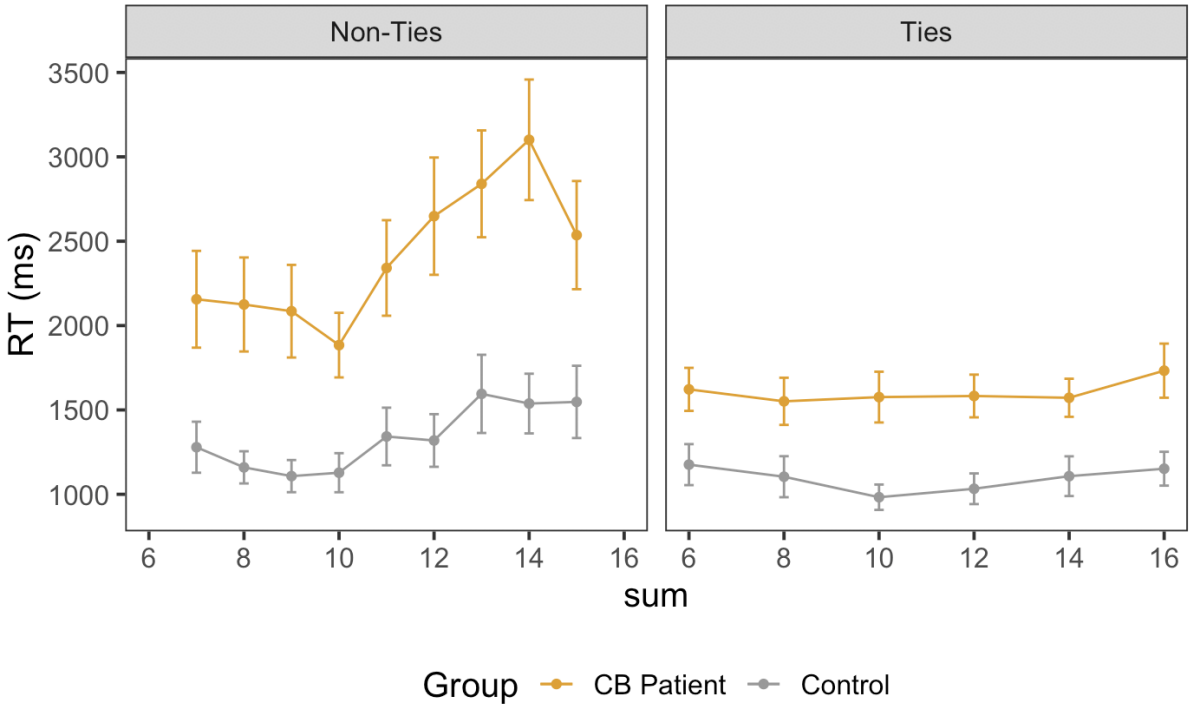
Support: NS092079
2018 Florence P. Kendall Scholarship from the Foundation for Physical Therapy Research

Title: Evidence that the cerebellum coordinates movement on the mental number line

Authors: *J. S. TSAY, M. KING, S. D. MCDOUGLE, R. IVRY;
Psychology, Univ. of California Berkeley, Berkeley, CA

Abstract: Neuropsychological and neuroimaging studies point to the involvement of the cerebellum in working memory tasks, although the nature of this contribution is poorly understood. McDougle et al., (in preparation) recently tested individuals with spinocerebellar atrophy (SCA) on two tasks that tap into working memory, mental rotation and memory search, with the SCA group only impaired on the former. They hypothesized that mental rotation involves the manipulation of a mental representation in a continuous manner, whereas memory search requires a sequential operation applied to distinct representations. To test this hypothesis in a new context, we compared SCA (n = 15) and control (n= 13) participants on an arithmetic task requiring the verification (true or false) of single-digit addition problems (e.g., 7 + 5 = 13). For problems such as these, RT becomes longer as the magnitude of the sum increases. This has

been attributed to the time required to traverse a mental number-line. In contrast, the RT function is relatively flat for addition problems involving the same number, or what are called “ties” (e.g., 4 + 4 = 9), presumably because the answer to these problems can be retrieved from an over-learned look-up table. The RT data for the SCA group showed a larger slope on the non-ties compared to the control group, but no slope difference was observed between the groups on the ties. These results provide further evidence that the cerebellum is recruited for “cognitive” tasks that required the continuous manipulation of a representation, perhaps reflecting an embodied form of internal simulation and a generalization of a functional role for this structure in coordinating movements.



Disclosures: **J.S. Tsay:** None. **M. King:** None. **S.D. McDougle:** None. **R. Ivry:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.04/L5

Topic: E.02. Cerebellum

Support: NSERC

Title: Cerebellar modulation of attention to distractor stimuli in a sensory conflict task: A transcranial magnetic stimulation study

Authors: *D. R. ANDREW, M. S. ADAMS, S. R. MUIR, W. R. STAINES;
Kinesiology, Univ. of Waterloo, Waterloo, ON, Canada

Abstract: Although the cerebellum has long been considered a motor structure, emerging evidence has highlighted the role of the cerebellum in higher order functions. Coordination of movement and cognition within multisensory environments requires the ability to orient ourselves to relevant stimuli, which is often described as attention. Studies have identified changes in connectivity in prefrontal and associative cortices, implicated in diverse attentional networks, following non-invasive stimulation of hypothesized attentional nodes within the right cerebellar hemisphere, although its specific modulatory role is not well discerned. This study sought to further specify the cerebellum's role in attention by assessing changes to the processing of sensory conflict following its transient inhibition. It was hypothesized that following transient inhibition of the cerebellum using continuous theta burst stimulation (cTBS), participants' ability to ignore a distractor stimulus would be attenuated; resulting in larger event related potentials (ERPs) in response to distractors and decreased accuracy on the task. Participants made a graded motor response to the amplitude of visual or tactile stimuli that were presented either individually or simultaneously and varied in amplitude. Attention was altered by having participants respond only to tactile or visual stimuli as instructed, prior to the start of each block; resulting in conditions in which participants received a relevant, an irrelevant, or a relevant stimulus with a distractor in the other modality. Somatosensory ERPs and performance were measured using electroencephalography (EEG) and grading accuracy respectively. These measures were collected pre and post cTBS to the right (Group 1) and left lateral (Group 2) cerebellum (centre of coil placed 1 cm below and 3 cm to the right or left of the inion). Results demonstrate that the somatosensory N70 decreased in response to unattended tactile stimuli versus when they were attended to. Prior to cTBS, the presence of a visual distractor during a tactile attended block demonstrated a smaller N70. Post right-cTBS, the presence of a distractor resulted in an increased N70 amplitude, suggesting an affected ability to ignore a distractor. Behavioural data demonstrates that after cTBS, grading of both visual and tactile stimuli is less accurate. These changes are not as pronounced for the left-cTBS group, suggesting that there is a localized attention node within the cerebellum. Understanding the cerebellum's role in these processes is critical as it may prove to be a clinically significant target for the treatment of the symptoms observed in behavioural disorders.

Disclosures: D.R. Andrew: None. **M.S. Adams:** None. **S.R. Muir:** None. **W.R. Staines:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.05/L6

Topic: E.02. Cerebellum

Support: HIAS17001 (GJB)

Title: The cerebellar dentate nucleus in autism: Are neurons and their perineuronal nets preserved despite missing purkinje cells?

Authors: *C. BRANDENBURG[1], B. WHITE[2], C. ENSOR[2], G. J. BLATT[1];
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Abstract: Purkinje cell (PC) dysfunction is the most consistent neuropathological finding in autism, with as many as 75% of cases showing reduced numbers. Human postmortem studies have also reported differences in PC size and gene expression in the autism brain. The lateral hemisphere displays the greatest PC decrease reported. However, the dentate nucleus (DN), which normally receives projections from the lateral hemisphere, did not seem to be affected in preliminary studies of total neuron numbers in autism, although very few postmortem cases have been analyzed. The DN harbors the greatest percentage of neurons in the brain surrounded by a perineuronal net (PNN). Genes involved in PNN formation and function have been implicated in autism. Given the known PC reductions in autism, we aimed to determine whether there are further deficits in neuronal numbers within the cerebellar circuitry, as DN neurons are likely to be impacted by PC deficits. PNNs around the DN neurons were also quantified and western blots for expression are underway. Immunohistochemistry was performed on human postmortem brain tissue from 19 control and 18 autism cases. From each case, five 40µm sections at every sixth interval through the DN were immunostained with nickel DAB anti-HPLN1, a link protein in the PNN. Neutral red was used as a counterstain to identify all neurons. A Zeiss Microbrightfield Stereoinvestigator system was used to quantify neuronal densities within the DN contour. Neurons falling within the software's dissector were quantified then divided by the total area counted. The density of neurons with PNNs, based on HPLN1 expression, was not different between control (mean= 1,682.27±417.51) and autism (mean= 1,658.57±228.93 neurons/mm^3). The density of neurons without a PNN also showed no differences (control mean= 1,487.74±386.44 and autism mean= 1,462.14±384.31 neurons/mm^3) and therefore total neuron numbers were similar (control mean= 3,170.01±632.64 and autism mean= 3,120.71±520.12 neurons/mm^3). Despite reports of significant reductions in the number of PCs in the lateral hemisphere of the cerebellum, similar reductions are not evident in the DN. Thus the targets of PC output within the DN appear to be preserved by the remaining PCs and inferior olive input. Furthermore, the proportion of neurons surrounded by PNNs compared to those without appear

to be unaltered. Further work is underway to determine whether activity-dependent components of the PNN, such as aggrecan, are affected while total PNN numbers remain unchanged.

Disclosures: C. Brandenburg: None. **B. White:** None. **C. Ensor:** None. **G.J. Blatt:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.06/L7

Topic: E.02. Cerebellum

Title: The influence of cerebellar transcranial direct current stimulation applied over multiple days on motor learning in an overhand throwing task

Authors: *L. LIMA DE ALBUQUERQUE, D. LIDSTONE, M. PANTOVIC, I. MUNOZ, M. K. ZUROWSKI, E. W. WILKINS, J. S. DUFEK, B. J. POSTON;
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Abstract: Cerebellar transcranial direct current stimulation (c-tDCS) has been shown to enhance motor skill and motor learning in relatively simple motor tasks involving the hand and arm. However, it is unknown if c-tDCS can enhance motor performance in complex, multi-joint tasks that involve coordination of the whole body. The purpose was to examine the influence of c-tDCS applied over multiple days on motor learning in an overhand throwing task. The study was a randomized, SHAM-controlled, between-subjects, double-blind experimental design. A total of 21 young adults (12 males, 9 females) were allocated to either a c-tDCS group or a SHAM group. Each subject completed three experimental sessions on consecutive days at the same time each day. In each session, subjects practiced overhand throwing trials to a small target located on a wall 6 meters away. A total of 7 trial blocks (10 trials per block) were performed each day and consisted of a baseline-test block, 5 practice blocks, and a post-test block. Anodal c-tDCS was applied to the cerebellum ipsilateral to the right hand during the practice blocks for 20 minutes. c-tDCS was delivered using previously determined effective parameters (current strength: 2 mA; anode: 3 cm right of the inion; cathode: right buccinator muscle) with a NeuroConn Stimulator that was placed in a small, tight-fitting backpack which did not restrict performance. Motor performance was quantified as the endpoint error (absolute distance of the ball's final endpoint relative to the target center). Endpoint error declined with practice for both groups over the 3 days. However, there were no significant interactions (all p values > 0.2). Thus, there were no significant differences for endpoint error between the 2 groups. These preliminary findings indicate that the application of c-tDCS during practice over 3 consecutive days does not improve motor learning in a complex overhand throwing task in young adults.

Disclosures: **L. Lima De Albuquerque:** None. **D. Lidstone:** None. **M. Pantovic:** None. **I. Munoz:** None. **M.K. Zurowski:** None. **E.W. Wilkins:** None. **J.S. Dufek:** None. **B.J. Poston:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.07/L8

Topic: E.02. Cerebellum

Title: Cerebellar high gamma activation during performance of a reaching task in MEG

Authors: F. W. CARVER[1], L. SEPE-FORREST[1], R. QUENTIN[2], T. HOLROYD[1], *R. COPPOLA[1], A. C. NUGENT[1];
[1]NIMH, Bethesda, MD; [2]NINDS, Bethesda, MD

Abstract: High-frequency electrophysiological activity is known to arise from cerebellar cortex during performance of sensorimotor tasks. However, observation of cerebellar activation at high frequencies is rare in non-invasive recordings with human subjects. Recently we have shown the ability to resolve task-dependent changes in high gamma power from the cerebral cortex using magnetoencephalography (MEG). In the current investigation, we seek to determine if high gamma can also be recorded from the cerebellar cortex with MEG. To do so, we employed a center-out reaching task known to elicit cerebellar high gamma activity in animal research. Ten right-handed healthy volunteers participated in the study in which they were asked to center a circular cursor using a joystick and then quickly reach for a target presented randomly at one of eight locations equidistant from the center. Subjects had to reach the target within 1.5 seconds during 80 trials. Linearly constrained minimum variance beamformers were used to localize neuromagnetic sources during the reach portion of successful trials. We calculated whole brain contrasts of power between reach and rest in a high-gamma frequency band (65-115Hz). Group T-tests of the resulting brain volumes revealed significant increases in high-gamma during reaching ($p<.001$, $q<.05$) in two connected clusters - one in the bilateral posterior cerebral cortex, and the other in the right lateral cerebellum. The cerebral cluster was centered on the bilateral superior parietal lobules and neighboring areas, with the majority of voxels in the precuneus. The cerebellar cluster was in the right lateral posterior lobe, with most voxels in lobules VI and VII. Both precuneus and lateral posterior cerebellum are expected to be active during a visuomotor task. What's unique here is the observation of high gamma activation in these regions with MEG. In the cerebral cortex the form and function of high-frequency activity is still under debate, although there is evidence that it is not oscillatory in nature, but instead results from asynchronous spiking in local cortical networks. There is more evidence of oscillatory activity at high frequencies in the cerebellum, but more research is needed to understand the exact

mechanisms involved. Our demonstration that high gamma can be recorded from cerebral and cerebellar cortices non-invasively with MEG opens up new avenues for investigating this activity in humans.

Disclosures: F.W. Carver: None. **L. Sepe-Forrest:** None. **R. Quentin:** None. **T. Holroyd:** None. **R. Coppola:** None. **A.C. Nugent:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.08/L9

Topic: E.02. Cerebellum

Support: JSPS KAKENHI Grant Number JP18K06524

Title: Neural connections between oculomotor neural integrators and vestibulo-cerebellum

Authors: T. SUGIMURA, *Y. SAITO;
Nara Med. Univ., Kashihara, Japan

Abstract: Gaze holding is primarily controlled by the oculomotor neural integrators, which are separated into the prepositus hypoglossi nucleus (PHN) for horizontal gaze and the interstitial nucleus of Cajal (INC) for vertical gaze. Although it has been argued that the neural connections from the integrators to the vestibulo-cerebellar cortex are significant in gaze holding, the properties of the integrator neurons that project to the cortex have not been well defined. In the present study, we examined the proportion of cholinergic PHN and INC neurons that were retrogradely labeled by injecting a dextran-conjugated Alexa 488 tracer into the cerebellar flocculus (FL) or uvula/nodulus (UN) using choline acetyltransferase (ChAT)-tdTomato transgenic rats, in which cholinergic neurons exhibit tdTomato fluorescence. When the tracer was injected into the FL unilaterally or the center of the UN, the retrogradely labeled neurons were observed in the PHN but not in the INC. The proportion of cholinergic PHN neurons that projected to the UN (21.7 ± 0.8 % in 6 rats) was significantly larger than the proportion of the neurons that projected to the FL (9.1 ± 1.5 % in 6 rats, $p < 0.0001$). The proportion of cholinergic PHN neurons that projected to the UN differed depending on the caudal (9.1 ± 1.3%), intermediate (23.3 ± 2.1%) and rostral (32.6 ± 2.0%) regions of PHN. To examine PHN neurons projecting to other cerebellar cortices than vestibulo-cerebellum, we injected the tracer into the anterior vermis [spino-cerebellar (SC) cortex] and the posterior hemisphere [cerebro-cerebellar (CC) cortex]. The proportions of cholinergic PHN neurons projecting to the SC and CC cortices were 23.3 ± 2.7 % and 19.1 ± 1.9 %, respectively, which were comparable to that of cholinergic PHN neurons projecting to the UN. INC neurons projecting to the SC and CC cortices were not found. These results suggest that the neural connections to the cerebellum from the oculomotor

neural integrator are limited to the PHN. In addition, cholinergic neurons that project to the FL are fewer than the neurons that project to the UN, SC, and CC cortices.

Disclosures: **Y. Saito:** None. **T. Sugimura:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.09/L10

Topic: E.02. Cerebellum

Support: NIH R01 NS092623
NIH F32 NS103216

Title: Spike sorting for multichannel recordings in floccular complex of the primate cerebellum

Authors: ***N. J. HALL**, D. J. HERZFELD, S. G. LISBERGER;
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Abstract: Multichannel, multi-neuron recordings in the cerebellar flocculus exacerbate two central problems of spike sorting. 1) Nearby neurons may exhibit firing rates that are very different from one another, resulting in asymmetric cluster densities. 2) Many neurons have extremely high firing rates: for example, Purkinje cells frequently have baseline firing rates > 80 Hz. High firing rates cause a very large number of spike overlaps, both within single channels and across multiple channels in the recorded voltage traces. Overlap can cause false separation of spikes within a single unit. We attacked these problems with a “divide and conquer” approach by modifying and combining two existing spike sorting methods. First, we find and cluster individual spike waveforms using the iso-cut method described by Chung et al. 2017. Iso-cut finds a non-parametric minimum density point in high dimensional space over the combined distribution of two clusters. If this density is sufficiently deviant from the expectation of a unimodal distribution, the two clusters are separated; otherwise they are combined. We included modifications that increase the ability of iso-cut to separate clusters that have a very different number of spikes. Second, we identify overlapping spike waveforms that may have been missed using the binary pursuit strategy introduced by Pillow et al. 2013. Binary pursuit involves minimizing the residuals of the fit between all known spike waveforms and the raw voltage recording that is being sorted. At every point in the voltage trace, a spike’s waveform is iteratively subtracted if the subtraction reduces the residual voltage. Third, we use all discovered waveform shapes and spike times to produce a set of adjusted spike clips - snippets of the voltage trace centered on a given spike time that have all other known spikes removed. These adjusted clips are then passed through the iso-cut algorithm anew for final spike clustering. Finally, we consolidate spikes across channels into single units and discard noise clusters. These

four steps typically result in ~99% spike detection and 96-99% correct sorting in simulated datasets with high firing rates. It resolves multichannel recordings of the spikes of neighboring Purkinje cells, which can include overlaps of greater than 10% of spikes even within a small, ~2 ms time window.

Disclosures: **N.J. Hall:** None. **D.J. Herzfeld:** None. **S.G. Lisberger:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.10/L11

Topic: E.02. Cerebellum

Support: Weinberg College of Arts and Sciences Summer Research Grant
NIH R37-NS39395

Title: Responses of mouse cerebellar Purkinje cells to omissions in regular trains of sensory stimuli

Authors: *G. W. ZEMPOLICH, S. T. BROWN, I. M. RAMAN;
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Abstract: The perception of time in the brain is likely to emerge from computations in neuronal circuits. The cerebellum, a major sensorimotor integrating region, is a good candidate to encode aspects of temporal perception, as it orchestrates movements with precise timing and allows animals to adapt to stimuli at specific intervals. Because the cerebellum appears specialized to detect sub-second intervals (200-1000 ms), we tested whether neurons in the cerebellum may in fact "count", similar to a metronome. Extracellular recordings were made from Purkinje cells in crus I/II of the cerebellum in ketamine-xylazine anesthetized and awake head-fixed mice. Mice were stimulated by 2-Hz trains of stimuli consisting of either a 50-psi, 10-ms air puff to the ipsilateral whisker pad (tactile) or an 80-dB, 60-ms whistle (auditory). The 26th stimulus of each train was omitted, and the trains with the omission were applied 40 times. Simple and complex spike firing rates from Purkinje neurons were analyzed to assess their responses to the stimuli in the train and to the 26th omission. The results demonstrate that different Purkinje cell responses in anesthetized mice could be categorized based upon the simple spike pattern evoked by each stimulus. In anesthetized mice, no cells responded to whistles, but all cells responded to air puffs, displaying either a suppression of firing, an elevation of firing, an elevation preceding a suppression phase, or multiple periods of suppression. In awake mice, cells responded with firing rate increases to both tactile and auditory stimuli. In both anesthetized and awake mice, cells fired complex spikes to tactile stimuli with high probability, but none fired to omitted stimuli, suggesting that complex spikes were linked to the sensory stimulus rather than the "error" of a

missed stimulus. While local field potentials and/or simple spikes in some cells showed a well-timed response just preceding the omitted air puff in anesthetized recordings, these omission-related responses were undetectable in awake mice. The results suggest that under some circumstances, cerebellar neurons may count on a sub-second time scale in that they can respond to violations in periodicity, but that arousal masks or alters these responses.

Disclosures: G.W. Zempolich: None. **S.T. Brown:** None. **I.M. Raman:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.11/L12

Topic: E.02. Cerebellum

Support: NIH grants NS041021
Mathers Foundation
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JSPS KAKENHI Grant-in-Aid for Young Scientists 17H04981

Title: Sensory experience remodels genome architecture in a neural circuit to drive motor learning

Authors: *P. VALNEGRI[1,2], T. YAMADA[3], Y. YANG[1,2], A. BONNI[2];
[1]Neurobio., Northwestern Univ., Evanston, IL; [2]Neurosci., Washington Univ. Sch. of Med., St Louis, MO; [3]Univ. of Tsukuba, Tsukuba, Japan

Abstract: Neuronal activity-dependent transcription couples sensory experience to adaptive responses of the brain including learning and memory. Mechanisms of activity-dependent gene expression including alterations of the epigenome have been characterized. However, the fundamental question of whether and how sensory experience remodels chromatin architecture in the adult brain *in vivo* to induce neural code transformations and learning and memory remains to be addressed. Here, *in vivo* calcium imaging, optogenetics, and pharmacological approaches reveal that granule neuron activation in the anterior dorsal cerebellar vermis (ADCV) plays a crucial role in a novel delay tactile startle learning paradigm in mice. Strikingly, using large-scale transcriptome and chromatin profiling, we have discovered that activation of the motor learning-linked granule neuron circuit reorganizes neuronal chromatin including through long-distance enhancer-promoter and transcriptionally active compartment interactions to orchestrate distinct granule neuron gene expression modules. Conditional CRISPR knockout of the chromatin architecture regulator Cohesin in ADCV granule neurons in adult mice disrupts enhancer-promoter interactions, activity-dependent transcription, and motor learning. These

findings define how sensory experience patterns chromatin architecture and neural circuit coding in the brain to drive motor learning.

Disclosures: P. Valnegri: None. **T. Yamada:** None. **Y. Yang:** None. **A. Bonni:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.12/L13

Topic: E.02. Cerebellum

Support: ERC Starting Grant 640093
FCT PTDC/MED-NEU/30890/2017

Title: Cerebellar output pathways for spatial and temporal locomotor calibration

Authors: D. M. DARMOHRAY[1], M. R. MACIEL[3], J. JACOBS[3], *M. R. CAREY[2];
[1]Champalimaud Ctr. For the Unknown, Lisboa, Portugal; [2]Champalimaud Ctr. For the Unknown, Lisbon, Portugal; [3]Champalimaud Fndn., Lisboa, Portugal

Abstract: Locomotor adaptation on a split-belt treadmill is a highly conserved form of motor learning in which externally-imposed gait asymmetries are reduced through recalibration of interlimb coordination. This form of learning requires the interposed cerebellar nucleus and has distinct spatial and temporal components that are adapted at different rates and are differentially lateralized in the cerebellum. Here, we investigate whether distinct cerebellar efferent pathways mediate learning in space and time. Axonal tracing from the cerebellar nuclei reveals many candidate premotor nuclei in the midbrain and brainstem that could underlie this form of learning. Dual color retrograde tracing from these premotor areas further demonstrates that interposed neurons projecting to specific downstream sites are spatially segregated and partially distinct. Finally, genetic manipulations of neural activity in specific cerebellar output pathways have differential effects on spatial and temporal learning, suggesting that these components of adaptation involve distinct neural circuits.

Disclosures: D.M. Darmohray: None. **M.R. Maciel:** None. **J. Jacobs:** None. **M.R. Carey:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.13/L14

Topic: E.02. Cerebellum

Support: Wenner Gren Foundation (Frant No. 9209)
NSF GRFP 1839287

Title: Selective modular expansion of the cortico-cerebellar system explains variation in brain size among primates and humans

Authors: *J. SMAERS, D. VANIER;
Stony Brook Univ., Stony Brook, NY

Abstract: Ascertaining to what degree the brains of model species are representative of human brains is crucial to neuroscientists. This is particularly true with regard to primate species, whose evolution is typified by extensive variation in brain size. An enduring question in this context is whether certain brain regions can be identified that vary in size more than others, and whether such highly variable regions explain variation in brain size across primates. We investigate the tempo and mode of evolution of brain organization using the largest combination of brain regions analyzed to date (36 brain regions representing over 90% of the brain, across 17 primate species, including humans). Results indicate that the constituent brain regions of the cortico-cerebellar system show the highest rates of evolution, demonstrate a modular pattern of evolution, and closely align with changes in overall brain size. These results indicate that primate brain evolution is primarily characterized by a conserved evolutionary trajectory towards an expansion of the cortico-cerebellar system. This suggests that a stable genetic and developmental structure underpins primate and human brain evolution. Our results thereby have important implications not only for the suitability of primates as models for humans, but for understanding the nature of primate and human cognition.

Disclosures: J. Smaers: None. **D. Vanier:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.14/L15

Topic: E.02. Cerebellum

Support: Mexico-PROMEP 103.5/10/7324

Title: Focal adhesion proteins and Calpain are involved in the reorganization of the actin cytoskeleton of Bergmann fibers

Authors: Y. BASTIAN[1], ***J. A. MENDEZ**[2];
[1]Unidad de Investigación Biomédica IMSS-Zacatecas, IMSS, Zacatecas, Mexico; [2]Inst. of Physics, Biophysics, Univ. Autonoma De San Luis Potosi, San Luis Potosí, Mexico

Abstract: In the cerebellum, the lamellar processes of Bergmann glia cells (BGC) interact very closely with the incoming synapses of Purkinje cells. Disturbance of BGCs AMPA receptors (AMPAr) induces the retraction of the lamellar processes and impairs the fine motor coordination of mice. Recent evidence shows that activation of AMPAr in BGC leads to the reorganization of the actin cytoskeleton through two processes: changes in the intensity of F-actin staining of Bergmann fibers and changes in the number of Bergmann fibers stained. Whereas the first process depends on the activation of RhoA in a signal pathway involving PI3-K, FAK and PKC, the second process depends on external calcium in a Rho-independent manner. Using F-actin staining as well as immunoprecipitation assays together with western blots, we found in coronal cerebelar slices that the change in the number of Bergmann fibers stained with fluorescent-Phalloidin is prevented by the inhibition of Calpain with both calpeptin and ALLN. We also found that in response to AMPAr activation, Spectrin and Actinin, proteins of the focal adhesion complex, are cleaved. Furthermore, cleavage of Spectrin and Actinin is prevented by the treatment with Calpain inhibitors and chelators of calcium. Our results suggest that remodeling of proteins of the focal adhesion in response to calcium influx is required for the reorganization of the actin cytoskeleton in BGC.

Disclosures: Y. Bastian: None. **J.A. Mendez:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.15/L16

Topic: E.02. Cerebellum

Support: NS041234

Title: Dopaminergic modulation of cerebellar UBCs

Authors: *E. CANTON, V. DUMRONGPRECHACHAN, Y. KOZOROVITSKIY;
Northwestern Univ., Evanston, IL

Abstract: The cerebellum is influenced by a wide range of neuromodulatory circuits. These circuits are likely to mediate significant effects on activity and plasticity within the cerebellum, thereby modulating motor control. Our previous work has focused on characterizing the functional expression of Drd1R (Dopamine receptor type 1) within lobules IX (Uvula) and X (Nodulus) of the cerebellar vermis, in transgenic Drd1a-Cre; Ai14 mouse line we find expression in unipolar brush cells, an excitatory granular layer interneuron. Using *ex vivo* electrophysiological recordings we have found that selective pharmacological activation of Drd1Rs leads to an increase in tonic firing rates and increases in NMDAR mediated excitatory inputs. We hypothesize that the source of dopamine onto UBCs are nodular purkinje cells which are known to express Tyrosine Hydroxylase. Purkinje cells are classically known to send their main projections to the cerebellar nuclei, recent work has shown Purkinje cells within lobules IX (Uvula) and X (Nodulus) in the vermis also make monosynaptic inhibitory connections with nearby Golgi and granule cells. By selectively expressing ChR2 in Purkinje cells we can evoke short latency inhibitory postsynaptic currents (IPSC) in UBCs. Cre dependent transynaptic retrograde modified rabies virus infection shows that nodular Purkinje cells send direct projections to UBCs. Future work will use a combination of optogenetic activation with dopamine sensor Dlight1.1 as well as fast scan cyclic voltammetry (FSCV) to directly find the source of dopamine on UBCs.

Disclosures: E. Canton: None. **V. Dumrongprechachan:** None. **Y. Kozorovitskiy:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

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Topic: E.02. Cerebellum

Support: NIH (5-R01-NS078311)
Office of Naval Research (N00014-15-1-2312)
National Science Foundation (CNS- 1714623)

Title: Training of marmoset monkey for head-fixed electrophysiological recordings from the cerebellum

Authors: *P. HAGE[1], E. SEDAGHAT-NEJAD[3], K. KARBASI[2], T. PALIN[4], R. SHADMEHR[5];
[1]Biomed. Engin., [2]Johns Hopkins Sch. of Med., Baltimore, MD; [4]Biomed. Engin., [3]Johns Hopkins Univ., Baltimore, MD; [5]Dept Biomed. Eng, Johns Hopkins Univ. Dept. of Biomed. Engin., Baltimore, MD

Abstract: The New Age Callithrix Jacchus, the common marmoset monkey, is a promising new animal model due to the species' socially-oriented behavior and potential for breeding transgenic generations. However, to date there have been little published work on behavioral training in the head-fixed protocol. Indeed, there is some doubt as to whether the animals can be trained to produce robust goal-directed behavior over hundreds or thousands of trials. Here, we report our results of a year-long protocol to train one animal to consistently achieve over 1000 successful reward-driven trials, while recording with high density electrodes from multiple simultaneously isolated Purkinje cells from the lobules 6 and 7 of the midline cerebellum. Our head-fixed procedure included use of CT imaging, computer aided design (CAD), and 3D printing of a titanium headpost. We then used an MRI to map the targeted cerebellar recording region and designed an electrode alignment apparatus for daily acute recording. Following surgery, we implemented a protocol for safely food restricting the monkey and then used the head-fixed protocol as the only means for feeding the animal. We present data from the system's implementation with 1 adult female marmoset monkey (4 years old), consisting of simple and complex spike recordings acquired from multiple simultaneously recorded Purkinje cells in lobules 7CbA(a), 6Cb(a-c), and 6Cb(e). Additionally, we demonstrate the efficacy and safety of the food-restricted behavioral training protocol, supported by a healthy maintenance of the monkey's weight paired with performance capabilities of up to 1500 successful trials per session. While acute and semi-chronic systems have recently been developed for targeted recording of locations in the cerebral cortex, the brain stem, and a variety of deep brain structures, our work allows for high resolution targeting of specific lobules of the cerebellum during eye movement tasks. Additionally, there exists no literature that establishes a safe and effective food-restricted behavioral training protocol that demonstrates the maintenance of health and promising task performance, as shown in this work. Our system and training methodologies provide useful tools to conduct a wide range of cerebellar neurophysiological studies, as well as a general system development pipeline which could be customized and implemented for the study of other neural processes.

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Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

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Program #/Poster #: 579.17/L18

Topic: E.02. Cerebellum

Title: Cerebellar and cerebral cortical responses to transcranial alternating current stimulation using an *in vivo* approach

Authors: *R. A. HEFFNER, R. DAVIS, F. ANDERSON, T. COFER, H. LU;
Philadelphia Col. of Osteo. Med. GA, Suwanee, GA

Abstract: Recent studies have suggested that transcranial electric stimulation could potentially be an effective therapy for cerebellar movement disorders. Our previous studies have explored the effects of anodal and cathodal transcranial direct current stimulation on cerebellar and cerebral cortices. The effect of transcranial alternating current stimulation (tACS) is included in this study to better our understanding of transcranial electrical stimulation. Local field potentials (LFPs) of the cerebellar and cerebral cortices were recorded with tACS (200 μA, 20 Hz). Power spectrum analysis was used to investigate cerebellar cortical activity in response to tACS. The results of the power spectrum analysis revealed that tACS decreases the peak amplitude at low-frequency (2 Hz) while the motor cortex remains unchanged. This decrease was observed in 8/10 recordings. In order to study the response of individual PCs to tACS, we successfully isolated 9 PCs from the cerebellar cortex. Six of these cells demonstrated a decrease in the average firing rate between pre- and post-stimulation (11.6 Hz), while 3 cells demonstrated a slight increase (1.6 Hz). The cross correlation level between cerebellum and cerebral LFPs demonstrated an increase in 4/8 recordings (0.02-0.045). Two of the recordings showed an decrease (0.005-0.02) and 2 recordings were unchanged. Nine recordings showed coherence between the two brain regions at 10 Hz, 5/9 displayed either an increase or decrease. Eight out of 9 recordings showed additional coherence from 85 to 95 Hz. This coherence change and it's meaning at high frequency will be further investigated.

Disclosures: R.A. Heffner: None. **R. Davis:** None. **F. Anderson:** None. **T. Cofer:** None. **H. Lu:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.18/L19

Topic: E.02. Cerebellum

Support: KAKENHI 18K06529

Title: Convergence of sensory-evoked signals via multiple pathways in the cerebellum

Authors: *T. ISHIKAWA[1], I. SUGIHARA[2], M. SHIMUTA[1];
[1]Dept Pharmacol, Jikei Univ. Sch. of Med., Tokyo, Japan; [2]Neurophysiol., Tokyo Med. & Dent. Univ., Tokyo, Japan

Abstract: The cerebellum receives various types of inputs via mossy fibers and climbing fibers, both of which convey signals from peripheral sensory organs and from the cerebral cortex. It is

not well-understood how those multiple types of signals are integrated in the cerebellar cortical circuit. To address this issue, we investigated somatosensory signals from the facial area of mice (VGAT-ChR2 mice) whose cortico-ponto-cerebellar pathway could be blocked by light illumination onto the somatosensory cortex. When we gave tactile stimulation to the upper lip, excitatory synaptic currents in granule cells appeared in two distinct timings in the in vivo whole-cell recordings in anesthetized mice (ketamine/xylazine). The early response (9.1 ± 0.5 ms latency, average ± s.e.m, n = 17) was not affected but the late response (31.0 ± 0.7 ms latency, n = 20) was suppressed by the light illumination, suggesting that they were direct trigeminal and indirect cortico-pontine responses, respectively. More than a half of the granule cells (15/27 cells) in our recording had both the early and the late excitatory synaptic response, while other cells (10/27 cells) had either the early or the late response. In current-clamp recording, action potentials were generated either in the early or in the late timing. Such two-phase responses were obtained in a wide area in crus II of the cerebellar cortex, from 5a- to 7+ aldolase C compartments. Consistent results were obtained in field potential recordings in the granule cell layer of awake mice. In Purkinje cells, the early simple spikes were not affected but the late simple spikes were suppressed by cortical photoinhibition. Interestingly, the complex spikes were also suppressed in the same manner. These results demonstrate that cerebellar granule cells relay diverse types of inputs from the trigeminal nuclei and the somatosensory cortex to Purkinje cells, which integrates those signals with ones from the somatosensory cortex via climbing fibers.

Disclosures: **T. Ishikawa:** None. **I. Sugihara:** None. **M. Shimuta:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.19/L20

Topic: E.02. Cerebellum

Support: University of Michigan Mcubed
University of Michigan School of Kinesiology Pilot Grant

Title: Effect of cerebellar theta burst stimulation on plasticity of interconnected parietal and motor areas

Authors: E. GOLDENKOFF[1], T. G. LEE[2], *M. VESIA[1];
[1]Sch. of Kinesiology, [2]Dept. of Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: Voluntary movement control and motor learning depend on plasticity in a number of spatially distributed but interconnected brain regions. Transcranial magnetic stimulation (TMS) has become a popular clinical tool for noninvasively modifying plasticity in brain networks.

TMS is not only capable of modulating activity in the targeted region beyond the duration of the stimulation itself, but also interconnected brain circuits. Yet, the mechanisms driving cortical plasticity in response to brain stimulation are not well understood. The cerebellum is an important structure involved in movement control and cognitive processing. Notably, cerebellar output projects to different interconnected cortical areas in the human motor system such as premotor, motor and parietal areas to support cognitive-motor function. Therefore, developing strategies to modulate plasticity processes between the cerebellum and cortex may provide a more mechanistic understanding at the brain circuit level of the effects of TMS underlying plasticity of neural networks and advance treatment of movement disorders. Previous work shows stimulation to the cerebellum can modulate cerebellar excitability and influence motor and cognitive behavior. However, the impact of cerebellar stimulation on neural activity of interconnected parietal and motor areas remains largely unknown. We address this gap in knowledge by evaluating whether spike timing-dependent plasticity (STDP) aftereffects in the human parieto-motor circuit change after cerebellar stimulation. We used theta burst stimulation to modulate cerebellar excitability. We used a cortico-cortical paired associative protocol (ccPAS) by means of TMS to induce STDP by repeatedly applying paired pulses over the posterior parietal cortex (PPC) and primary motor cortex (M1). We measured M1 excitability and PPC-M1 connectivity at baseline, immediately after cerebellar TBS and immediately, 15, 30, 45, 60 min after ccPAS. Preliminary results reveal that cerebellar inhibition modulates parieto-motor connectivity, which leads to an increase in motor excitability by ccPAS. Our ongoing work will test whether the plastic change is anatomically and temporally specific. These findings indicate that cerebellar TBS can noninvasively trigger a targeted change of plasticity in a parieto-motor circuit.

Disclosures: E. Goldenkoff: None. **T.G. Lee:** None. **M. Vesia:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.20/L21

Topic: E.02. Cerebellum

Support: KAKENHI

Title: Neuronal signals regulating and monitoring of synchronized saccade timing in the primate deep cerebellar nuclei

Authors: *R. TAKEYA, M. TANAKA;
Hokkaido Univ. Sch. Med., Sapporo, Japan

Abstract: Several lines of evidence shows that the cerebellum is essential for synchronized movements. To explore the underlying mechanism, we examined neuronal activity in the cerebellar dentate nucleus in monkeys performing the synchronized saccade task (Takeya et al., 2017), in which the animals made sequential saccades to alternately presented visual stimuli. The target appeared periodically at a fixed interval of 400, 550 or 700 ms (selected randomly for each trial), and every synchronized saccade (± 20% interval) was reinforced with a liquid reward. In the control condition, the target interval was randomized within each trial, and every reactive saccade (> 150 ms following the target onset) was reinforced.
So far, we have recorded from 70 task-related neurons which can be classified into four clusters: Ipsilateral (n = 19), Contralateral (5), Bilateral (24), and Postsaccade (22) neurons. The Bilateral neurons appeared to be more involved in synchronized than reactive saccades because 47% of them exhibited > 20% increase in firing modulation for synchronized saccades, while this proportion was small for the other types of neurons (21, 0, 32% for Ipsi, Contra and Postsac neurons, respectively). Many neurons exhibited ramping preparatory activity with slopes proportional to the inter-saccadic interval, and showed a significant partial correlation between the preparatory activity (150-300 ms before saccades) and inter-saccadic interval (26, 40, 79 and 14% for Ipsi, Contra, Bilateral and Postsac neurons, respectively). For the 19 Bilateral neurons, significant correlation was found for ipsilateral (n = 5), contralateral (6), or bilateral saccades (8). Since each saccade timing may alter depending on the temporal error of previous saccades, we examined partial correlation between saccade latency and postsaccade neuronal activity (50-200 ms). Again, the proportion of neurons with a significant correlation was greatest for the Bilateral neurons (79%; 5, 5 and 9 neurons for ipsi, contra and both directions, respectively) compared to the other types of neurons (32, 40 and 50% for Ipsi, Contra and Postsac neurons, respectively). Among 14 Bilateral neurons with a significant correlation for ipsilateral postsaccadic activity, 12 neurons also showed a significant partial correlation for contralateral preparatory activity, suggesting that they might regulate contraversive saccade timing using the error signals for ipsiversive saccades. Thus, our results show that the output node of the lateral cerebellum carries relevant signals to motor control and error monitoring for synchronized saccades. In particular, the Bilateral neurons might play a prominent role.

Disclosures: **R. Takeya:** None. **M. Tanaka:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.21/L22

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

Support: NIH Grant R01-MH091424

Title: Regulatory control of microglial phagocytosis by estradiol and prostaglandin E2 in the developing rat cerebellum

Authors: *M. PEREZ-POUCHOULEN, S. J. YU, C. R. ROBY, N. BONSAVAGE, M. M. MCCARTHY;
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Abstract: Microglia are essential to sculpting the developing brain and they achieve this in part through the process of phagocytosis which is regulated by microenvironmental signals associated with cell death and synaptic connectivity. We have shown that in the cerebellum, microglial phagocytosis reaches its highest activity during the third postnatal week of development but the factors regulating this activity are unknown. Here, we explored the relationship between the PGE_2-estradiol pathway and microglia in the maturing cerebellum since the signaling pathway involving prostaglandin E_2 (PGE_2) stimulation of the estrogen synthetic enzyme aromatase, peaks during the 2^{nd} postnatal week and is a critical regulator of Purkinje cell maturation. Thus, we treated developing rat pups, from postnatal day (PN) 8 to 12, with pharmacological inhibitors of estradiol (formestane, 5 µg / 0.05 ml s.c.) and PGE_2 (nimesulide and indomethacin, 5 µg / 0.05 ml s.c.) synthesis and then stained microglia with the universal marker Iba1 to count microglia engaged in phagocytosis as well as phagocytic cups in the vermis and cerebellar hemispheres at PN17. Formestane reduced the number of phagocytic cups in the vermis, but not in the cerebellar hemisphere at PN17. Similar results were found after treatment with nimesulide and indomethacin. In contrast, treatment with estradiol or PGE_2 had little effect on microglial phagocytosis in the developing cerebellum. We also treated more rat pups with estradiol (5 µg/0.05 ml dissolved in sesame oil), PGE_2 (2.5 µg/µl) or vehicle and found they had little effect on microglial phagocytosis in the developing cerebellum. We conclude that endogenous estrogens and prostaglandins upregulate the phagocytic activity of microglia during a select window of postnatal cerebellar development, but exogenous treatment with these same signaling molecules does not further increase the already high levels of phagocytosis. This may be due to an upper threshold or evidence of resistance to exogenous perturbation. NIH Grant R01-MH091424 to M.M.M.

Disclosures: M. Perez-Pouchoulen: None. **S.J. Yu:** None. **C.R. Roby:** None. **N. Bonsavage:** None. **M.M. McCarthy:** None.

Poster

579. Cerebellum: Cortex and Nuclei II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 579.22/L23

Topic: H.01. Animal Cognition and Behavior

Support: Startup Package for AG

R01MH101547 to FF
T32NS007431 to WH

Title: Eye-blink conditioning in awake and intact ferrets

Authors: *R. P. PATEL[1], C. ZHOU[2], C. J. BENNETT[4], H. EYBPOSH[5], R. RUCHO[4], G. LABROZZI[4], C. CAI[4], R. KOLAGANI[3], J. TURNER[4], W. A. HUANG[2], F. FROHLICH[2], A. GIOVANNUCCI[5];
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Abstract: The cerebellum is the brain area that enables agility in motor, sensory and cognitive domains. It provides fast-forward computing modules that support other brain regions in complex tasks, like the movements of a tennis champion or the articulation of complex sentences. Despite its critical role in motor and cognitive functions, basic questions underlying cerebellar function, such as neural population dynamics and plasticity mechanisms, are still highly debated. The difficulties lie in sampling populations of cerebellar neurons during complex yet quantifiable behavioral conditions. Investigations that can achieve this critical requirement offer mechanistic insights into cerebellar function and aid in the development of therapies to restore and treat ailments of the cerebellum, including motor dyspraxia.
Eyeblink conditioning (EBC) is a tractable, quantifiable behavioral paradigm that allows for probing of cerebellar activity during the different phases of motor learning. In EBC, animals gradually learn to close the eyelid in the presence of a neutral stimulus (light flash), after such stimulus has been repeatedly paired with an air-puff to the cornea. While electrophysiology of EBC-controlling areas has been performed in multiple species during learning (mice, rabbits, and rats), calcium imaging has so far been impossible because of their location deep in the brain, which hinders their optical accessibility. Therefore, the population dynamics of cerebellar neurons during this task are unexplored. Here we propose to employ the ferret preparation as an animal model to study neuronal subpopulations dynamics during EBC learning. Unlike rodent models, ferrets present a superficial and optically accessible EBC-controlling area.
As a first step, we probed the viability of this preparation by training awake intact ferrets in EBC. By pairing a mild air puff to the whisker with a blink-eliciting air puff to the cornea, we have, for the first time to our knowledge, successfully trained ferrets in EBC in a head-fixed manner. Conditioned responses (CRs) were detectable after a few sessions and continued to increase throughout the training. With this behavioral preparation in place, we aim to answer population coding questions, like error signal encoding and the role of different neuronal subpopulations in the production of CRs.

Disclosures: **R.P. Patel:** None. **C. Zhou:** None. **H. Eybposh:** None. **W.A. Huang:** None. **F. Frohlich:** Other; FF is the founder, CSO, and majority owner of Pulvinar Neuro LLC.. **A. Giovannucci:** None.

Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.01/L24

Topic: E.03. Basal Ganglia

Support: Veterans Affairs BLR&D Merit Review award
Shirley and Leon Cadieux Secondary Dystonia Research Fund

Title: A novel basal ganglia thalamocortical normal and pathological motor circuitry model

Authors: *D. KUMBHARE[1,4], G. WEISTROFFER[2,4], M. S. BARON[3,5];
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Abstract: Although the rate-based classical basal ganglia (BG) circuitry model provides an invaluable framework for conceptualizing BG-thalamocortical (BGTC) connections, the model has major limitations. As part of our investigations of the pathophysiology of movement disorders, we have performed multi-nuclei multi-neuronal recordings from the globus pallidus (GP; rodent equivalent of GP externa (GPe), entopeduncular nucleus (EP; equivalent of GP internus (GPi)), subthalamic nucleus (STN), pallidal receiving thalamus, and motor cortex in head restrained awake rats under resting and movement conditions. We have investigated these key nuclear regions in normal and different rat models of dystonia and parkinsonism using various optogenetic and pharmacological manipulations. From these studies, we propose a novel BGTC model, which accounts for observed pathophysiological features of dystonia, an illustrative common movement disorder.
Per our modeling, under dystonic *resting* conditions, GPe, STN, and GPi neurons are altered from normally tonic and fast to pathologically slow and highly irregular and bursty. The suppressed BG output signaling from EP causes insufficient hyperpolarizing input to ventrolateral (VL) thalamus. This, in turn, causes VL neurons to fire tonically, rather than in the intended burst baseline 'ready' mode.
With movement, due to different overlapping mechanisms, GABAergic inhibitory striatal neurons projecting to GPe are excessively burst activated, which produces excessive silencing of GPe neurons. Also, failure of GPe-STN auto-stabilizing prevents highly specific BG output signaling and instead induces pathological synchrony. Non-discriminate, excessively suppressed GABAergic inhibitory GPe signaling, in turn, causes GPi neurons to non-discriminately burst activate. The prominent hyperpolarizing GABAergic input from GPi non-discriminately switches VL neurons to a 'movement', albeit pathological, burst mode. Moreover, the indiscriminate and temporally inaccurate GPi motor output produces non-select and highly erroneous

thalamocortical burst signaling. This ultimately induces pathological corticospinal motor signals which lead to the characteristic sustained co-contractions and overflow muscle activation features of dystonia.
This novel BGTC model is anticipated to advance our understanding of the underlying pathophysiology of different movement disorders.

Disclosures: D. Kumbhare: None. **G. Weistroffer:** None. **M.S. Baron:** None.

Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.02/L25

Topic: E.03. Basal Ganglia

Support: Veteran Affairs BLR&D Merit Review Award
Shirley and Leon Cadieux Secondary Dystonia Research Fund

Title: Parkinsonism and dystonia originate differentially along highly discrete cortical basal ganglia motor subcircuits

Authors: *G. WEISTROFFER[1,3], D. KUMBHARE[2,3], M. S. BARON[5,4];
[1]Biomed. Engin., [2]Dept. of Neurosurg., Virginia Commonwealth Univ., Richmond, VA; [3]Res., [4]Southeast Padrecc, Hunter Holmes McGuire VA Med. Ctr., Richmond, VA; [5]Neurol., VCUMC/VCUHS, Richmond, VA

Abstract: *Background*. The basal ganglia-thalamocortical (BGTC) motor network is organized into segregated re-entrant subcircuits originating from distinct primary and premotor motor territories. We previously reported that a precise neurotoxic ibotenate lesion in the ventral motor territory of the globus pallidus (GP; rodent equivalent to GP externa (GPe)) induces dystonia, while a discrete dorsal lesion induces parkinsonism. To delineate these two subcircuits, we injected multi-synaptic anterograde and retrograde neuronal viral tracers into the two identified GP hotspots and the associated cortical hotspots.
Methods. Under the guidance of microelectrode recording, florescent tagged vesicular stomatitis virus (rVSV) was locally administered (7.56E+10 TU/ml, 0.4-1.4 μl) into the previously defined parkinsonian or dystonia hotspot in GP (n=18 rats). After 2-4 days, the rats were perfused, and the brains were processed. Successful discrete targeting of injections into the GP hotspots was affirmed by induction of the anticipated motor condition upon delayed local viral induced neuronal degeneration.
Results. Dense, circumscribed anterograde labeling of neurons was observed in the thalamus and motor cortex. Initial rats (n= 5) injected with a higher viral dose (>1.2 μl) and maintained for 4 days post-injection consistently developed unilateral dystonia indistinguishable from that

induced by ibotenate lesions. Based on computational modeling of the observed histological labeling, the GP dystonia hotspot projected primarily to primary motor cortex (L2.2, A2.1, D2.5) and the parkinsonian hotspot to secondary motor cortex (L1.5, A2.4, D2).
Significance. This study provides compelling evidence that two representative movement disorders, dystonia and parkinsonism, originate along separate and largely segregated primary and secondary motor BGTC subcircuits, respectively. This has important implications for developing new approaches to treating various movement conditions in humans.

Disclosures: G. Weistroffer: None. **D. Kumbhare:** None. **M.S. Baron:** None.

Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.03/L26

Topic: E.03. Basal Ganglia

Support: NSF CBET-1848029

Title: Distinct striatal population dynamics during voluntary movement under healthy and disease conditions

Authors: *D. ZEMEL, H. J. GRITTON, M. F. ROMANO, X. HAN;
Boston Univ., Boston, MA

Abstract: The dorsal striatum, a major structure of the basal ganglia circuit, guides voluntary movement by coordinating various cortical and sub-cortical neural activities. Disruption of striatal function can lead to movement disorders such as Parkinson's disease (PD). However, striatal neural population dynamics during voluntary movement in healthy and disease conditions are not fully characterized. Recently, we found that in healthy mice activation of pavalbumin positive cells (PV) facilitates movement while activation of cholinergic interneurons synchronize activity within medium spiny neurons (MSN) networks to signal the end of a movement bouts. Here, we performed simultaneous local field potential (LFP) recording and Ca^{2+} imaging in the dorsal striatum of mice during voluntary movement under healthy conditions, as well as 6-hydroxydopamine (6-OHDA) induced low dopamine Parkinsonian conditions. Under healthy conditions, we found that high-speed movement periods and low-speed movement periods correspond to distinct network states with unique neural population dynamics and different predominant LFP oscillations. High-speed movement periods are characterized by higher correlation between the activity of MSN pairs, higher firing rates of PV interneurons, and reduced LFP beta (12-20Hz) oscillation power compared to low-speed movement periods. Upon dopamine depletion, striatal network gradually transitioned towards a state with elevated beta oscillation power. These results provide new insights into neural population dynamics and bulk

LFP patterns in the striatum under healthy conditions, as well as provide informative description of the changes in population activity upon dopamine depletion in a PD model.

Disclosures: D. Zemel: None. **H.J. Gritton:** None. **M.F. Romano:** None. **X. Han:** None.

Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.04/L27

Topic: E.03. Basal Ganglia

Support: the National Natural Science Foundation of China (Grant No. 31871070)

Title: Regulation of Parkinsonian motor behaviors by a diencephalon-midbrain circuitry

Authors: *L. LI, Y. LI, X. LI;
Zhejiang Univ., Zhejiang, China

Abstract: Parkinson`s disease is a debilitating neurodegenerative disorder with classical parkinsonian motor symptoms including bradykinesia, rigidity, rest tremor, postural and gait impairment. Despite Lewy bodies and loss of dopaminergic neurons in the substantia nigra, the disease pathology remains poorly understood. In our study, we discovered a diencephalon-midbrain circuitry that when optogentically activated promptly induced Parkinsonian motor impairments such as rotations, increased freezing, bradykinesia and decreased motor coordination on rotarod in mice. While optogenetic inhibition of this circuitry had no observable impact on motor performance of normal mice. Either optogenetic activation or inhibition of the circuitry affected level of anxiety as revealed by open field test. Intriguingly, in 6-OHDA established parkinsonian mice model, optogenetic inhibition of this circuitry ameliorated motor performance of modeled mice. Our study revealed a novel circuitry involved in parkinsonian motor symptoms and provided potential therapeutic targets for PD.

Disclosures: L. Li: None. **Y. Li:** None. **X. Li:** None.

Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.05/L28

Topic: E.03. Basal Ganglia

Support: Grainger Foundation Grant

Title: Deep brain stimulation of the Tourette Syndrome target (centromedian-parafascicular complex) results in striatal dopamine efflux in the rat

Authors: *A. E. RUSHEEN[1,2], A. S. BARATH[2], H. SHIN[2], J. ROJAS CABRERA[2], K. E. BENNET[3,2], C. D. BLAHA[2], Y. OH[2,4], K. H. LEE[2,4];
[1]Med. Scientist Training Program, [2]Dept. of Neurologic Surgery, [3]Div. of Engin., [4]Dept. of Physiol. and Biomed. Engin., Mayo Clin., Rochester, MN

Abstract: Background: Tourette syndrome (TS) is a neurodevelopmental disorder characterized by the chronic presence of both motor and vocal tics. Epidemiologic studies show that over 100,000 children are affected with TS and often exhibit behavioral comorbidities that interfere with scholastic performance and social development. For severely affected subjects, deep brain stimulation (DBS) has emerged as a treatment option. While many targets for DBS therapy have been identified, an effective target is the centromedian-parafascicular complex (CMPf) of the thalamus. Despite the clinical benefit of DBS, the neurobiological mechanism by which DBS of the CMPf alleviates symptoms of TS is not understood. Based on previous studies, we hypothesize that DBS alters striatal extracellular dopamine concentrations resulting in a reduction in motor tics. **Methods**: In urethane anesthetized rats, the parafascicular nucleus (Pf) (ML:+1.2, AP:-4.6, DV:-6.1) was electrically stimulated using a concentric bipolar electrode and dopamine concentrations recorded in the striatum with a carbon fiber microelectrode (ML:+2, AP:+1.2, DV:-4.1). Fast scan cyclic voltammetry was used to measure stimulation-evoked phasic changes in dopamine concentrations. In addition, multiple cyclic square wave voltammetry, a novel technique developed in our laboratory, was used to measure stimulation-evoked basal changes in dopamine concentrations. Pharmacological confirmation of the dopamine responses was performed with nomifensine (20 mg/kg i.p.), a dopamine reuptake inhibitor. **Results**: Electrical stimulation of the Pf (0.3-0.5 mA amplitude, 60-90 Hz frequency, 2 ms biphasic pulse width) elicited a stimulation time-locked phasic 2.2±.9 nA increase in oxidation current at 0.6 V, indicating extracellular dopamine release in the striatum (n=3 rats). This increase in dopamine release was directly correlated with both stimulation frequency and intensity. Basal dopamine levels were recorded over 5 hrs in response to 4 s, 5 min, and 20 min stimulation, with time-locked fluctuations in extracellular dopamine concentrations. Finally, nomifensine administration enhanced the phasic stimulation-evoked response by ~150%, confirming the recorded responses were due to dopamine. **Conclusions**: These findings suggest that DBS of the CMPf alters extracellular striatal dopamine concentrations which may be important in the mechanism by which DBS alleviates motor symptoms of TS. Precisely how DBS alters extracellular dopamine concentrations, and if stimulation-evoked changes in striatal dopamine concentrations are correlated with motor tic amelioration, are the subjects of future studies.

Disclosures: A.E. Rusheen: None. **A.S. Barath:** None. **H. Shin:** None. **J. Rojas Cabrera:** None. **K.E. Bennet:** None. **C.D. Blaha:** None. **Y. Oh:** None. **K.H. Lee:** None.

Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.06/L29

Topic: E.03. Basal Ganglia

Title: Phase-dependent electrical stimulation modulates phase-amplitude coupling in Parkinson's disease

Authors: *Y. SALIMPOUR[1], K. A. MILLS[2], W. S. ANDERSON[1];
[1]Neurosurg., Johns Hopkins Sch. of Med., Baltimore, MD; [2]Neurol., Johns Hopkins Univ., Baltimore, MD

Abstract: Cross-frequency coupling (CFC) is a neural mechanism for large scale information transmission across the cortical and subcortical network in the brain. Phase-amplitude coupling (PAC) in which the amplitude of the faster oscillation is coupled to the phase of slow rhythm, is one of the most common quantitative representations of CFC. PAC has been suggested to be the potential mechanism for regional and cross-network integration of distributed information processing in the cortical and subcortical structures. In a healthy brain, PAC accompanies learning and memory. and changes in PAC have been associated with neurological diseases such as Parkinson's disease (PD). It has recently been reported in PD patients that the level of PAC is abnormally larger than the control group. Additionally, effective treatment such as medication and deep brain stimulation are associated with normalization of PAC. Among different brain neuromodulation techniques, phase-dependent stimulation has a strong potential to modulate PAC levels. With only limited evidence from animal studies, there has been no direct observation of PAC modulation as a result of phase-dependent stimulation of the human cortex. In this study, phase-dependent stimulation was directly applied to the motor cortex and superior temporal cortex of human subjects intraoperatively. Stimulation locked to the peak of beta oscillations increased beta-gamma coupling in the motor cortex and trough stimulation reduced the coupling level. Similarly, stimulation at the theta band peak intensified the theta-gamma coupling over the superior temporal cortex. These results taken together imply the capacity of phase-dependent stimulation for modulating PAC level and demonstrate possible applications in neurological disorders associated with abnormal PAC.

Disclosures: Y. Salimpour: None. **K.A. Mills:** None. **W.S. Anderson:** None.

Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

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Program #/Poster #: 580.07/L30

Topic: E.03. Basal Ganglia

Support: NIH P01NS087997
Nell Johnson Dystonia Research Acceleration Fund

Title: Diverse mechanisms lead to common dysfunction of striatal cholinergic interneurons in distinct genetic mouse models of dystonia

Authors: *M. SCARDUZIO[1], K. ESKOW JAUNARAJS[1], M. E. EHRLICH[3], L. L. MCMAHON[2], D. STANDAERT[1];
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Abstract: Dystonia is a movement disorder typically resulting in twisted postures via abnormal muscle contraction. Three common forms of isolated human dystonia result from mutations in the *TOR1A* (DYT1), *THAP1* (DYT6), and *GNAL* (DYT25) genes. Experimental models carrying these mutations facilitate identification of possible shared cellular mechanisms of pathophysiology. Clinical and experimental data indicate striatal cholinergic dysfunction in dystonia. Recently, in male *Dyt1*$^{\Delta GAG/+}$ mice (model of DYT1) we reported elevated extracellular striatal acetylcholine by *in vivo* microdialysis and "paradoxical excitation" of cholinergic interneurons (ChIs) in response to dopamine D2 receptor (D2R) agonism by *ex vivo* slice electrophysiology. The paradoxical excitation involved muscarinic receptors (mAChRs) and was caused by a switch in D2R coupling from canonical $G_{i/o}$ to non-canonical β-arrestin signaling. We sought to determine whether these mechanisms in *Dyt1*$^{\Delta GAG/+}$ mice are shared with *Thap1*$^{C54Y/+}$ knock-in and *Gnal*$^{+/-}$ knock-out, respectively DYT1 and DYT6 dystonia mouse models. We found *Thap1*$^{C54Y/+}$ mice of both sexes have elevated extracellular striatal acetylcholine and D2R-induced paradoxical ChI excitation, which was reversed by mAChR inhibition. In contrast, elevated extracellular acetylcholine was absent in male and female *Gnal*$^{+/-}$ mice, but the paradoxical D2R-mediated ChI excitation was retained and only reversed by inhibition of adenosine A_{2A} receptors, not by mAChR inhibition. The $G_{i/o}$-biased D2R agonist failed to increase ChI excitability, suggesting a possible switch in coupling of D2Rs to β-arrestin, as previously seen in *Dyt1*$^{\Delta GAG/+}$. These data show that while elevated extracellular acetylcholine levels are not common across these genetic models of human dystonia, the D2R-mediated paradoxical excitation of ChIs is shared and is caused by altered function of distinct G-protein coupled receptors.

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Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.08/L31

Topic: E.03. Basal Ganglia

Support: NIH Grant AA021505 (JW)
NIH Grant AA025932 (JW)
NIH Grant AA 024659 (RM)

Title: Striatal cholinergic interneurons and fetal alcohol exposure-induced behavioral flexibility

Authors: ***J. WANG**, A. BINETTE, X. XIE, X. WANG, L. SMITH, R. MIRANDA; Neurosci. and Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr., Bryan, TX

Abstract: Numerous studies suggest that prenatal alcohol exposure (PAE) alters cognitive flexibility. Behavioral flexibility is mediated in part by cholinergic interneurons (CINs) in the striatum. However, it is not clear whether CINs contribute to PAE-induced changes in behavioral flexibility. To assess this possibility, we trained female Ai14 mice to consume high levels of alcohol for 6 weeks using the intermittent access to 20% alcohol two-bottle choice procedure, and the Ai14 mice were mated with alcohol-naïve male ChATCre mice. We found that both male and female PAE offspring exhibited elevated locomotor activity, suggesting that PAE causes hyperactivity. To investigate the contribution of CINs to alcohol intake of these PAE offspring, we infused AAV-DIO-hM3Dq into the dorsomedial striatum (DMS) and found that chemogenetic excitation of DMS CINs via hM3Dq increased home-cage alcohol intake. CIN excitation is known to increase striatal dopamine release via acetylcholine that acts on nicotinic receptors on dopaminergic terminals in this area. We thus tested the effect of a nicotinic receptor antagonist, DHβE, on the CIN-mediated increase in alcohol intake, and observed that DHβE completely abolished the increase. Lastly, we tested behavioral flexibility of PAE offspring and found that male mice exhibited a deficit in reversal learning of operant self-administration using sucrose and food pellets. Our data suggests that PAE-induced inflexible behavior may be associated with alterations in striatal CINs.

Disclosures: **J. Wang:** None. **A. Binette:** None. **X. Xie:** None. **X. Wang:** None. **L. Smith:** None. **R. Miranda:** None.

Poster

580. Basal Ganglia: Pathophysiology

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Topic: E.03. Basal Ganglia

Support: Russian Science Foundation (18-15-00009)
Dystonia Medical Research Foundation Research Grant

Title: Difference in pallidal single unit activity in cervical dystonia with jerky and sinusoidal head tremor

Authors: *A. SEDOV[1], S. USOVA[1], U. SEMENOVA[1], A. GAMALEYA[2], A. TOMSKIY[2], S. B. BEYLERGIL[3], H. A. JINNAH[4], A. G. SHAIKH[3];
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Abstract: Two common movement disorders, dystonia and tremor, frequently overlap. Their biological relationships remain unclear. One hypothesis is that tremor and dystonia are due to the same fundamental biological process. A second hypothesis is that tremor and dystonia are due to distinct biological processes which frequently co-occur. Here we test these hypotheses by measuring the physiological activity of the globus pallidus in the most common form of dystonia, cervical dystonia, which frequently combines with tremor of the head. We compared three groups of patients, those with no tremor at all (pure dystonia), those with jerky head oscillations (dystonic tremor), and those with sinusoidal tremor. We used microelectrode recording from 13 CD subjects undergoing deep brain stimulation (DBS) surgery under local anesthesia. We analyzed the spontaneous activity of 727 pallidal neurons (398 GPi and 329 GPe). Clustering of spike-train recordings allowed classification of pallidal activity according to burst, pause, and tonic neurons - the types of neurons expected in dystonia patients. We found the differences in cells distribution between analyzed groups of patients. Burst GPi neurons were more common in pure dystonia or dystonic tremor groups compared to the sinusoidal tremor group. Pause GPi and GPe neurons were more common in the sinusoidal tremor group compared to the pure dystonia or dystonic tremor groups. In addition to their frequent prevalence, the pause neurons in sinusoidal tremor group had lower firing rate and were more irregular. The number of spikes within the burst were higher and inter-burst intervals were longer in sinusoidal tremor group. Neurons of patients with pure dystonia and dystonic tremor had similar parameters. We also found bihemispheric asymmetry in the dystonic tremor and pure dystonia groups, while such asymmetry was not present in the sinusoidal oscillation group. These results revealing

differences in the physiology of pallidal neurons of dystonic and sinusoidal tremor patients, suggest their distinct mechanistic underpinings.

Disclosures: **A. Sedov:** None. **S. Usova:** None. **U. Semenova:** None. **A. Gamaleya:** None. **A. Tomskiy:** None. **A.G. Shaikh:** None. **S.B. Beylergil:** None. **H.A. Jinnah:** None.

Poster

580. Basal Ganglia: Pathophysiology

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Topic: E.03. Basal Ganglia

Support: CHDI Foundation
NIH-NINDS Grant NS041280-07
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Title: Reversal of subthalamic nucleus dysfunction in Q175 Huntington's disease mice through viral vector mediated lowering of mutant Huntingtin

Authors: *J. F. ATHERTON, J. KONDAPALLI, D. WOKOSIN, M. D. BEVAN;
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Abstract: The subthalamic nucleus (STN) is an element of cortico-basal ganglia-thalamo-cortical circuitry critical for action suppression. Huntington's disease (HD) is a progressive neurodegenerative disorder that results from an expanded CAG repeat in the gene encoding huntingtin (Htt) protein. In the initial stages of HD, action suppression is impaired, resembling the effects of STN lesioning or inactivation. The Q175 knock-in mouse model of HD, which expresses full length human mutant htt with ~179 CAG repeats, is associated with abnormal intrinsic and synaptic properties in cortical and striatal neurons together with neuronal degeneration and behavioral abnormalities. We previously found that the intrinsic activity of STN neurons from Q175 het mice is diminished at 6 months of age compared to wild type littermates (WT). Firing disruption is due to increased activation of NMDA receptors leading to activation of K_{ATP} channels. The aim of this project is to further characterize STN abnormalities in HD using the Q175 mouse model and to explore potential strategies for correcting STN dysfunction.
To assess mitochondrial redox state mice were injected in the STN with AAV to express redox-sensitive GFP (roGFP) in neuronal mitochondria. 2-photon imaging of roGFP showed increased oxidation of STN neuronal mitochondria in Q175 het mice relative to WT. Disrupted firing in Q175 was rescued to WT levels by decomposition of H_2O_2 by catalase and alleviated by expression of the antioxidant regulator NRF2. Proteomic and RNAseq analysis of the STN revealed changes in the levels of proteins related to cell excitability, mitochondrial function,

redox pathways, and cell signaling. Viral expression of a zinc finger protein (ZFP) targeting mutant Htt reduced transcription of mutant Htt in the STN by 58% (measured with qPCR). Viral reduction of mutant Htt for 2 months rescued autonomous STN activity. Together, these data argue that dysfunction of firing in the STN is a consequence of mitochondrial oxidant stress. Rescue of intrinsic activity through mutant Htt reduction suggests that STN dysfunction is in large part cell autonomous and may represent a target for symptomatic and/or disease-modifying therapies.

Disclosures: **J.F. Atherton:** None. **J. Kondapalli:** None. **D. Wokosin:** None. **M.D. Bevan:** None.

Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.11/L34

Topic: E.03. Basal Ganglia

Support: CHDI

Title: Basal ganglia output in the Q175 model of Huntington's disease

Authors: *A. TIRAN-CAPPELLO, M. D. BEVAN;
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Abstract: Huntington disease (HD) is caused by expansion of trinucleotide repeats in exon 1 of the huntingtin gene and is associated with the progressive dysfunction and/or degeneration of neurons, astrocytes, and oligodendrocytes in the cortico-basal ganglia thalamo-cortical circuit and the emergence of debilitating psychomotor symptoms. The mechanisms underlying the pattern and sequence of HD dysfunction and degeneration are poorly understood but are thought to arise from toxic-gains-of-function, which impair neuronal and glial physiomes both directly through cell-autonomous effects and indirectly through the derangement of the circuits in which these cells are embedded. Interestingly, BAC-transgenic and knock-in (KI) HD murine models have revealed that profound, complex alterations in the properties of neurons and glial cells impair the cortico-basal-ganglia-thalamo-cortical circuit long before overt cell loss. For example, cortical, striatal, pallidal, and subthalamic nucleus cells exhibit highly abnormal physiological properties that compromise energetics, redox balance, proteostasis, intracellular signaling, ionic gradient regulation, action potential propagation, cellular excitability, and synaptic transmission and integration. These data argue that aberrant basal ganglia processing and output are likely to contribute to the psychomotor symptoms of HD. However, the properties of basal ganglia output neurons in HD models have not been characterized. To address this deficit, we have embarked on a series of *in vitro* and *in vivo* electrophysiological, anatomical, and molecular studies to

investigate the cellular and synaptic properties of substantia nigra pars reticulata (SNr) neurons in the Q175 KI model of HD. Our initial studies suggest that the autonomous firing of SNr neurons is not altered in HD mice. We are now studying the synaptic patterning of these cells using electrophysiological recording in conjunction with optogenetic identification and manipulation approaches.

Disclosures: A. Tiran-Cappello: None. **M.D. Bevan:** None.

Poster

580. Basal Ganglia: Pathophysiology

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Topic: E.03. Basal Ganglia

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NINDS 1R01NS101354
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NIH F31 NS106827

Title: Altered synaptic connectivity onto a distinct subset of striatal neurons in levodopa-induced dyskinesia

Authors: *A. E. GIRASOLE[1], M. RYAN[3], M. M. MCGREGOR[2], R. PALETZKI[4], R. BRAKAJ[2], C. R. GERFEN[5], A. B. NELSON[1];
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Abstract: Action selection requires coordinated function of the striatal direct and indirect pathways. In Parkinson's disease, loss of dopaminergic inputs alters this balance, leading to motor deficits. While dopamine replacement therapy with levodopa alleviates parkinsonian symptoms, treatment is limited by the development of drug-induced abnormal involuntary movements, termed levodopa-induced dyskinesia (LID). Recently, a unique and stable subpopulation of predominantly direct pathway striatal neurons, captured using an activity-dependent mouse line (FosTRAP), was found to contribute to dyskinesia. Understanding the distinct cellular and synaptic features of this population could inform our understanding of heterogeneity within the direct pathway, as well as the cellular and circuit mechanisms of LID. Here we used optogenetically identified single-unit recordings, monosynaptic retrograde rabies tracing, and slice electrophysiology to identify the unique cellular and circuit properties of this novel subpopulation compared to striatal direct pathway neurons more generally. *In vivo*, we found FosTRAP neurons fired at exceptionally high rates in response to levodopa, which in turn correlated with dyskinesia severity on a fine timescale. Further, we see that FosTRAP neurons

receive increased excitatory synaptic input at the functional level, with little alteration in the anatomical distribution of synaptic input, compared to direct pathway neurons more generally. These findings describe physiological and functional heterogeneity within the striatal direct pathway in the context of LID, and identify a potential underlying cellular mechanism. These results highlight the need for cell-type specific strategies for treating LID, and point the way to new therapeutic targets.

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Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

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Program #/Poster #: 580.13/L36

Topic: E.03. Basal Ganglia

Support: Proyecto VIEP-BUAP

Title: Chronic L-DOPA induces activation of SRF in the striatum of a dyskinetic rat model

Authors: *I. D. LIMÓN PÉREZ DE LEÓN[1], D. L. RODRÍGUEZ-REYES[1], V. PALAFOX-SÁNCHEZ[2], I. MARTÍNEZ-GARCÍA[3];
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Abstract: According to several studies about the molecular mechanism underlying L-DOPA induce-dyskinesia has been found that overexpression of the delta FosB protein could be as a molecular mediator of persistent adaptations in the striatum allowing the dyskinesia. However remains to be elucidated how the *fosB* gene is overactivated during a dyskinetic process. The serum response factor (SRF) has been involved in the synaptic plasticity, the activation of SRF is mediated by the phosphorylation at serine 103 and it could bind in the *fosB* promoter region to promote its expression, but is still unknown if chronic levodopa induced the activation of SRF in striatum of dyskinetic rats. The objective of the present study was to evaluate if L-DOPA induce the activation of SRF in medium spiny neurons (MSN) in the striatum of dyskinetic rats. Male Wistar rats received unilateral 6-OHDA-injection in the medial forebrain bundle by stereotaxic surgery. Fifteen days post-surgery, the rats were evaluated in the cylinder test to determinate the dopaminergic lesion. The rats received a daily intraperitoneal injection of 10 mg/Kg of L-DOPA during 16 days to develop *abnormal involuntary movements* (AIMs). We study the SRF and p-SRF^{Ser103} in MSN of direct and indirect pathway in dorsolateral striatum. The results showed that the dyskinetic group showed an exacerbated p-SRF^{Ser103} immunorreactivity in MSN of direct and

indirect pathway in dorsolateral striatum respect to control group administrated with L-DOPA. Therefore, this data suggest that L-DOPA induce the activation of SRF in the direct and indirect pathway of basal ganglia. Also phospho-SRF^{Ser103} could be an important striatal biomarker of dyskinesia induced by L-DOPA.

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Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.14/L37

Topic: E.03. Basal Ganglia

Support: TL1TR001428

Title: Parkinsonian beta power during rest and movement in the globus pallidus internus and subthalamic nucleus

Authors: *R. S. EISINGER[1], J. CAGLE[2], E. OPRI[3], J. ALCANTARA[3], S. CERNERA[2], K. FOOTE[4], M. S. OKUN[5], A. GUNDUZ[3];
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Abstract: Background: Over the years, an expansive body of literature has linked beta-frequency (12-30Hz) power to movement initiation and suppression throughout the basal ganglia and motor cortex. In Parkinson's disease (PD), pathologically high levels of beta activity reflect specific symptomology and normalize with pharmacologic or surgical intervention. Although beta characterization in the subthalamic nucleus (STN) of PD patients undergoing deep brain stimulation (DBS) patients has now been translated into novel adaptive DBS paradigms, limited studies have characterized beta power in the globus pallidus internus (GPi), another popular DBS target.
Methods: To address this shortcoming, for the first time, we set out to directly compare beta power in the STN and GPi during rest and movement in people with PD. A total of 33 subjects completed a simple behavioral experiment - consisting of periods of rest and button presses - leading to LFP recordings from 13 (11 participants) STN and 26 (22 participants) GPi nuclei. We examined overall beta power as well as beta power dynamics (i.e., beta bursts).
Results: We found higher beta power during both rest and movement in the GPi, which also showed greater beta desynchronization during movement. Beta power is positively associated with bradykinesia and rigidity severity, however in our data these relationships were present only in the GPi cohort. With regards to beta dynamics, bursts were similar in duration and frequency between the GPi and STN, but the GPi showed stronger bursts, which were also correlated to

bradykinesia-rigidity severity.
Conclusions: These results overall suggest that relative to the STN, beta in the GPi may be readily detected, modulates more with movement, and may relate more to clinical impairment. Taken together, this could point to the GPi as a potentially effective target for beta-based closed loop DBS.

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Poster

580. Basal Ganglia: Pathophysiology

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Topic: E.03. Basal Ganglia

Support: NIH Grant NS107734

Title: Learning contributes to Parkinsonian motor impairment and requires activation of indirect pathway spiny projection neurons

Authors: *T. H. C. CHEUNG[1], Y. DING[1], X. ZHUANG[2], U. J. KANG[1];
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Abstract: In Parkinson's disease (PD), dopamine (DA) neuron loss leads to profound motor impairment. Surprisingly, the beneficial effects of the DA precursor L-DOPA can persist long after its plasma level has returned to baseline. This long-duration response (LDR) of L-DOPA is observed both clinically and in animal models, but its neural mechanism is unknown. Here, we use unilateral 6-hydroxydopamine lesion and two distinct motor tasks to show that motor performance of tasks learned before DA depletion worsened gradually despite full depletion. This worsening is driven by learning, as it is experience-dependent and task-specific, caused by pairing specific task exposure with a DA-depleted state. In addition, both the induction of L-DOPA's LDR and its subsequent decay after L-DOPA withdrawal are also experience-dependent and task-specific. c-Fos staining shows that gradual decay of motor performance is associated with both reduced activation of direct-pathway spiny projection neurons (dSPNs) and increased activation of indirect-pathway SPNs (iSPNs), consistent with dSPNs' role in promoting movements and iPSNs' role in inhibiting movements. However, iSPN activation (by D2R antagonist) is sufficient to cause gradual motor impairment in DA-intact mice, whereas blocking iSPN activation (D2R-knockdown, chemogenetics, or A2A receptor antagonist) prevented gradual motor impairment, and this occurred despite reduced dSPN activation. Targeted ablation of cholinergic interneurons show that they are uninvolved in gradual Parkinsonian motor

impairment. We further show that LDR induction require CB1 receptors, consistent with iSPN long-term depression; whereas LDR decay require NMDA receptors, consistent with iSPN long-term potentiation. Surprisingly, we found that D1R agonist was able to both induce LDR and prevent LDR decay; however, unlike D2R agonist or L-DOPA, the effect of D1R agonist requires intra-striatal GABA-A receptors, suggesting an indirect D1R effect that requires intra-striatal microcircuitry. In summary, DA depletion causes gradual Parkinsonism mediated by task-specific learning and iSPN activation. D2R and D1R play dissociable roles: D2R activation directly blocks gradual Parkinsonism, whereas D1R activation blocks it indirectly via intra-striatal GABA signaling.

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Poster

580. Basal Ganglia: Pathophysiology

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Title: Real time monitoring of circuit plasticity reveals a role for orbitofrontal-striatal pathway in cocaine-induced hyperlocomotion

Authors: *S. BARISELLI[1], N. MIYAZAKI[1], A. V. KRAVITZ[2];
[1]NIH, Bethesda, MD; [2]NIDDK, Natl. Inst. of Hlth., Bethesda, MD

Abstract: The dorsal striatum integrates glutamatergic and dopaminergic inputs. Although several studies clarified the roles of dopamine in regulating neuronal firing and cortical excitatory synaptic transmission *in vitro*, its role *in vivo* remains largerly unexplored. Here, we studied the effects of hyperdopaminergic states on neuronal firing and cortical input efficacy in the dorso-medial striatum (DMS) of awake mice. We found that cocaine increased overall striatal activity, at both direct and indirect pathways, and increased input efficacy of orbitofrontal cortex (OFC) projections. Moreover, by monitoring the OFC-DMS inputs in real-time, we found that high-frequency stimulation (HFS) in awake mice weakened striatal excitatory inputs and attenuated cocaine-induced hyperlocomotion. Thus, the real-time monitoring of striatal inputs allowed us to identify circuit adaptations underlying hyperdopaminergic states, to develop an evidence-based approach to manipulate relevant circuits and rescue aberrant behavioral traits.

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Poster

580. Basal Ganglia: Pathophysiology

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Support: Medical Research Council, UK (MC_UU_12024/1)
Sir Henry Wellcome Postdoctoral Fellowship to CGM (209120/Z/17/Z)

Title: Phase-dependent closed-loop modulation of beta-frequency network oscillations in Parkinsonian rats

Authors: *M. ROTHWELL, C. MCNAMARA, A. SHAROTT;
MRC Brain Network Dynamics Unit, Dept. of Pharmacol., Univ. of Oxford, Oxford, United Kingdom

Abstract: Abnormally sustained oscillations in the beta frequency band (15-40Hz) are a consistent feature of the cortico-basal ganglia circuits of the parkinsonian brain. Effective pharmacological and surgical treatments reduce the power and network synchronization of these oscillations. Such manipulations, however, also modulate many other neuronal processes unrelated to the disease. Post-hoc analysis of beta-frequency stimulation of the subthalamic area in Parkinson's disease patients has demonstrated that oscillation amplitude is modulated by the phase at which stimulation is delivered. Computational studies suggest such phase-dependent modulation of neuronal oscillators could result from shifting the relative timing of neuronal activity. Applying such phase-dependent stimulation in a closed-loop manner, whereby pulsatile stimulation is consistently delivered to a specific phase of the ongoing oscillation, could lead to a more selective modulation of symptoms and reduced side effects. To test this hypothesis, we performed closed-loop phase-dependent stimulation in 6-OHDA hemi-lesioned rats, which display robust power increases in the high-beta band (28-40Hz) across the cortex and basal ganglia. We utilized a digital circuit-based system to produce a continuous online phase-estimate, which enabled the speed and accuracy required to perform accurate online phase-locked stimulation despite the transient, burst-like nature of the oscillations. Such phase-estimates were calculated from an electrocorticogram recorded above the motor cortex and used to control the timing of electrical stimulation of the globus pallidus external segment (GPe). Within individual animals, stimulation of GPe on some cortical phases led to amplification of the amplitude of the cortical beta oscillation, while others led to suppression, demonstrating network-level modulation. Motor performance during stimulation at the suppressing and amplifying phases was compared to no stimulation and continuous high-frequency stimulation using the Catwalk system, which provides various measures of locomotor performance while animals run on a linear track. Overall, these results suggest that phase-dependent closed-loop

modulation could provide a viable method to modulate pathological beta oscillations in Parkinson's disease.

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Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

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Program #/Poster #: 580.18/L41

Topic: E.03. Basal Ganglia

Title: Dorsal striatum volume increase after electroconvulsive therapy correlates with improvement of psychomotor symptoms in late life depression

Authors: M. G. A. VAN CAUWENBERGE[1], L. EMSELL[1], F. BOUCKAERT[1], K. VANSTEELANDT[1], F.-L. DE WINTER[1], M. LAROY[1], C. C. ADAMSON[2], A. DOLS[3], M. L. STEK[4], *J. VAN DEN STOCK[1], M. VANDENBULCKE[1];
[1]KU Leuven, Leuven, Belgium; [2]Murdoch Childrens Res. Inst., Melbourne, Australia; [3]GGZ inGeest Amsterdam, Amsterdam, Netherlands; [4]VUmc Amsterdam, Amsterdam, Netherlands

Abstract: Depression is among the top ten causes of impaired health worldwide. Primarily a mood disorder, depression is also associated with cognitive and motor dysfunction. The term psychomotor dysfunction (PMD) covers both decrease (retardation) and increase (agitation) of gross and fine movement, facial expression and gait in psychiatric illness. Clinical PMD has a prevalence of 20% in depression and is more common in the elderly. The presence of PMD predicts chronicity and better response to electroconvulsive therapy (ECT). Previous research on the neurobiology of PMD revealed white matter lesions and atrophy in the fronto-striato-pallido-thalamic circuit, but the pathophysiology and contribution to motor symptoms has not been clarified.
The present study aimed to identify whether PMD in late life depression (LLD) correlates with gray matter volume of the basal ganglia and whether volumetric changes following ECT relate to PMD improvement. A two-center (VU-GGZ Amsterdam, KU Leuven) prospective cohort study was conducted between January 2011 and December 2013, including 110 patients with LLD (> 65 yr.), eligible for ECT and with no other major neurological or psychiatric illness. Participants were clinically evaluated 1 week before, 1 week and 6 months after an averaged 6-week ECT course using outcome measures of mood (MADRS), cognition (MMSE) and psychomotor function (CORE). Brain MRI was available for 67 patients on the first two time points and 24 patients at six months. Automated volumetric analysis was conducted bilaterally on four regions

of interest: the caudate nucleus, putamen, globus pallidum and nucleus accumbens. Statistical analysis included GLM at baseline, Wilcoxon signed rank test and linear mixed models for longitudinal comparison. A p-value <0.05 was defined significant, Bonferroni correction was applied. Volumetric outcome was analyzed in a linear regression model with CORE, sex, age, number of ECT sessions, psychosis and site of scanning as predictors.
At baseline, psychomotor retardation (CORE retardation) correlated inversely with left and right caudate nucleus volume. One week after ECT, all clinical outcome measures improved and volume increases occurred bilaterally in the caudate nucleus, the putamen and the right accumbens nucleus. Improved psychomotor functioning correlated with volume increase of the left caudate nucleus and left putamen. Number of ECT sessions and psychosis predicted this volume increase. Six months after ECT, clinical improvement persisted, but volumetric differences could not be detected. This data suggests that dorsal striatum volume is a predictor of PMD in LLD and a possible target for intervention.

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Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.19/L42

Topic: E.03. Basal Ganglia

Support: NIH grant P50NS091856

Title: Optogenetic silencing of cholinergic neurons of the basal forebrain evokes falls and impairs cued turning in rats with striatal dopamine loss

Authors: *A. KUCINSKI, K. B. PHILLIPS, M. SARTER;
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Abstract: Falls, gait and balancing deficits, and attentional impairments are common symptoms in about half of the patients with Parkinson's Disease (PD) and are associated, in addition to striatal dopamine (DA) losses, with loss of cortical and thalamic acetylcholine (ACh). We previously established a rat model (dual, ‘DL’ rats) of PD falls which result from dorsomedial striatal DA and cortical ACh losses, and which reflect the loss of compensatory attentional supervision of complex movements. DL rats exhibit a high propensity for falls on a beam traversal task that taxes attentional control of gait, balance and movement sequencing. Here we hypothesized that optogenetic silencing of BF cholinergic neurons in rats with striatal DA losses would also evoke falls, thereby allowing a precise temporal determination of risk factors for

falls. ChAT-Cre rats received bilateral infusions of the Cre-dependent light-activated chloride channels (AAV-8-Ef1a-DIO iC++-EYFP) into the BF and were implanted with fiber optic cannulae to inhibit BF cholinergic neurons. Rats were previously familiarized with the traversal of a 3-m stationary or rotating (8 RPM) squared rod. In half of the runs, rats expressing the opsin or a EYFP control received two 1-s, 4-6 mW pulses per run, the first right after rats initiated traversals and the second halfway along the beam. Optogenetic stimulation increased the rate of falls significantly, by 64% on the stationary rod and by 65% on the rotating rod. Falls in rats without DA losses, or which expressed the control construct in the presence of striatal DA losses, were not affected by the laser pulses. As we previously demonstrated that DL rats also exhibit deficits in cued turning while walking on a treadmill the effects of optogenetic inhibition of BF cholinergic neurons were also assessed in this secondary task. Laser stimulation during the 2-s turn cue in rats with DA losses reduced the rate of successful turns, but not of cue-evoked successful stops. These results further validate that inhibition of BF cholinergic neurons unmasks the impact of striatal DA loss for gait, balance and movement sequencing and selection. Future experiments will determine whether optogenetic enhancement of cholinergic signaling can prevent falls and improve cued turning in DL rats, and thus potentially serve as a therapeutic approach to improve movement control and prevent falls.
Supported by NIH grant P50NS091856 (Morris K. Udall Center for Excellence in Parkinson's Disease Research)

Disclosures: A. Kucinski: None. **K.B. Phillips:** None. **M. Sarter:** None.

Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.20/L43

Topic: E.03. Basal Ganglia

Support: NS094754
MH112883

Title: A diencephalic pathway for movement initiation and rescue of Parkinsonian symptoms

Authors: *G. D. R. WATSON[1], R. N. HUGHES[2], E. PETTER[3], H. H. YIN[4];
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Abstract: The parafascicular nucleus (Pf) of the thalamus projects to the subthalamic nucleus (STN), a major target for deep brain stimulation (DBS) in Parkinson's disease (PD), but the function of this projection remains unknown. Here, we used optogenetics, 3D motion capture, *in vivo* electrophysiology and 1-photon calcium imaging, unsupervised behavioral classification,

and viral-based neuroanatomical tracing to examine the contribution of Pf efferents to movement generation in mice. We discovered that Pf neurons are highly correlated with movement velocity and excitation of Pf neurons generates turning and orienting movements. Movement initiation was not due to Pf projections to the striatum, but rather its projections to the STN. Optogenetic excitation of the Pf-STN pathway restores movement in a common mouse model of PD with complete akinesia. Collectively, our results reveal a thalamo-subthalamic pathway regulating movement initiation, and demonstrate a circuit mechanism that could potentially explain the clinical efficacy of DBS for relief of PD motor symptoms.

Disclosures: G.D.R. Watson: None. **R.N. Hughes:** None. **E. Petter:** None. **H.H. Yin:** None.

Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.21/L44

Topic: E.03. Basal Ganglia

Support: CIHR Foundation Grant FDN-143210
CIHR Foundation Grant FDN-143209
Canadian Partnership for Stroke Recovery
Brain Canada
Huntington Society of Canada

Title: Forelimb motor learning results in specific refinements in intertrial motor variability, is associated with striatal plasticity and is impaired in mouse models of Huntington's disease

Authors: *C. L. WOODARD[1], M. D. SEPERS[1], J. D. BOYD[1], A. L. SOUTHWELL[2], M. R. HAYDEN[1], T. MURPHY[1], L. A. RAYMOND[1];
[1]Univ. of British Columbia, Vancouver, BC, Canada; [2]Col. of Med., Univ. of Central Florida, Orlando, FL

Abstract: In order to assess motor learning over long time scales in mice and mouse models of disease, we have designed an automated, self-directed behavioural testing system which is accessible to group-housed mice from their home-cage and can be accessed at will, 24 hours per day. This design eliminates the need for the animal to be exposed to novel environments, and minimizes experimenter interaction, significantly reducing two of the largest stressors associated with animal behaviour. Additionally, mice can be passively trained on a difficult task over weeks or months of testing with comparatively little effort, allowing us to more easily study longitudinal changes in motor skill. In this system, mice use their forelimb to pull a small lever either to a specific position or with a specific velocity in order to receive water drops. Group-housed mice can be individually tracked using subcutaneously implanted RFID capsules, and

high-resolution lever position analysis as well as video recording allows for assessment of learning and quantification of motor kinematic parameters. Mice assessed using this system can successfully use trial-and-error learning to improve their performance of the task over several weeks. Animals reduce intertrial variability specifically on the task-relevant parameter (either maximum lever position or lever velocity), while the intertrial variability of other parameters does not change. Acute slices taken from the brains of mice trained on this task show hemisphere-specific electrophysiological changes in dorsolateral striatum medium spiny neurons (MSNs). Specifically, the amplitude of spontaneous excitatory post-synaptic currents (sEPSCs) is lower, and the presynaptic probability of release is higher, in the hemisphere contralateral to the trained forelimb as compared to the ipsilateral hemisphere. We are currently using this system to assess motor learning and forelimb kinematics in the YAC128 and Q175-FDN models of Huntington's disease, and have found deficits in the ability of these mice to reduce intertrial variability of kinematic parameters with training. This platform should prove useful for both the study of neurophysiological mechanisms of motor learning, and for preclinical drug trials toward improved treatments in HD and other neurodegenerative disorders.

Disclosures: C.L. Woodard: None. **M.D. Sepers:** None. **J.D. Boyd:** None. **A.L. Southwell:** None. **M.R. Hayden:** None. **T. Murphy:** None. **L.A. Raymond:** None.

Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.22/L45

Topic: E.03. Basal Ganglia

Support: R01 NS07730
NIH NINDS K08-NS072183

Title: Dystonic-like movements in a mouse model of task-specific dystonia are stereotyped and distinct from innate behaviors

Authors: *K. KERNODLE[1], W. T. DAUER[2], D. K. LEVENTHAL[3];
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Abstract: We previously established a mouse model of task-specific dystonia that develops dystonic-like movements after repeated training on the single pellet skilled reaching task. These mice carry a human dystonia mutation and have no dystonic-like movements during natural behaviors. However, dystonic-like movements emerge during training on the skilled reaching task. This scenario is broadly similar to humans with task-specific dystonia, which typically develops following extensive training on a highly dexterous motor task. The movements that

develop in the mice are visually similar to innate grooming behaviors. We used a deep learning algorithm to generate 3-dimensional trajectories of the dystonic-like movements as well as visually similar movements. Although both movement types are highly stereotyped, dystonic-like movements are asymmetric between forepaws whereas grooming is symmetric. Additionally, the frequency of dystonic-like movements is higher than visually similar grooming movements, with paws appearing out of phase with each other more frequently. These results support the use of learning algorithms for movement classification and allow unique studies of dystonic-like movements in a mouse model of task-specific dystonia.

Disclosures: K. Kernodle: None. **D.K. Leventhal:** None. **W.T. Dauer:** None.

Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.23/L46

Topic: E.03. Basal Ganglia

Support: SIMONS 514879

Title: Spatiotemporal dynamics of striatal circuits during repetitive behaviors in autism spectrum disorder

Authors: *A. M. VICENTE[1], G. J. MARTINS[1], V. B. PAIXAO[2], R. M. COSTA[1];
[1]Columbia Univ., New York, NY; [2]Champalimaud Fndn., Lisbon, Portugal

Abstract: Autism Spectrum Disorder (ASD) is a developmental disorder characterized by a set of symptoms including repetitive behaviors. Repetitive motor patterns have long been considered to be inflexible actions dependent on habitual circuitry. Striatal direct and indirect pathway projection neurons (dSPN and iSPN) are essential for action initiation and performance as well as habit formation. While dSPNs appear to support continuation of ongoing actions, iSPNs seem to regulate switching from current actions. Furthermore, corticostriatal plasticity is critical for decreases in behavioral variability during learning. Since regulation of the coordinated activity of dSPN and iSPN is likely essential in controlling repetitive actions, we decided to investigate their role during natural and learned behaviors in a genetic mouse model of ASD (*Del16p11.2* heterozygous mice). To achieve this goal, we first imaged dSPNs and iSPNs in freely moving *Del16p11.2* mice and littermate controls, while using an unbiased behavior classification to extract their movement patterns. We observed that behavioral cluster similarity in *Del16p11.2* heterozygous mice is increased compared to their littermate controls, suggesting a greater degree of stereotypy for these animals. Previous results have shown stronger correlations between local SPN activity, suggesting the existence of functional domains within striatal circuitry. We observed an increase in cross-correlations between SPNs in *Del16p11.2* mice compared to

controls, which can denote changes in corticostriatal connectivity. To study stereotypy in learned behavior, we have used a task newly developed in the lab to investigate learning and performance of heterogeneous sequences, where animals have to learn to perform a specific sequence of nose pokes to receive a water reward. *Del16p11.2* mice performed a higher number of nose pokes and presented increased stereotypy in learned sequences. However, when the rewarded sequence was changed, *Del16p11.2* mice showed no impairment, and even a faster transition to the new sequence, and therefore no signs of behavior and cognitive inflexibility. These experiments reveal the changes in striatal organization in ASD, with spatial and temporal resolution, and how those affect behavior.

Disclosures: A.M. Vicente: None. **G.J. Martins:** None. **V.B. Paixao:** None. **R.M. Costa:** None.

Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.24/M1

Topic: E.04. Voluntary Movements

Support: R21 DC016135

Title: Inhibition of signaling and metabolic pathways in the Pink1-/- rat model of early-onset Parkinsonism

Authors: *C. A. KELM-NELSON, M. R. CIUCCI;
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Abstract: Parkinson disease (PD) is a progressive, neurodegenerative disease with early-stage pathology hypothesized to manifest in the brainstem. Loss of function in the PTEN induced kinase 1 (*Pink1*) causes autosomal recessive PD, an early-onset form of the disease. At 8 months, the *Pink1*-/- rat model of PD exhibits detectable limb and cranial sensorimotor deficits as well as brainstem pathology including reduced catecholamine concentrations and abnormal, aggregated alpha-synuclein. The aim of the present study was to identify differentially expressed genes (DEGs) using high throughput RNA-seq in the brainstems of *Pink1-/-* male and female rats as compared to their respective age-matched wildtype (WT) controls and determine their relationship to the *Pink1* gene. A set of significant, annotated DEGs were identified in both males and females. KEGG pathway enrichment analysis was used to compare the gene set to existing network datasets. Briefly, in males, pathways (*genes*) of interest include pentose and glucuronate interconversions (*AKR1B10, UGT1A9*), and glycine, serine and threonine metabolism (*PSAT1, MAOB*). In females, glutathione metabolism (*GSTM3, SMS*), PPAR signaling (*UBC, SLC27A6*), and metabolism (*TPMT, GSTm3*) pathways were identified.

WGCNA was used to identify significant biological networks of interest; *Pink1* was a central module with many interconnecting genes of interest. Separate analysis of male and female modules that included *Pink1* also had different genes suggesting a sex-specific difference. In general, the data suggest that loss of *Pink1* influences signaling and oxidative stress pathways within the brainstem. The next step in this work is to link specific neurobiological change with limb and cranial sensorimotor behavior.

Disclosures: C.A. Kelm-Nelson: None. **M.R. Ciucci:** None.

Poster

580. Basal Ganglia: Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 580.25/M2

Topic: E.03. Basal Ganglia

Support: NIH Grant RO1 DA027222

Title: Behavioral sensitization to methylphenidate is modulated by glutaminergic signaling in the caudate nucleus

Authors: *N. KING, S. FLOREN, N. KHARAS, M. THOMAS, N. DAFNY;
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Abstract: Methylphenidate (MPD) is the most widely prescribed psychostimulant for the treatment of attention deficit hyperactivity disorder, and is growing in use as a recreational drug and academic enhancer. MPD acts on the reward/motive and motor circuits of the CNS to produce its effects on behavior. The caudate nucleus (CN) is known to be a part of these circuits, so a lesion study was designed to elucidate the role of the CN in response to acute and chronic MPD exposure. Five groups of n=8 rats were used: control, sham CN lesions, non-specific electrolytic CN lesions, dopaminergic-specific (6-OHDA toxin) CN lesion, and glutaminergic-specific (ibotenic acid toxin) CN lesions. On experimental day (ED) 1, all groups received saline injections. On ED 2, surgeries took place, followed by a 5-day recovery period (ED 3-7). Groups then received six daily MPD 2.5 mg/kg injections (ED 9-14), then three days of washout with no injection (ED 15-17), followed by a re-challenge with the previous 2.5 mg/kg MPD dose (ED 18). Locomotive activity was recorded for 60 minutes immediately after each injection by a computerized animal activity monitor. The electrolytic CN lesion group responded to the MPD acute and chronic exposures similarly to the control and sham groups, showing an increase in locomotive activity, i.e. sensitization. The dopaminergic-specific CN lesion group failed to respond to MPD exposure both acute and chronically. The glutaminergic-specific CN lesion group responded to MPD exposure acutely but failed to manifest chronic effects. This confirms the dopaminergic system of the CN is necessary for MPD to manifest its acute and chronic

effects on behavior, and demonstrates that the glutaminergic system of the CN is necessary for the chronic effects of MPD such as sensitization. Thus, the CN plays a significant role in the expression of acute and chronic effects of MPD exposure.

Disclosures: **N. King:** None. **S. Floren:** None. **M. Thomas:** None. **N. Dafny:** None.

Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 581.01/M3

Topic: E.04. Voluntary Movements

Support: National Institutes of Health/National Institute of Neurological Disorders and Stroke
US Department of Veterans Affairs

Title: Gating of sensory input during grasping in humans with spinal cord injury

Authors: R. VASTANO[1], ***M. A. PEREZ**[1,2,3];
[1]Dept. of Neurolog. Surgery, The Miami Project to Cure Paralysis, Univ. of Miami, Miami, FL; [2]Bruce W. Carter Dept. of Veterans Affairs Med. Ctr., Miami, FL; [3]Shirley Ryan Ability Lab., Chicago, IL

Abstract: Somatosensory information is filtered at different levels of the ascending sensory pathway during voluntary movements including grasping. Evidence has shown that the integrity of afferent (sensory) axons projecting through the spinal cord dorsal columns to the brain in humans with spinal cord injury (SCI) is impaired. How sensory input is gated along the ascending sensory pathway during gross and fine grasping in humans with SCI remains largely unknown. To address this question, we assessed somatosensory evoked potentials (SSEPs) from contralateral somatosensory cortex (S1) following the electrical stimulation (intensity 10% of M-max) of the ulnar nerve (600 pulses at 5 Hz, 0.1 ms of duration) at rest and during precision and power grip (at 5 % and 30 % of maximal voluntary contraction (MVC), in humans with and without chronic incomplete SCI. We found in control subjects that sensory gating at subcortical levels and in S1 increased during power grip compared with precision grip with increasing levels of voluntary contraction. In SCI participants, sensory gating occurred at subcortical levels and in S1 during 30 % of MVC to a larger extent during power grip compared with precision grip. These findings indicate that humans with SCI gate sensory input mainly during gross compared with fine grasping behaviors. We argue that this reflects the reorganization of neural pathways following SCI.

Disclosures: **R. Vastano:** None. **M.A. Perez:** None.

Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 581.02/M4

Topic: E.04. Voluntary Movements

Support: NIH Grant NS095873
NIH Grants NS082151

Title: Multifinger interaction and coordination in levodopa naive Parkinson's disease patients: An uncontrolled manifold analysis

Authors: *P. B. DE FREITAS, Jr[1], S. M. FREITAS[2], M. M. LEWIS[3], X. HUANG[4], M. L. LATASH[5];
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Abstract: According to the uncontrolled manifold (UCM) hypothesis, the total force (F_{TOT}) produced by two or more fingers of a hand is stabilized by co-varied commands to individual fingers. Thus, inter-trial variance in the finger force space is higher in directions that do not affect F_{TOT} (within the UCM) compared to directions that affect F_{TOT} (orthogonal to the UCM), resulting in a signature inequality: $V_{UCM} > V_{ORT}$. This inequality and high action stabilizing synergy are reflected by a high index of synergy ($\Delta V >> 0$). If a person plans to increase F_{TOT} quickly, a high ΔV is clearly ineffective, so the controller reduces ΔV in a predictive manner just before (~200 ms) the change in F_{TOT}. This phenomenon has been addressed as anticipatory synergy adjustments (ASA). Earlier studies reported lower indices of F_{TOT}-stabilizing synergies and smaller and shorter ASAs in individuals with Parkinson's disease (PD). Testing levodopa-naïve PD patients would allow disambiguating the effects of PD from possible effects of long-term exposure to the levodopa. Thirteen levodopa-naïve PD patients and 13 healthy controls performed a variety of four-finger and one-finger tasks including maximal voluntary contraction (MVC). The main task involved four-finger accurate steady F_{TOT} production at 5% MVC, followed by a quick force pulse into the 25%-MVC target, and return to the initial F_{TOT} level. The outcomes used to assess action stability were V_{UCM}, V_{ORT}, and ΔV. The time of ASA initiation (t_{ASA}) and the magnitude of the ΔV_Z drop ($\Delta\Delta V_Z$) provided information about the ASAs. Overall, levodopa-naïve PD patients were weaker (lower MVC) than controls. Also, PD subjects showed a lower synergy index, ΔVz, than controls, due to the high inter-trial variance component affecting F_{TOT} (i.e. V_{ORT}). Moreover, levodopa-naïve PD subjects showed a trend toward shorter and smaller ASAs in preparation for the force pulse, mainly in the non-dominant hand. These

results confirm earlier reports regarding the effects of PD on multi-finger synergy indices. The data show that these differences are due to PD-associated changes in neural circuitry rather than long-term levodopa exposure. Our findings support the idea that changes in indices of multi-finger synergies may be used for early detection of PD-related changes in the basal ganglia, as levodopa-naïve PD patients already show detectable changes in indices of stability.

Disclosures: P.B. de Freitas: None. **S.M. Freitas:** None. **M.M. Lewis:** None. **X. Huang:** None. **M.L. Latash:** None.

Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 581.03/M5

Topic: E.04. Voluntary Movements

Title: Measurement of finger range of motion in patients receiving therapy for hand paralysis: Accuracy and precision of a custom-built electrogoniometer

Authors: L. I. ZEIN[1], N. MAKOWSKI[2], *C. M. MILLER[1], J. KNUTSON[2];
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Abstract: Finger range of motion (ROM) is the amount of finger movement a person has, and is therefore a vital component of hand functionality. Therefore, assessing improvement in finger-ROM is valuable when evaluating the effectiveness of neurorehabilitation treatments in patients with hand paralysis. The goal of this study was to evaluate the accuracy and precision of a new, custom-built electrogoniometer compared to that of a standard goniometer. The custom-built electrogoniometer attaches to a finger and has three magnets and three Hall-effect sensors, each magnet-sensor pair positioned near each of the three finger joints. The Hall-effect sensors measure changes in magnetic fields as the finger extends and flexes. The changing magnetic fields are converted to changing voltage outputs, which are converted by software to joint angle values for the metacarpophalangeal (MCP), proximal interphalangeal (PIP), and distal interphalangeal (DIP) joints. To measure the accuracy and precision of the electrogoniometer, a hinged wooden dowel was set at a fixed angle, and the three sensors of the electrogoniometer were used to measure the angle 10 times, with removal and repositioning between measurements. The mean of the measured angles was within 0.2% (MCP), 4.3% (PIP), and 2.1% (DIP) of the set angle value, each less than the 5% typically considered the threshold for acceptance as accurate. The range of angles measured with the electrogoniometer was 3.7° (MCP), 3.6° (PIP), and 1.2° (DIP), all lower than those reported for the standard goniometer. The coefficients of variation of 2.3% (MCP), 2.1% (PIP), and 1.0% (DIP) were also less than the 2.4% (MCP), 2.9% (PIP), and 6.2% (DIP) measured with the standard goniometer. These data suggest that the custom-built electrogoniometer is accurate and has greater precision than a

standard goniometer. An additional advantage is that, unlike standard goniometers, the electrogoniometer can measure all three joint angles simultaneously and dynamically. Widespread availability of this device could improve assessment of finger range of motion in patients receiving neurorehabilitation for hand paralysis. Currently, we are creating procedures for manufacturing more electrogoniometers via 3D printing and determining their calibration arrays. After completion of this project, human studies to validate the reliability of the electrogoniometer is a next step.

Disclosures: L.I. Zein: None. **N. Makowski:** None. **C.M. Miller:** None. **J. Knutson:** None.

Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 581.04/M6

Topic: E.04. Voluntary Movements

Support: NIDCD R56DC016274

Title: Somatosensory cortical excitability changes earlier in human motor learning than motor cortex excitability

Authors: *H. OHASHI[1], P. L. GRIBBLE[2], D. J. OSTRY[3];
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Abstract: Motor learning is associated with plasticity of primary motor and somatosensory cortex. It is known from animal studies that tetanic stimulation to each of these areas individually induces long-term potentiation in the counterpart. In this context it is possible that changes in motor cortex play a causal role in somatosensory change and that changes in somatosensory cortex determine changes in motor areas of the brain. To better understand the relative contribution of motor cortical and somatosensory plasticity in humans, here we assess the time course of changes in primary somatosensory and motor cortex during a motor skill learning task. If motor learning is driven by motor cortical plasticity, changes in motor excitability should be seen early in learning, and those changes should predict behavioral improvement. In contrast, if somatosensory plasticity plays a predominant role in learning, then somatosensory excitability changes should be seen early in learning and should be related behavioral measures of skill acquisition. In the present study, learning was assessed using a force production task. The excitability of primary somatosensory cortex was measured using somatosensory evoked potentials in response to median nerve stimulation. The excitability of primary motor cortex was measured using motor evoked potentials elicited by single-pulse transcranial magnetic stimulation. These two measures were interleaved with blocks of motor learning trials. We found

that the earliest changes in cortical excitability during learning occurred in somatosensory cortical responses and these changes preceded changes in motor cortical excitability. Changes in somatosensory evoked potentials were correlated with behavioral measures of learning whereas changes in motor evoked potentials were not. These findings are consistent with the possibility that plasticity in somatosensory cortex drives early stages of motor learning.

Disclosures: H. Ohashi: None. **P.L. Gribble:** None. **D.J. Ostry:** None.

Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 581.05/M7

Topic: E.04. Voluntary Movements

Support: U01NS108922
UH3NS107714

Title: Transient and tonic grasp force signals in motor cortex

Authors: *B. DEKLEVA[1], K. M. QUICK[1], J. M. WEISS[1], J. E. DOWNEY[3], N. G. HATSOPOULOS[4], M. BONINGER[1], J. L. COLLINGER[2];
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Abstract: The fundamental purpose of upper limb control is to interact with and manipulate objects. Integral to that function is the ability to generate and modulate the strength of grasp. As we develop brain-computer interfaces to restore arm and hand function lost due to spinal cord injury, amputation, or other neuromotor impairment, we must find ways to robustly decode grasp force. Simple, linear decoding methods have proven successful in allowing control of kinematic variables like reach velocity. However, decoding static sustained grasp force is difficult because many cortical signals are transient in nature. In order to obtain a reliable, consistent cortical signal that can be used to control grasp, we must understand the various types of transient and tonic cortical signals underlying grasp force control. We investigated these components by recording population activity from primary motor cortex (using microelectrode arrays) as a participant with tetraplegia observed and mimicked a variety of object interaction tasks in a virtual environment. While grasping a stationary object, cortical signals showed strong correlation with the attempted grasp force at all times (from pre-contact until object release). In tasks involving object carry, we observed signals related to force at grasp onset, but could not reliably distinguish grasp force throughout the remainder of the grasp. The only features consistent across all types of tasks were transient signals at the onset of grasp and at the time of object release. Based on these observations, we developed a novel, Kalman-filter-inspired grasp

force decoder that relies on transient neural activity. This architecture allows for maintained force output even if tonic signals related to grasp force are lost or diminished. During an online brain-computer interface grasp-and-carry task, the transient-based decoder significantly improved the participant's ability to: (1) achieve initial target grasp forces, and (2) maintain those forces throughout object transfer, compared to a standard Kalman filter approach. This improved decoder functionality demonstrates how an understanding of physiological phenomena can inform and improve BCI decoding.

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Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 581.06/M8

Topic: E.04. Voluntary Movements

Support: Blue Cross Blue Shield Foundation of Michigan

Title: Interactions between hand force steadiness, tactile acuity, and perceived function in children with upper limb peripheral nerve injury

Authors: *R. N. LOGUE[1], R. E. BIALEK[1], C. S. MEYERSON[1], L. J.-S. YANG[2], S. H. BROWN[1];
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Abstract: Hand force steadiness is a critical aspect when holding and manipulating objects, particularly at low force levels. However, standard clinical assessments of hand function typically involve measures of maximum grip and pinch force that are rarely used in everyday activities. While age-related impairments in force steadiness have been well documented (Ranganathan et al., 2001; Marmon et al., 2011), little is known regarding this aspect of hand function in clinical populations due, in part, to the lack of appropriate assessment techniques. This study aimed to determine the relationship between hand steadiness, tactile ability and activities of daily living in older children with conservatively treated upper limb peripheral nerve injury. Eight children with neonatal brachial plexus palsy (NBPP) (mean age: 12.25 y) and 11 age-matched controls (mean age: 12.0 y) participated in the study. Despite significant upper limb muscle weakness, all NBPP participants attended school and participated in community activities. Participants produced unilateral grasp forces equivalent to 5% of each individual's maximum voluntary force by squeezing a force transducer. Target and matching forces were displayed on a computer screen and participants were instructed to reach the target zone and

maintain the force for 3-4 sec. The task was repeated 4 times using the affected and the unaffected hands. Monofilament testing was used to measure tactile registration. A custom-designed spatial pattern device was used to assess tactile perception. Self-reported hand function was measured using the ABILHAND questionnaire. Affected hand steadiness was significantly worse in the NBPP compared to their unaffected hand ($p<0.01$) and the nondominant hand in the control group as evidenced by higher variability (coefficient of variation) scores ($p<0.01$). No between hand differences were observed in tactile registration. In contrast, the amount of processing time required to correctly identify tactile patterns was significantly greater in the affected hand compared to control values ($p<0.05$) despite similar levels of accuracy in both groups. Hand steadiness was predictive of self-reported hand function ($p<0.05$) and also correlated with the amount of time required to perceive tactile patterns ($p<0.05$). These findings of impaired force control in NBPP may reflect deficits in the central processing of hand-related sensory feedback that, in turn, impact self-reported function. Further, measures of hand steadiness may predict hand use in children with NBPP and underscore the need for more objective measures of motor and sensory function in upper limb peripheral nerve injury conditions.

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Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 581.07/M9

Topic: E.04. Voluntary Movements

Support: AHA Grant #16BGIA27250047

Title: Functional cortical activation deficits during manual tasks in older adults with type II diabetes

Authors: *S. L. GORNIAK, A. HERNANDEZ, L. POLLONINI;
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Abstract: The overall aim of this project was to evaluate the relationship between outcomes in manual sensorimotor behavior and cortical activation in older adults with Type II Diabetes (T2D). Our recent studies have shown that adults with T2D experience declines manual sensorimotor function that are not associated with a diagnosis of diabetic peripheral neuropathy; however, it is not clear if cortical deficits are responsible. Currently, no specific consistent structural deficits have been identified as a cause to motor deficits in persons with T2D. Twenty-one (21) community-dwelling T2D patients (age = 65 ± 6 years, A1c = 7.5 ± 1.1) and twenty-one

(21) age- and sex-matched healthy controls (age = 66 ± 6 years, A1c = 5.4 ± 0.3) were recruited and evaluated in this cross-sectional study (all females). Tactile detection and motor performance were evaluated while study participants donned cortical functional near-infrared spectroscopy devices (fNIRS) in one testing session. Tactile detection was evaluated via fingertip vibration; motor performance was evaluated by isometric pinch force production at two force levels using the thumb and index finger of the right hand. Bilateral cortical regions of interest (ROIs) included: PFC, SMA, M1, S1, and Brodmann area 40. Health state, metabolic (eg. glycated hemoglobin values, A_{1c}), and menopausal status data were collected. No differences in tactile function were found between the two groups. No between group ROI activation differences were found in the tactile stimulation task. Deficits in fine motor performance were found in the T2D group in both motor tasks ($p < 0.01$). Reduced HbO responses were found across all ROIs in the T2D group ($p < 0.05$) during performance of the lower force level motor task. Group-based ROI activations did not show significant differences during the high force production task. Performance and ROI activation differences in the T2D group in the low force motor task were not impacted by metabolic health state measures ($p > 0.2$). These data are the first to indicate functional cortical deficits in older adults with T2D, particularly in the performance of fine motor tasks. This suggests a potential combination of central and peripheral deficits leading to functional declines in older adults with T2D.

Disclosures: **S.L. Gorniak:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; American Heart Association. **A. Hernandez:** None. **L. Pollonini:** None.

Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 581.08/M10

Topic: D.08. Visual Sensory-motor Processing

Support: LABEX SMART

Title: Integrative properties and connectivity of brain sensory motor pathways in humans

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Abstract: SEPs are used to evaluate the transmission in the sensory pathway at cortical level. In EEG and MEG, it is possible to collect SEP early (N20-P35) and late potentials (N60, P100). The aim of this project was to characterize the different components of SEP by characterizing the activation of brain areas based on source location and studying the relationship between sensory inputs and EEG/MEG signals (outputs), and by studying the connectivity of the cortical network. In this study, we were particularly interested in late SEP components because it has been hypothesized that they are less dependent on sensory inputs while they have been studied to a much lesser extent than early components. We collected SEPs in 19 healthy subjects by coupling multichannel EEG and MEG (74 channels for both) and we stimulated the median nerve at the wrist level at 4 intensities normalized to the intensity for perceptual threshold. Eye blinks artifact on the EEG time series were corrected using ICA. MEG time series were filtered from external noise and identified artefacts were corrected using PCA. Source reconstruction was calculated using the distributed model. We averaged the signals of all the subjects over 3 time windows corresponding to N20, N60 and P100, and for the 4 stimulation intensities. Then, we studied the link between the size of the 3 components and the stimulus intensity in different ROIs (S1, S2, M1, PM, SMA, PPC, areas 39-40, temporal and occipital lobes). For studying the functional connectivity, we used a Morlet wavelet analysis of the inter-region synchronization method to study the fast oscillation (500-1000 Hz) and those less than 200 Hz. Whatever the ROIs, the early component N20 increased with the stimulus intensity but not the late components. However, the spatial resolution was not good enough to evaluate the connectivity based on averaged SEPs only. Slow and fast oscillations were observed at the latency of both early and late components. The next step is to study the synchronization of these oscillations between the different ROIs for a better discrimination of the neural networks involved in sensory, cognitive and motor integrations at the cerebral level, underlying early and late SEP components, respectively dependent and independent of sensory inputs.

Disclosures: **S. Hssain-Khalladi:** Other; LABEX SMART, Sorbonne Université, Paris, France. **A. Giron:** None. **C. Huneau:** None. **C. Gitton:** None. **D. Schwartz:** None. **N. Georges:** None. **M. Le Van Quyen:** None. **G. Marrelec:** None. **V. Marchand-Pauvert:** None.

Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 581.09/M11

Topic: E.04. Voluntary Movements

Support: PSC-CUNY Awards (68854-00 46)

Title: A mixture of deafferented and intact digits' enrollment reveals motor inefficiency during moment-compensatory grasping tasks

Authors: *W. ZHANG[1], A. CARTERON[1], C. BENSON[2], B. HAHN[2];
[1]City Univ. of New York / CSI, Staten Island, NY; [2]Staten Island Univ. Hosp., Staten Island, NY

Abstract: Somatosensory feedback is essential in assisting human motor execution. Disturbed peripheral sensory inputs would interfere with the process of descending motor commands in both behavioral and synergetic control aspects. These observations in hand movement control lead to force control deficits, including reduced maximal force, altered force sharing patterns, weakened force covariation, and disturbed force synchronization. However, the question of how the disturbed and intact sensory inputs integrate and interact with each other to assist the motor program execution in moment control has not been studied. We recently developed a deafferentated hand model by using anesthesia on selective (not all) digits of the hand in order to simulate a redundant system with mixed-sensory motor elements.
The current study investigated the effects of selective digital deafferentation on moment control produced in grasp tasks as a function of object centers of mass (CM). Subjects performed same experimental tasks in two sessions: 1) anesthesia session, when somatosensory inputs were blocked via digital anesthesia in index, middle and the thumb of subject's right hand; and 2) control session, when digital sensation remained intact. Fourteen (7M, 7F) healthy, right handed, young adults participated in this study. Subjects were asked to lift and hold for 4 seconds a customized invert-T-shape device by using five digits while minimizing the object tilt. Object CM could be altered to: 1) the thumb's side (CM_T); 2) the center (CM_C); and 3) the fingers' side (CM_F). Subjects performed seventeen consecutive trials in each CM block, without pre-knowledge of the CM change. Five force/torque sensors (ATI nano) on sides and one position/orientation sensor (Polhemus) on the top of the device to record individual digit's kinetics and object kinematics.
After selective digital anesthesia, subject were capable to produce proper task-required compensatory moment to remain object orientation in anticipatory control phase (at object lift onset), but not in motor adaptation phase (during object hold). Despite subjects' strategic modulation on force and force sharing as a function of object CM, the removal of sensory feedback evoked significant moment production in both against and antagonist components that cancelled out each other. These findings indicate the mixture of sensory-blocked and -intact digits' enrollment post a larger challenge for the central nervous system when dealing with mixed sensory feedback inputs in a motor task adaptation. Given selective digital sensory deprivation, the resultant motor performance may be achieved with the cost of significant motor inefficiency.

Disclosures: W. zhang: None. **A. Carteron:** None. **C. Benson:** None. **B. Hahn:** None.

Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 581.10/M12

Topic: E.04. Voluntary Movements

Support: NIH Grant P2CHD0886844

Title: Combined brain and hand stimulation to improve hand movement after stroke, a pilot randomized trial

Authors: *A. SETHI[1], E. SANTARNECCHI[2], A. PASCUAL-LEONE[3];
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Abstract: Eighty five percent of stroke survivors experience weakness of one upper extremity, which limits their ability to perform daily tasks. Currently there are no effective interventions to improve hand function in moderate-to-severe chronic stroke. Using the principles of neuroplasticity, we developed a novel intervention, which combines non-invasive brain stimulation with functional electrical hand stimulation for individuals with moderate-to-severe impairments. The purpose of this study was to investigate the feasibility of this intervention in individuals with chronic stroke. We assessed the preliminary efficacy of the intervention in 16 participants. All participants received a total of 18 treatment sessions three times a week for 6 weeks. Each treatment session lasted for 1.5 hours where participants practiced grasping and releasing meaningful objects with the functional electrical stimulation of the weak hand. Simultaneously, participants received 30 minutes of non-invasive brain stimulation via weak random noise currents to the affected primary motor cortex. Eight participants received real brain stimulation, while the rest received sham-brain stimulation. We assessed the preliminary efficacy of the intervention on Fugl Meyer Upper Extremity Subscale, which assess the voluntary control of the affected hand after stroke. The participants who received real brain stimulation showed significantly greater improvement in hand movement ($t = 1.9$; $p = .04$). Combined transcranial random-noise stimulation and functional electrical hand stimulation is feasible to administer in individuals with moderate-to-severe impairments after chronic stroke. The combined transcranial random-noise stimulation and functional electrical hand stimulation shows promise in improving affected hand movement in this population. Future studies are warranted to examine the efficacy of this intervention.

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Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 581.11/M13

Topic: E.04. Voluntary Movements

Title: Motor planning assessment during intraoperative functional mapping in glioma surgery

Authors: *J. J. SÁNCHEZ-DUEÑAS[1], A. B. SANDOVAL-BONILLA[2], F. DELGADO[3]; [1]Doctorado en Neurociencias de la Conducta, Univ. Nacional Autónoma De México UNAM, Ciudad de México, Mexico; [2]Unidad de Neurocirugía, Hosp. de Especialidades, CMN Siglo XXI, [3]Unidad de Resonancia Magnética, Hosp. de Oncología, CMN Siglo XXI, Inst. Mexicano del Seguro Social, Ciudad de México, Mexico

Abstract: The goal of the present study was to describe the assessment of complex motor processing in an intraoperative continuous task during awake surgery.
We report the case of an 18-years-old male patient with left low-grade glioma, who is a student of dance and scenic arts, he didn't experience cognitive and motor disturbance previous to surgery. MRI demonstrated a lesion that invades the primary motor cortex, supplementary motor cortex and white-matter fasciculi (pyramidal tract, superior longitudinal fasciculus and superior segment of arcuate fasciculus). Preoperative fMRI BOLD (finger-tapping task and foot ballet positions) and tractography were performed pre and post-surgically. Various motor areas were identified and confirmed by electrical cortical mapping during awake surgery. Were a hundred percent correspondence between localization of motor tasks fMRI BOLD signal and electrical cortical stimulation of inferior precentral gyrus (primary motor cortex), during monopolar electric stimulation in tumour exeresis were identified the pyramidal tract, superior longitudinal fasciculus and superior segment of the arcuate fasciculus. When motor or language performance exhibited a sudden interruption, aggressive motor contraction or language disorder were discontinued the extraction of tissue. Weren´t observed motor disorders or aphasia in the post-surgical outcome. We conclude that the implementation of functional techniques of neuroimaging and neuropsychological assessment for surgical planning, in addition to continuous task during awake surgery improve the long-term functional and cognitive outcome of patients with low-grade gliomas in the primary and supplementary motor cortex and white-matter bundles and contribute to a higher resection of the tumour.

Disclosures: J.J. Sánchez-Dueñas: None. **A.B. Sandoval-Bonilla:** None. **F. Delgado:** None.

Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

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Program #/Poster #: 581.12/M14

Topic: E.04. Voluntary Movements

Support: NSERC PDF to RLW
NSERC Discovery Grant to JTE

Title: Touchpoints directed at 2D objects reveal medial axis sensitivity despite gross deficits in forced-choice shape discrimination: Evidence from visual form agnosia and cortical blindness

Authors: *R. L. WHITWELL, J. K. DUNKLE, J. T. ENNS;
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Abstract: Object shape guides object recognition and object-directed actions like reaching and grasping. Classic work has shown that the in-flight kinematics of reach-to-grasp movements and their touchpoints express object shape information in individuals with compromised shape perception that followed damage to ventral-stream structures (e.g., Goodale et al. 1991). These studies constitute a cornerstone of the two visual systems hypothesis (Goodale & Milner, 1992) and its multi-visual-system descendants. Recent work with normally-sighted populations has shown that the freely chosen end points from point-to-touch movements directed at targets reveal the target-shape's medial axis, which is a metric that is specific to object shape. Here we ask whether or not this medial-axis phenomenon extends to exclusively dorsal-stream representations of shape, by testing DF, who has visual form agnosia resulting from lesions that encompass the shape-sensitive ventrolateral cortical area (LOC) bilaterally, and MC, who is cortically-blind following lesions that also encompass much of her occipital cortex bilaterally, including LOC. Each patient touched pebble-like shapes shown on a touchscreen in random positions and orientations. DF and MC could not reliably discriminate amongst the shapes in same/different, oddball, and 1-back tasks, confirming their deficits in visual shape perception. Nevertheless, both DF's and MC's touchpoints each fell significantly closer to the centre-of-mass and the medial axis than would be expected by chance alone. Moreover, the increase in their performance moving from forced-choice shape-discrimination to touchpoint selection fell significantly-beyond the distribution of differences expected from a sample of normally-sighted controls. In a second investigation in normally-sighted individuals, we show that reducing the duration of the shapes to 300ms significantly and dramatically reduces oddball-discrimination, yet only minimally influences touchpoint sensitivity to the medial axes of the shapes. Taken together, these findings strongly indicate that, in addition to centre-of-mass, other shape metrics such as the medial axis inform dorsal-stream mediated visually-guided movements.

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Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

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Program #/Poster #: 581.13/DP07/M15

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: E.04. Voluntary Movements

Support: The Malone Seed Fund

Title: Assessing hand dexterity after stroke in 3D

Authors: *J. XU[1], S. KUMAR[1], K. OLDS[2], J. BROWN[3], J. CARDUCCI[3], A. FORRENCE[2], K. W. JOHN[2];
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Abstract: The dexterous hand control is the hallmark of human skill and intelligence. Among most stroke patients with hemiparesis, the loss of fine finger control and dexterity is often permanent, even after regaining a substantial amount of grip strength. In a recent longitudinal acute stroke recovery study, we found that hand dexterous control, measured by finger individuation in the direction of finger flexion, and its recovery are supported by a separate system than strength (Xu et al., 2017). However, traditional clinical assessments of dexterous hand function provide only holistic qualitative measures, and are often contaminated by strength and other behavioral compensation strategies. Here we assessed dexterous finger function in healthy participants and chronic stroke patients using a novel device that can sensitively tract isometric forces produced at all five fingertips simultaneously in 3D. Finger-joint individuation was measured for the metacarpophalangeal (MCP) and the proximal interphalangeal (PIP) joints for each finger with extension, flexion, abduction, and adduction. Two hand postures were tested: wrist pronation and neutral postures. Each participant's natural force trajectories were first assessed at all 6 directions in the 3D space. Participants were then instructed to isolate each individual finger-joint by pushing towards four different target force levels along their natural force paths, while keeping all the other fingers and joints immobile. Four target-force levels based on each subject's strength level up to 10 Newtons were tested. Our preliminary results showed superior independence of the thumb than the four fingers, flexion/extension than ab/adduction. In chronic stroke patients, thumb appears to be the most independent finger, and ab/adduction are the most impaired dimension. In addition, our data also show a compression of workspace for each finger after stroke, manifested as within-effector joint enslaving. In summary, our device and paradigm shows promise for assessing hand dexterity and its impairment in 3D, using fine-grained isometric force data.

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Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

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Topic: E.04. Voluntary Movements

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Title: Forced-use therapy improves recovery of hand motor function after sensorimotor cortex lesions in macaca mulatta

Authors: *W. G. DARLING[1], M. A. PIZZIMENTI[2], D. L. ROTELLA[1], J. GE[3], K. S. STILWELL-MORECRAFT[4], R. J. MORECRAFT[5];
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Abstract: Previously we showed that motor function of the preferred hand (contralesional/more affected hand) recovers to variable levels depending on lesion volume after unilateral injury to the arm/hand area of sensorimotor (frontoparietal) cortex (Darling et al. 2016 Exp Neurol 281:37). Following the injury, recovery was considered spontaneous as there was very limited motor testing of the preferred/contralesional hand weekly for 8 weeks, and then biweekly thereafter. Notably, 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). We now test the hypothesis that forced-use therapy of the preferred hand can further improve recovery of hand fine motor function following sensorimotor cortex injury. Eight monkeys received unilateral lesions of arm/hand areas of M1, lateral premotor cortex, S1 and the rostral part of superior parietal lobule. Four monkeys recovered spontaneously and four monkeys received forced-use therapy of the preferred/contralesional hand beginning two weeks after the lesion. Therapy was provided three days/week using a device that allowed only the preferred/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. Two motor skill testing devices were used in both groups that allowed testing of both hands for the duration of the post-lesion survival period (Morecraft et al. 2015). In addition, post-recovery hand preference was also computed based on 3 post-lesion learned nonuse (LNU) tests done near the end of the survival period and using a hand preference test in the cases receiving therapy. After recovery, in all spontaneous cases hand preference switched from the contralesional to the ipsilesional hand, whereas all forced-use therapy cases returned to the original (contralesional) hand preference. Furthermore, recovery of reach and manipulation skill was better in the forced-use therapy group but was quite variable in both groups perhaps due to variations in lesion size. These data show that spontaneous recovery after sensorimotor cortex lesions is variable, with the ipsilesional hand becoming preferred in tasks where the monkey could choose which hand to use. In contrast, forced-use therapy in monkeys with similar lesions produces good-excellent recovery and, notably, with return to the contralesional (more affected) hand being preferred in a fine motor task that allows the monkey choice of which hand to use.

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Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

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Topic: E.04. Voluntary Movements

Support: NRF-2016M3A9B6902954
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KGC1021911

Title: Assessment of hand motor function in a cynomolgus monkey model of ischemic stroke using endovascular transient middle cerebral artery occlusion

Authors: C.-Y. JEON[1], **J. WON**[1], K. KIM[1], J. SEO[1], H.-G. YEO[1], J. PARK[1], Y.-J. AHN[1], S.-R. LEE[1], K. YI[2], C.-H. CHOI[2], S.-H. CHA[2], *Y. LEE[1];
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Abstract: Ischemic stroke occurs as a result of arterial occlusion and leads to irreversible brain injury. Upper extremity disability after stroke is the primary factor affecting activities of daily living in stroke patients. The aim of this study was to evaluate hand motor function in a non-human primate model of ischemic stroke.
A female cynomolgus macaques was used in this study. We performed magnetic resonance imaging (MRI) and evaluated hand motor performance using the hand dexterity task (HDT) to examine the pathophysiological and neurobehavioral alterations before and after middle cerebral artery occlusion (MCAO) to induce cerebral ischemia.
We found that the ischemic infarct expansion was progressively inhibited, which was consistent with the enhanced functional recovery of the affected hand over the course of 12 weeks after MCAO. We also observed that the total performance time decreased significantly with increasing success rate for both hands on the HDT. Interestingly, compensatory strategies and retrieval failure were improved in the acute post-stroke phase.
These results indicated that deficits in fine motor skills following ischemic stroke could be improved during the post-stroke period. Taken together, these finding provide a basis for the evaluation of hand motor function after ischemic stroke.

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Poster

581. Sensorimotor Transformation: Physiology and Pathophysiology

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Program #/Poster #: 581.16/M18

Topic: E.04. Voluntary Movements

Support: MRC
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Wellcome Trust

Title: Slow-conducting pyramidal tract neurons in macaque and rat

Authors: *A. KRASKOV[1], D. S. SOTEROPOULOS[3], I. S. GLOVER[3], R. N. LEMON[2], S. N. BAKER[3];
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Abstract: Anatomical and electrophysiological approaches to study the distribution of conduction velocities within the primate corticospinal tract have produced very contrasting accounts, known as the “corticospinal discrepancy”. While anatomical studies have emphasized the huge preponderance of fine fibres with diameters of 0.5-3 µm, recordings of antidromic responses evoked in pyramidal tract neurons (PTNs) by stimulation of the pyramidal tract (PT) are dominated by responses of neurons with short antidromic latencies (ADLs), indicating large, fast conducting axons. Slow conducting PTNs are likely to have thin axons and small cell bodies which suggests a number of possible explanations for the ‘corticospinal discrepancy’: (i) failure of PT stimuli to excite the finer PT axons; (ii) well-known bias of extracellular recording methods towards large neurons; (iii) failure to invade the soma-dendritic membrane; and (iv) recurrent synaptic inhibition of slow PTNs resulting from stimulation of fast corticospinal axons. We investigated these factors in the motor cortex of anaesthetised macaque monkeys (n=3) and rats (n=2), by searching for PTNs with long antidromic latencies, using a recording electrode with 32 closely-spaced contacts. We identified 21 rat PTNs with antidromic latencies of 2.6 to 14.6 ms, and 67 macaque PTNs ranging from 3.9 ms to 7.2 ms. Most PTNs had antidromic thresholds less than 300 µA; they had small spikes and were present on less than half of the recording contacts. In contrast, spikes from the largest, fastest-conducting PTNs were large and appeared on all contacts. Most slow PTNs showed no signs of failure of antidromic invasion. The impact of recurrent inhibition was tested using a number of approaches, including (i) changing anaesthetic depth, (ii) high intensity PT stimulation and (iii) cortical microinjection of bicuculline, a $GABA_A$ antagonist, to block inhibition pharmacologically. In no case did we find evidence that recurrent inhibition prevented antidromic invasion of slow PTNs.
Our results demonstrate that modern high-density silicon probes allow successful recordings

from slow PTNs, and suggest that electrode recording bias is the main reason why previous studies have been dominated by large, fast PTNs.

Disclosures: A. Kraskov: None. **D.S. Soteropoulos:** None. **I.S. Glover:** None. **R.N. Lemon:** None. **S.N. Baker:** None.

Poster

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Title: Descending cortical pathways bidirectionally modulate forelimb tactile feedback in the cuneate nucleus

Authors: J. M. CONNER, ***A. S. BOHANNON**, D. J. BUTLER, E. AZIM;
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Abstract: A critical challenge for the mammalian motor system is managing the intricate coordination of muscles in the arms and hands to interact with the world. Coordinated movement depends on constant interaction between feedforward neural circuits that produce motor output and feedback systems that report sensory consequences and external perturbations. Fundamental to this process are mechanisms for controlling how sensory information influences motor systems in a task-dependent manner - for example, attenuating feedback signals when disruptive and augmenting them when advantageous. While the precise mechanisms for modulating somatosensory feedback during voluntary movement remain largely unknown, it has been proposed that descending cortical systems play a central role in adjusting the strength of sensory signals, thereby regulating their influence on motor output. We are exploring how peripheral feedback is regulated at the level of the main cuneate, a brainstem nucleus that serves as a major conduit of ascending sensory information arising from the forelimbs and upper body. Leveraging viral and genetic tools in mice, we find that direct peripheral projections to cuneolemniscal neurons, which convey sensory signals to the neocortex via the thalamus, are primarily composed of tactile, as opposed to proprioceptive, afferents. Moreover, through a combination of anatomical and electrophysiological studies, we identify two discrete descending cortical pathways that target distinct components of cuneate circuitry - one consisting of corticospinal

collaterals that directly target cuneolemniscal neurons; and a second unique set of corticofugal collaterals that innervate inhibitory circuits in the cuneate shell, suppressing cuneolemniscal activity via feedforward inhibition. *In vivo* electrophysiology and behavioral studies are revealing the functional implications of descending modulation of tactile feedback for dexterous forelimb movement. Together, these findings identify distinct corticofugal pathways that exert bidirectional modulation of forelimb sensory gains, providing a potential circuit basis for filtering disruptive feedback while simultaneously enhancing the transmission of salient sensory signals during limb movement.

Disclosures: J.M. Conner: None. **A.S. Bohannon:** None. **E. Azim:** None. **D.J. Butler:** None.

Poster

582. Animal-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 582.01/M20

Topic: E.04. Voluntary Movements

Support: WT090955AIA
WT110027/Z/15/Z
NWO-VICI 016.130.662
203139/Z/16/Z

Title: Skill acquisition increases myelination and strengthens functional connectivity in the sensorimotor circuit of the adult rat

Authors: *C. SAMPAIO-BAPTISTA[1], A. DE WEIJER[1], A. VAN DER TOORN[2], W. M. OTTE[2], A. WINKLER[1], A. LAZARI[1], P. SALVAN[1], D. BANNERMAN[1], R. M. DIJKHUIZEN[2], H. JOHANSEN-BERG[1];
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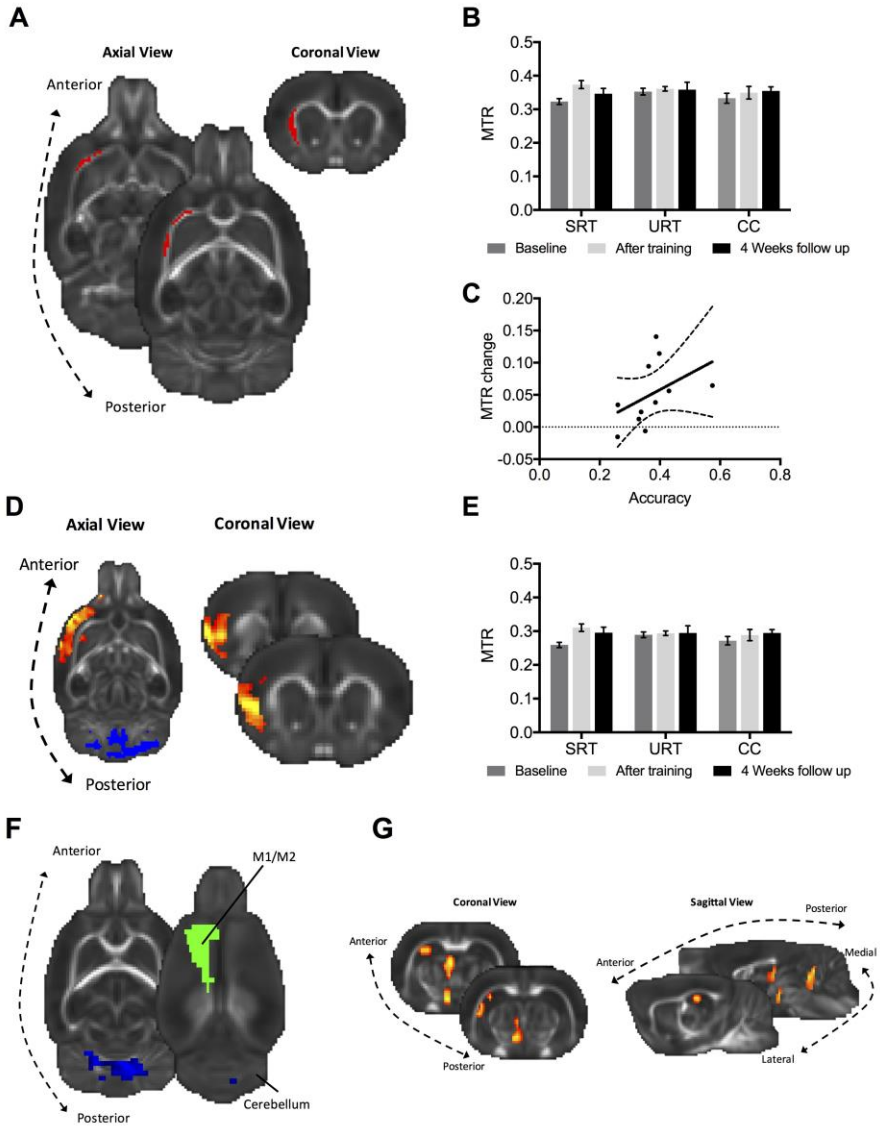
Abstract: The effects of skill learning on whole-brain structure and functional networks has been extensively investigated in humans but has yet to be explored in rodents. Forelimb reaching training in rodents results in well-established focal functional and structural reorganization within the motor cortex and cerebellum, indicating distributed alterations in both structure and function. Here we trained adult rats in skilled reaching and used multimodal whole-brain *in vivo* MRI to assess both structural and functional plasticity over time. This approach allows us to interpret and integrate our results with both animal and human literature.
Adult rats (4 months old) were randomly assigned and trained either in the skilled reaching task (n=12) or in the unskilled version of the task (n=12) for 11 days. Caged controls were also used for comparison (n=12). All rats underwent *in vivo* MRI scanning on a 4.7 T system at baseline and after training. Magnetization transfer ratio (MTR), diffusion weighted and resting-state fMRI

were acquired. The FSL package (www.fmrib.ox.ac.uk/fsl) was used for data analysis. Voxel-wise analysis statistics were performed with non-parametric permutation testing, with a cluster-forming threshold of $t > 2$, and 5000 permutations were used to determine corrected p-values. Following motor learning, we found significant increases in MTR ($p < 0.05$, fully corrected), an indirect assessment of myelin content, in white matter tracts that primarily connect sensory and motor regions (Fig. 1A, B), as well as, within sensory cortical areas and to a lesser extent in the cerebellum (Fig. 1D, E). A trend towards increases in functional connectivity between motor cortex and cerebellum were also detected ($p = 0.09$, fully corrected, Fig. 1F). Both structural (Fig. 1C) and functional brain changes (Fig. 1G) correlated with task performance ($p < 0.05$, fully corrected). Skilled training therefore leads to myelin increases in pathways that connect sensorimotor regions, and in functional connectivity increases between areas involved in motor learning.



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Poster

582. Animal-Reaching Motor Learning

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Program #/Poster #: 582.02/M21

Topic: E.04. Voluntary Movements

Support: HHMI
NIH

Title: Changes in neural population activity underlying the learning of novel arm dynamics

Authors: ***X. SUN**[1], D. J. O'SHEA[1], E. M. TRAUTMANN[1], M. D. GOLUB[2], S. VYAS[3], T. G. FISHER[1], S. RYU[4], K. V. SHENOY[5];
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Abstract: The motor system can flexibly learn to produce skilled movements and may implement distinct strategies in different learning contexts. Changes in neural population activity that parallel behavioral learning have been studied under various learning contexts, such as visuomotor rotation, brain-computer interface learning, etc. However, most of these learning contexts do not necessitate generating novel patterns of muscle forces, and little is known about how neural population activity changes to facilitate learning when novel movement dynamics are required. Here, using a curl force field learning paradigm, we investigated neural population mechanisms for learning new movement dynamics and their relationship with behavioral generalization.
We trained rhesus monkeys to first reach to one of 12 targets, and then adapt to a curl field active only for one target. After monkeys adapted to the force field, reaches to untrained targets using an "error clamp" were interleaved with the adaptation trials. Monkeys displayed gradual behavioral adaptation to the force field, and this learning was generalized to adjacent targets, following a bell-shaped curve: newly learned hand forces were transferred to nearby untrained reaches. We recorded neural activity in PMd and M1 when monkeys performed the task using Utah arrays and Neuropixels probes. We found that preparatory and peri-movement neural activity displayed distinct and systematic changes to implement learning of new hand forces. During adaptation, preparatory neural states gradually shifted away from the "baseline repertoire" (the set of neural states for reaching to all targets pre-learning). The "after-learning repertoire" (the set of neural states for reaching to all targets in error clamp trials) was separated

from baseline repertoire. Surprisingly, this shift in preparatory states was observed preceeding reaches to both the trained and untrained targets, and therefore was a global change correlated with learning but not specific to the trained target. During learning, peri-movement neural states also shifted away from the baseline repertoire. In contrast with preparatory states, the shift in peri-movement neural states occurred immediately during learning and reflected the online feedback control of compensatory hand force. Peri-movement state shifts were local, and paralleled the bell-shaped behavioral generalization.
These findings begin to illustrate how systematic changes in neural population activity facilitate learning novel movement dynamics and how neural circuits learn to adapt activity patterns to changing task demands.

Disclosures: **X. Sun:** None. **D.J. O'Shea:** None. **E.M. Trautmann:** None. **M.D. Golub:** None. **S. Vyas:** None. **T.G. Fisher:** None. **S. Ryu:** None. **K.V. Shenoy:** F. Consulting Fees (e.g., advisory boards); Neurolink.

Poster

582. Animal-Reaching Motor Learning

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National Defense Science and Engineering Graduate Fellowship
UCSF Discovery Fellows Program
Markowski-Leach Fellowship, the UCSF Medical Scientist Training Program

Title: Coordination between local and distributed population dynamics drives skilled motor behaviors

Authors: *K. DEROSIER[1,3], T. VEUTHEY[1,3], K. GANGULY[2,3];
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Abstract: The connectivity pattern of mammalian cortex, characterized by dense local and sparse cross-area connections, suggests an important role for interactions between local population dynamics and population dynamics that coordinate across areas. Analysis of population dynamics in cortex has generally used methods that maximize variance within a single region before comparing these local dynamics to each other. However, such methods may

not be appropriate for analyzing coordination between regions. These methods may dismiss as noise fluctuations that represent cross-area population dynamics. Importantly, recent work shows that population activity in visual cortex contains a 'communication subspace' which captures variance distributed across areas (Semedo et al. 2019 Neuron). However, it is unknown whether such communication subspaces are relevant for behavior and learning. Here, we address this question in the motor cortical network, where local population dynamics are known to change with learning but cross-area population dynamics remain uncharacterized. This study aims to measure interactions between cross-area population dynamics and local population dynamics in primary motor (M1) and premotor (M2) cortex, and to assess the behavioral relevance of cross-area population dynamics during motor skill learning. We used multisite recordings in M1 and M2, along with computational modeling, to analyze how local and cross-area population dynamics interact during skilled reach learning (n=4 rats). We found that local activity patterns in each region were distinct from cross-area activity patterns throughout learning. Surprisingly, we found the correlation of cross-area dynamics did not change with learning, suggesting that changes in functional connectivity do not drive learning. However, emergence of high amplitude cross-area dynamics time-locked to behavior did coincide with learning, and cross-area activity amplitude was predictive of single-trial behavior. This supports a model where changes in the amplitude drive learning. Consistent with this, M2 inactivation via muscimol (n=3 animals) disrupted behavior and dampened M1 cross-area dynamics while maintaining the fundamental relationship between M1 population activity and behavior. Together, our results indicate that cross-area M1-M2 population dynamics are important for driving skilled movements, in part through their influence on local dynamics.

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Poster

582. Animal-Reaching Motor Learning

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Program #/Poster #: 582.04/M23

Topic: E.04. Voluntary Movements

Support: NRF Grant 2018R1A6A3A11050549

Title: Neuronal ensemble encoding bimanual motor coordination in mice

Authors: ***M. JEONG**[1], H. LEE[1], E. WANG[2], D. JANG[1], B. LIM[3], S.-B. PAIK[1], D. KIM[1]; [1]KAIST, Daejeon, Korea, Republic of; [2]UCSD, La jolla, CA; [3]Biol. Sci., UCSD, La Jolla, CA

Abstract: The use of forelimbs to manipulate objects is a behavioral trait widespread among many mammals. Though it is well known that each hemisphere of motor-related brain regions control movements of each side of forelimbs, how neurons are encoding action sequences to

move both forelimbs in a precise order remains still elusive. Here, we developed a bimanual press paradigm where mice learn to press left and right pedals via different forelimbs in a specific sequence for a reward. We confirmed that success rates continuously increased and the mice successfully learned the task during three weeks training. We expect to find out neural mechanisms of sequential bimanual coordination using this rodent behavioral model with calcium imaging, single unit recording, and optogenetics.

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Poster

582. Animal-Reaching Motor Learning

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Topic: E.04. Voluntary Movements

Support: The Ministry of Internal Affairs and Communications
JSPS KAKENHI Grant Number 16K01490
JSPS KAKENHI Grant Number 17H00742

Title: Error signals in the red nucleus that drive adaptation in reaching: Comparison with errors in the cerebral cortices

Authors: *M. INOUE[1], S. KITAZAWA[2,3,4];
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Abstract: Errors in reaching could result from imperfect motor commands (motor error) or from target movements (target error). We have recently shown that motor error in the primary motor and the premotor cortices as well as in area 5 drives adaptation to compensate for the motor error, whereas target error in area 7 drives adaptation to compensate for the target error (Inoue et al., 2016; Inoue & Kitazawa 2018). The red nucleus (RN) receives inputs from many regions in the cerebral cortex and sends output to the climbing fibers of the cerebellar cortex via the inferior olivary nucleus. We thus aimed at testing whether the RN encodes motor and/or target errors and whether the errors are causally related to adaptation in reaching.To test this hypothesis, we recorded neuronal activities of RN while two monkeys made rapid reaching movement toward a visual target that appeared at a random location on a tangent screen. In one condition (prism condition) the motor error was augmented in a random direction by using a motor-driven prism device. In another (target-jump condition), the target jumped in a random direction to introduce

target errors. Of the 81 RN neurons we recorded, 12 RN neurons encoded motor error alone, 10 neurons encoded target error alone, and 13 neurons encoded both. Repetitive pairing of reaching movements with microstimulation to each recording site revealed that motor errors were compensated when the neuron of the stimulation site encoded motor error (n = 14). By contrast, target errors were compensated when the neuron of the stimulation encoded target error (n = 15). These results suggest that the RN provides signals for adapting to the target errors in addition to those for adapting to the motor errors.

Disclosures: M. Inoue: None. **S. Kitazawa:** None.

Poster

582. Animal-Reaching Motor Learning

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Program #/Poster #: 582.06/M25

Topic: E.04. Voluntary Movements

Support: MRC Grant: MR/P012922/1

Title: Investigating flexion synergies post-CST lesion in a NHP

Authors: *A. J. GOTT[1], S. N. BAKER[1], R. SHADMEHR[2], S. T. ALBERT[3], J. W. KRAKAUER[4];
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Abstract: Investigating changes in motor pathways following a motor cortical lesion (such as after a stroke) are important for understanding recovery post-injury. Whilst partial recovery of normal movement is commonly seen in stroke patients over time, some develop spasticity or synergies (an obligate co-contraction of muscles which are not agonists). The flexion synergy of the upper limb involves inappropriate elbow flexion produced during shoulder abduction; this has considerable impact on reach extent and range of movement. It is not clear why synergies develop, and to date no primate model of this phenomenon has been reported. In this preliminary study, we made objective measurements capable of detecting synergies in a monkey before and after a cortical ischaemic lesion. The single female rhesus macaque monkey was trained to perform a simple reach task with movement originating from 4 set positions for a small food reward. EMG activity from 11 muscles located in the arm and shoulder were recorded during performance of this task. Three synchronised video cameras captured the full range of movement at high frame rate, allowing subsequent kinematic analysis. After a period of capturing baseline data, an ischaemic lesion of the primary motor cortex was produced using injections of endothelial-1 over a period of 2 hours. The size and location of the lesion were confirmed using

MRI 7 days later. Beginning 2 days post-lesion, further recordings during reach task performance were made, and EMG and kinematic data were compared with the pre-lesion recordings. We found significant changes to EMG activity in many of the muscles beginning a week post-lesion, in patterns that were broadly consistent with post-stroke synergies seen in human patients. These preliminary data demonstrate the feasibility of generating a monkey model for the development of post-stroke synergies.

Disclosures: A.J. Gott: None. **S.N. Baker:** None. **R. Shadmehr:** None. **S.T. Albert:** None. **J.W. Krakauer:** None.

Poster

582. Animal-Reaching Motor Learning

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Program #/Poster #: 582.07/M26

Topic: E.04. Voluntary Movements

Support: NIH Grant 1R43AG059509
UT-Dallas Funding Support

Title: A wireless operant behavior system for fine motor assessments in standard rack-mounted home cages

Authors: *A. M. SLOAN[1], C. A. SANCHEZ[2], D. K. BORN[1], C. A. THORN[3];
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Abstract: Current methods for longitudinally assessing skilled motor function in aging rodent models are labor intensive and time-consuming to administer frequently over long timescales. The proliferation of new rodent genetic models for motor diseases in which age is a primary risk factor adds new urgency to the need to develop more efficient methods for phenotyping motor function. We report the development of 'OmniHome', a wireless, battery-powered operant behavior system designed for unsupervised administration of skilled motor testing in standard, unmodified rack-mount home cages. Initial validation testing of 'OmniHome' tracked behavioral performance of PARK/DJ-1 knockout rats and aged-matched wild-type controls on an isometric pull task conducted semi-continuously in the animals' home cages over 4+ months.

Disclosures: A.M. Sloan: A. Employment/Salary (full or part-time):; Vulintus, Inc.. 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.; PI - 1R43AG059509, PI - 1R43MH119734. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual

property rights/patent holder, excluding diversified mutual funds); Vulintus, Inc.. **C.A. Sanchez:** None. **D.K. Born:** A. Employment/Salary (full or part-time):; Vulintus, inc.. **C.A. Thorn:** None.

Poster

582. Animal-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 582.08/M27

Topic: E.04. Voluntary Movements

Title: A 3 dof pneumatically-actuated robotic system for complex reaching tasks in rodents compatible with electrophysiology

Authors: *B. J. GEREKE[1], B. R. NELSON[3], K. E. BOUCHARD[2];
[2]Biol. Systems and Engin., [1]Lawrence Berkeley Natl. Lab., Berkeley, CA; [3]Neurosci., Univ. of California Berkeley, Berkeley, CA

Abstract: Reaching and interacting with objects are complex behaviors that require precise coordination of effectors comprised of many degrees of freedom (i.e., shoulder, elbow, wrist and finger joints). How broadly distributed brain circuits organize such precisely coordinated behaviors is poorly understood. The use of complex tasks (e.g., center-out reaching) in non-human primates (NHPs) has led to important advancements in identifying the neural correlates of sensorimotor planning, execution, and adaptation. Despite these successes, NHPs have limitations in terms of data throughput and amenability to many neuroscientific tools. Thus, there has been a movement in recent years to develop behavioral tasks for rodents comparable to those studied in NHPs. Most current rodent forelimb motor tasks are limited to simple pushing/pulling of levers/joysticks, or to reaching for food pellets. Such tasks lack either directionality or the option to dynamically perturb movements, require excessive training or experimenter intervention, and/or are incompatible with electrophysiological and imaging tools. Here, we describe a novel directional reaching task for rodents which overcomes many of these limitations. We developed a three dof pneumatically-actuated robot that is able to precisely position handles of various shapes and sizes in front of either freely-moving, or head-restrained rats. We demonstrate that rats rapidly learn to reach toward, grasp, and pull the handle to their mouths for liquid reward. The task is fully automated, and rats are able to learn the behavior and perform a large number of trials even within a single session. Reaches are detected in real-time and selectively recorded by multiple synchronized high-speed cameras. This allows for the potential to track joint kinematics using multiview markerless 3D pose estimation approaches. Licking is detected by IR beam break which ensures compatibility with electrophysiology. The use of pneumatics allows the stiffness of the system to be controlled and enables fast perturbations of variable magnitude/duration to be applied to the handle in different directions and points along the reach trajectory. The entire system is cheap, built from off-the-shelf and 3D

printed parts, and multiple systems can be housed in a single room. These features combine the richness of a primate behavioral task with the methodological amenability and high-throughput advantages of rodents. It is anticipated that this combination will enable questions related to sensorimotor processing, planning, adaptation and decision-making to be studied at a new level of detail that is currently more difficult to achieve in primates.

Disclosures: B.J. Gereke: None. **B.R. Nelson:** None. **K.E. Bouchard:** None.

Poster

582. Animal-Reaching Motor Learning

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 582.09/M28

Topic: E.04. Voluntary Movements

Support: The University of Texas at Dallas

Title: Exploring the necessity of dopamine in vagus nerve stimulation induced motor map expansion

Authors: *J. BROUGHER, C. A. THORN;
Univ. of Texas At Dallas, Richardson, TX

Abstract: Vagus Nerve Stimulation (VNS) is capable of inducing plasticity in the motor cortex (M1), which can be measured through increased cortical map representation of specific motor movements. VNS's pro-plasticity mechanisms are not well understood, though it is known to require the release of neuromodulators, including norepinephrine and acetylcholine. Dopaminergic enervation of M1 has been shown to be necessary for skill acquisition at the behavioral level and dendritic spine growth at the molecular level, suggesting that dopamine (DA) may be also be critical for many forms of M1 plasticity. We therefore wished to determine whether DA is required for VNS-induced map expansion to occur. To do so we selectively eliminated DA projections to M1 using 6-OHDA lesions to the forelimb motor area. Animals subsequently underwent a VNS-paired training paradigm known to result in motor map expansion. Male and female adult Long-Evans rats were trained to stable proficiency on a lever-pressing task requiring skilled forelimb reaching. Rats were then implanted with a vagus nerve cuff electrode around the left vagus nerve in the neck and received 6-OHDA (or vehicle) infusions in M1 to lesion M1-projecting DA cells. Following recovery from surgery, rats received 10 additional behavioral training sessions in which VNS (or sham stimulation) was paired with correct lever press performance (4 groups; n = 12 per group). Animals were excluded if they failed to reach at least 700 total stimulations across all 10 sessions. After the final behavioral session, animals were anesthetized and intracranial microstimulation was performed to quantify the motor map representations in M1. Experiments were performed blinded to drug

treatment condition. Histological analysis was performed to verify DA lesions. Data were analyzed for sex differences. Preliminary data from these studies suggests that DA may not be required for VNS-induced map expansion to occur. If confirmed, these results could indicate that VNS may engage a different set of pro-plasticity mechanisms in M1 than natural skill learning. These studies provide insight into the role of neuromodulator signaling in multiple forms of cortical plasticty.

Disclosures: J. Brougher: None. **C.A. Thorn:** None.

Poster

582. Animal-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 582.10/M29

Topic: E.04. Voluntary Movements

Support: University of Texas at Dallas

Title: Noradrenergic alpha-2 receptor antagonism inhibits vagus nerve stimulation dependent enhancement of motor cortical plasticity

Authors: *C.-T. TSENG, S. J. GAULDING, C. A. THORN;
Cognition and Neurosci., Univ. of Texas At Dallas, Richardson, TX

Abstract: Vagus nerve stimulation (VNS) paired with rehabilitation training can induce specific plasticity in motor cortex (M1) and restore the motor functions following stroke. In rats, it is known that VNS paired with skilled forelimb training results in the expansion of motor representations of the trained limb in M1; however, the mechanisms underlying VNS-induced cortical plasticity remain unclear. Previous studies demonstrate that VNS drives phasic firing of the locus coeruleus, and selective lesions to the noradrenergic neurons enervating M1 block VNS-induced map expansion. These previous studies suggest that local noradrenergic neuromodulation may be required for VNS-dependent plasticity. In particular, alpha-2 noradrenergic receptor (α2-AR) activation has been shown to inhibit HCN channels in rat prefrontal pyramidal cells, leading to enhanced dendritic integration and synaptic plasticity. In this study, we test the hypothesis that α2-AR activation is required for VNS dependent reorganization of rat motor cortex by locally infusing yohimbine (YOH), a selective α2-AR antagonist, into M1 while rats receive VNS paired with training. We further ask whether direct blockade of HCN channels with ZD7288 can rescue VNS-dependent plasticity in M1 in the presence of α2-AR antagonism. In these experiments, 35 male and 35 female Sprague Dawley rats were trained to perform a lever pressing task that requires skilled forelimb reaching. Once stable proficiency on the task was reached rats were implanted with VNS cuff electrodes and intracranial cannula targeting the forelimb area of M1. After recovery from surgery, rats

underwent 10 sessions of training in which VNS, or sham stimulation, was paired with each correct lever press. YOH, ZD7288, or vehicle, were locally infused into M1 30 minutes prior to each training session. After the final session, intracortical microstimulation was used to quantify motor map representations in M1. All experiments were performed by personnel blinded to the treatment conditions, and data were analyzed for sex differences. Preliminary results from these studies indicate that inactivation of α2-AR with YOH prevents VNS-induced motor map expansion in both male and female rats. Data from ongoing experiments in which ZD7288 was co-administered with YOH are suggestive of a trend toward the ability of HCN channel blockade to partially restore VNS-dependent plasticity. By investigating the involvement of α2-AR-mediated inhibition of HCN channel signaling during VNS dependent motor map expansion, the results of these studies provide novel insight into the neuromodulatory mechanisms underlying VNS-mediated cortical plasticity.

Disclosures: C. Tseng: None. **S.J. Gaulding:** None. **C.A. Thorn:** None.

Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 583.01/M30

Topic: E.04. Voluntary Movements

Support: Simons Foundation Collaboration for the Global Brain

Title: Selective gating of dynamical modes in a thalamo-cortical system

Authors: *J. JARAMILLO[1], K. SVOBODA[2], X.-J. WANG[1,3];
[1]New York Univ. Ctr. for Neural Sci., New York, NY; [2]HHMI / Janelia Farm Res. Campus, Ashburn, VA; [3]Shanghai Res. Ctr. for Brain Sci. and Brain-Inspired Intelligence, Shanghai, China

Abstract: The brain is often portrayed as a complex system of discrete interacting components, but it is not known how the brain exploits such a distributed and dynamic architecture. For example, there is mounting evidence for the involvement of subcortical structures in cognitive processes that were typically attributed to the cortex alone, but whether and how subcortical structures modulate cortical computations relevant for cognitive processes remains unclear. A notable function of several thalamic nuclei is to convey information to the cortex from subcortical structures such as the cerebellum and basal ganglia. In this modeling study we propose a circuit mechanism by which these subcortical structures, indirectly via the thalamus, modulate cortical dynamics. We put forward a circuit model of thalamo-cortical interactions that is constrained structurally by tracing and *in vitro* studies and functionally by multisite recordings in the mouse during a two-alternative forced choice task. In our model, a cortical area consists of

a set of coupled excitatory and inhibitory neural populations that exhibit low-dimensional dynamics, here referred to as “dynamical modes”. In the context of delayed two-alternative forced choice tasks, some of these cortical modes are functionally relevant: a ramping mode is related to winner-take-all processes involved in decision making while a stimulus-absent persistent mode is related to short-term memory maintenance. We contend that thalamo-cortical projections induce a reconfiguration of the cortical network, effectively changing its dynamical landscape. As a consequence, some cortical dynamical modes will be amplified or modified while others will be suppressed, a dynamical process we refer to as ‘thalamic gating of dynamical modes’. We explored how thalamo-cortical connectivity and the input current to the thalamus - corresponding to external stimulation or to salient subcortical structures such as the cerebellum and basal ganglia - influence such thalamic gating. Our simulation results suggest a distributed dynamical organization whereby subcortical nodes induce a reconfiguration of the cortical network that allows distinct cortical output modes to flexibly control behavior.

Disclosures: **J. Jaramillo:** None. **K. Svoboda:** None. **X. Wang:** None.

Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

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Program #/Poster #: 583.02/M31

Topic: E.04. Voluntary Movements

Support: Simons foundation collaboration on the global brain SCGB 542969SPI

Title: Analysis of neural representations of movement and internal states by video-based prediction in a short-term memory task

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Abstract: A key question in systems neuroscience is understanding neural representations in cognitive tasks. These tasks are typically considered in terms of abstract cognitive performance, yet it is known that animals may associate particular postures or movements with different task features such as different choices in an alternative-choice-task. More generally, cognitive and emotional states are associated with typical movements, e.g., pacing when nervous, creating a difficulty in assignment of neural representation to the internal state or the movement. Understanding the neural representations underlying internal states stands to benefit from a richer understanding of how posture and movements during cognitive tasks relate to neural representations.

We trained artificial neural networks to predict animal behavior and single-neuron spike rates in multiple brain areas from videos of mice performing a short-term memory task. Mice were trained to discriminate a sensory stimulus into one of two categories, hold this discrimination in memory for a few seconds and then report its identity by two different actions (lick-left or lick-right). High-speed (300 Hz) multi-view video of the face and paws of the mouse was acquired together with extracellular recordings using 2-4 Neuropixels probes. We were able to accurately (90 %) predict upcoming actions from videos taken during the stimulus presentation epoch or memory epoch. Generalization to mice not present in the dataset was also possible, though accuracy was improved by adding a session of data from the mouse to be predicted into the dataset. We were also able to predict a substantial proportion of variability in single-trial spike rate from videos, well beyond what is predictable from trial-averaged activity (PSTHs). Predictability varied considerably across neurons, from no predictability to above 90 %. Areas more associated with motor control (e.g. the medulla for facial movements), had higher single-trial explained variance than areas related to motor preparation (e.g. Anterior Lateral Motor cortex). We compare the performance from video-based prediction to prediction from static images and from tracked facial features (using DeepLabCut), and found that prediction based on raw video was more accurate.
Finally, the main disadvantage of using artificial neuron networks are the well-known difficulties in interpreting the source of the information they use to solve the task they were trained to perform. We employed multiple visualization techniques to understand the factors driving behavioral and neural predictability.

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Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 583.03/M32

Topic: E.04. Voluntary Movements

Support: HHMI
Simons Collaboration on the Global Brain
CIHR Fellowship
Wellcome Trust Fellowship

Title: Mesoscale analysis of motor planning and movement initiation across multiple brain regions

Authors: ***L. D. LIU**[1,2], S. CHEN[2,3], A. WANG[4], M. N. ECONOMO[2,5], T. WANG[2], X.-J. WANG[6], S. DRUCKMANN[4], K. SVOBODA[2], N. LI[1];

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Abstract: Movement planning is reflected in neuronal activity across multiple brain regions seconds before movements occur (Svoboda & Li, CONB 2018). The dynamics of multi-regional circuits gives insight into the mechanisms of motor planning and the initiation of movement. Recent advances in large-scale electrophysiology (e.g. Neuropixels probes) provide the opportunity for simultaneous recordings of neuronal activity across multiple brain regions. We used two to four Neuropixels probes to record from up to a dozen brain areas simultaneously. Our goal is to produce comprehensive, whole brain 'activity maps' for mice during decision-making, motor planning and movement initiation.

Head-restrained mice performed a delayed-response task. Mice make a sensory discrimination, followed by a delay epoch during which they plan a directional lick movement, and then followed by a response epoch during which they execute the movement. We have previously identified the anterior lateral motor cortex (ALM) as a region critical for motor planning and movement initiation. Based on anatomy, we targeted brain areas that form multi-regional networks with ALM for electrophysiological recordings. Each electrode track was recovered and imaged in three dimensions. Individual electrode sites were mapped into a standardized brain atlas based on the imaging data and electrophysiological measurements.

We present data from ALM and connected areas in the thalamus, basal ganglia, superior colliculus, cerebellum, and medulla. Neural activity in ALM encodes the behavioral choice long before movements, whereas activity in the medulla in addition correlates with jaw, tongue and other facial movements with millisecond time-scale precision. Encoding models based on facial movements could explain variance in neural activity (see also accompanying poster by Wang et al), but the encoding is much more precise for medulla activity compared to ALM activity. During the delay epoch, a subpopulation of medulla neurons showed rhythmic activity in phase with future tongue movements at 7-10 Hz; other neurons exhibited ramping activity that collapsed just before tongue movement onset. These measurements suggest that medulla orofacial central pattern generators are already engaged during the delay epoch and under active inhibition (similar to a mechanical clutch). These experiments reveal detailed multi-regional neuronal dynamics underlying movement planning and initiation.

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Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 583.04/M33

Topic: E.04. Voluntary Movements

Title: Attractor dynamics gate cortical information flow during decision-making

Authors: *A. FINKELSTEIN[1], L. FONTOLAN[1], M. N. ECONOMO[1], N. LI[1,2], S. ROMANI[1], K. SVOBODA[1];
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Abstract: Perceptual decision-making involves information flow from sensory to motor areas. When sensation and action are separated in time, the chosen course of action should be robustly represented in memory until movement execution, while also being flexible in case additional relevant sensory information becomes available. If and how communication between sensory and motor areas is dynamically gated remains unknown. We trained mice to report detection of stimuli with directional licking, following a brief delay epoch separating sensation and action. To precisely control activity in the sensory cortex, we used direct photostimulation of genetically defined neurons in the vibrissal somatosensory cortex (vS1) as a 'sensory stimulus'. We found that stimuli biased future actions only when presented during early, but not late, stages of decision-making - suggesting temporal gating of incoming information from the sensory cortex. Neurons in the anterior lateral motor cortex (ALM) - a crucial node in the decision-making circuit that controls directional-licking - showed preparatory activity that predicted the upcoming movement, similar to behaviors with natural sensory stimuli (Svoboda, Li 2018). Stimuli caused similar transient neural responses throughout the sample and delay epochs in both vS1 and ALM, implying that sensory information was not gated in vS1 or on its way to ALM. Instead, gating occurred at the level of ALM dynamics: Preparatory activity in ALM became progressively more robust to incoming stimuli, and this robustness increased with additional behavioral training. To investigate how robustness of preparatory activity results in gating we trained recurrent neural networks (RNNs) to reproduce the heterogeneous neuronal activity patterns recorded in ALM (Rajan et al 2016). Remarkably, RNN dynamics predicted the temporal gating observed in the data, even though the network was trained only with early stimuli. Analysis of RNN dynamics revealed that our results are consistent with a discrete attractor model. In this model a non-selective external ramping input gradually separates the two basins of attraction corresponding to alternative motor plans, resulting in increase of robustness of the selected motor plan. Taken together our results demonstrate a mechanism for temporal gating of cortical information flow during decision-making that allows early flexibility and late robustness of the motor plan.

Disclosures: A. Finkelstein: None. **L. Fontolan:** None. **M.N. Economo:** None. **N. Li:** None. **S. Romani:** None. **K. Svoboda:** None.

Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

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Program #/Poster #: 583.05/M34

Topic: E.04. Voluntary Movements

Support: NIH grant EY007023

Title: A new interpretation of visual cortical areas in mice

Authors: *M. HU[1], R. V. RIKHYE[2], M. GOARD[3], M. G. M. KUMAR[4], H. MURTHY[4], M. SUR[1];
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Abstract: Much like other mammals, mouse visual cortex is composed of multiple areas, each containing a separate representation of the visual field. Early studies (Caviness, 1975; Drager, 1975; Wagor, Mangini and Pearlman, 1980) found that the region lateral to V1 contains at least two complete representations, labeled V2 and V3, whereas the region medial to V1 contains two partial representations, labeled Vm-r (medial rostral region) and Vm-c (medial caudal region) respectively. Subsequent work (Kalatsky and Stryker, 2003; Wang and Burkhalter, 2007; Marshel et al., 2011; Garrett et al., 2014; Zhuang et al., 2017; Waters et al., 2019) reported a number of extrastriate areas lateral and medial to V1. The sizes of these extrastriate areas are much smaller and more variable than V1. In an attempt to reconcile these studies, we used wide-field and single-cell calcium imaging from awake, head-fixed mice, which transgenically expressed GCaMP6f, to functionally segment the entire visual cortex. We further characterized the responses of neurons within each segmented area to drifting gratings and natural scene movies. Our key observations are two-fold. First, the lateral regions align closely with consistent features of extrastriate visual cortex in other species. Specifically, RL and LM together constitute a single and complete representation, consistent with its potential function as a second tier representation along the extrastriate pathway (V2), whereas AL functions as a third tier representation (V3). The regions within AL, RL/LM and V1 that represent the central visual field are organized closely next to each other in a narrow band which resembles the ‘foveal confluence’ (Zeki 1969; Newsome et al., 1986; Maunsell and van Essen, 1987; Gattass et al., 1988, 2005; Tootell et al., 1998; Schira et al., 2009, 2010) described in other species. These interpretations are strongly supported by the shared vertical meridian border between V1 and RL+LM, and the split representation of the horizontal meridian at the lateral border of RL+LM, including with AL. Second, the two medial areas (AM, PM) align closely with distal visual cortex (prostriata) recently described in marmosets (Yu et al., 2012) and humans (Mikellidou et

al., 2017; Tamietto & Leopold, 2018), and they similarly share a peripheral visual field border with V1. We propose a framework of mouse visual cortex organization that follows the same global principles of visual cortex maps in other species, with variations in local layout that possibly reflect the ecological adaption of vision in these species.

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Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

Location: Hall A

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Program #/Poster #: 583.06/M35

Topic: E.04. Voluntary Movements

Support: NIH grants EY007023
NIH grants EY028219

Title: Involvement of the locus coeruleus network in an attention-demanding sensory discrimination task

Authors: *V. BRETON-PROVENCHER, M. SUR;
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Abstract: Speed and accuracy on tasks involving high levels of uncertainty depend on arousal and attention. For example, driving during a downpour requires heightened attention compared to driving during a sunny day. Recent human and theoretical studies have described a link between uncertainty, arousal, and locus coeruleus (LC) activity. However, due to limitations of causal interrogation of brain function in these studies, how behavioral uncertainty may recruit the LC neuronal network remains unclear. Furthermore, while this recruitment implies regulation of noradrenaline (NA), the neuronal substrates of such a process are unknown. Here we used an attention-demanding task in head-fixed awake mice to assess the role of LC circuits in decisions during high uncertainty. We have used a go/no-go auditory discrimination task in which the mouse must quickly decide to enact or withhold a lever press after hearing a tone to obtain a reward or avoid a punishment. To introduce uncertainty and increase attentional demand, we vary the intensity and the timing of the auditory cues. Direct recordings of LC-NA neurons using phototagging display a high level of modulation of LC-NA spiking activity to specific task epochs. NA activity increases rapidly following the presentation of the tone during correct responses on ‘go’ trials, or after the delivery of reinforcements for both ‘go’ and ‘no-go’ trials. The level of uncertainty, with respect to the identity of the auditory stimulus, scales this response of NA neurons. We are now investigating the involvement of inhibitory neurons of the LC network, the LC-GABA neurons, in the behavior using phototagging. We are also silencing the

activity of LC-NA or LC-GABA neurons using archaerhodopsin targeted at each population, to evaluate the causal contribution of the different components of the LC network for task execution. Collectively, our results indicate that decision-making during high levels of uncertainty recruits NA activity.

Disclosures: V. Breton-Provencher: None. **M. Sur:** None.

Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

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Topic: E.04. Voluntary Movements

Support: NIH Grant EY007023
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NIH K99 MH112855

Title: Prefrontal cortex-superior colliculus interactions during visually guided decision-making

Authors: R. HUDA, ***K. G. CRUZ**, A. SULLINS, M. SUR;
Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: Perceptual decision-making requires mechanisms for promoting and inhibiting specific choices in accordance with task goals. The prefrontal cortex has long been implicated in guiding goal-oriented choices by generating control signals and selectively modulating the activity of downstream target structures. A similarly large body of work also ascribes an important role for midbrain circuits in choice selection and execution. Yet, how prefrontal and midbrain circuits interact to facilitate goal-oriented choices remains unresolved.
To address this question, we developed a two-alternative forced choice visual decision making task in which head-fixed mice report the spatial location of a target stimulus while suppressing responses to simultaneously presented distractor cues. Mice learn this task well and perform hundreds of trials per session, allowing us to construct high-quality psychometric functions. Our previous work, in combination with other recent studies, suggests that a subdivision of the mouse prefrontal cortex, the anterior cingulate cortex (ACC), is a crucial anatomical node for coordinating visually-guided behavior. Our anatomical studies show that the ACC provides direct top-down inputs to the superior colliculus (SC). We are defining the function of ACC-superior colliculus interactions using a combination of areal and projection-specific optogenetic manipulations during behavior. Results to date suggest that the ACC and SC play opposing, but complementary functional roles in the task. Targeted projection-specific inactivations suggest that the ACC exerts top-down inhibitory control over the SC. We are currently using two-photon calcium imaging to assess the physiological responses of ACC neurons that target the SC and

determine their specific role in the decision-making process. Overall, our work suggests that the prefrontal cortex exerts top-down inhibitory control over midbrain circuits to facilitate goal-oriented choices.

Disclosures: R. Huda: None. **K.G. Cruz:** None. **A. Sullins:** None. **M. Sur:** None.

Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

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Program #/Poster #: 583.08/M37

Topic: E.04. Voluntary Movements

Support: NIH grants EY007023
Picower Fellowship

Title: Dynamic control of visually-guided locomotion through cortico-subthalamic projections

Authors: *E. M. ADAM, T. JOHNS, M. SUR;
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Abstract: Voluntary movement is fundamental as our means to act upon the world. We are interested in how the brain controls actions aligned with an organism's behavioral goals. We developed a behavioral task where mice run on a treadmill through a virtual runway and stop at visual landmarks to collect reward. The task enables a voluntary on-off visually guided locomotion pattern, constructed of sudden initiations and sudden halts. Where do control signals enabling such a pattern emanate from and how are they processed to control locomotion? Extracellular recordings in the mesencephalic locomotor region (MLR) reveal neural activity tuned to that locomotion pattern. The visually guided nature of the task further implicates cortical control, hypothesized to be over MLR. Such a control can however only be indirect, as there are no significant projections from cortex to MLR. We find that prefrontal cortex (PFC) projections to subthalamic regions (specifically the subthalamic nucleus and zona incerta) mediate stop commands, thereby posing the region as a direct controller onto MLR. Through a combination of simultaneous in-vivo extracellular recordings of PFC and MLR, calcium imaging of PFC projection neurons, axonal optogenetic manipulations in subthalamic regions, and targeted recordings of identified subthalamic neurons, all in behaving animals, we are reconstructing the dynamical nature of the control mechanism and the neural circuitry by which it is implemented.

Disclosures: E.M. Adam: None. **T. Johns:** None. **M. Sur:** None.

Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

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Program #/Poster #: 583.09/M38

Topic: E.04. Voluntary Movements

Support: NIH EY007023
NIH EY028219

Title: Modulation of neuronal coding by astrocytes during motor learning

Authors: C. DELEPINE[1], ***K. LI**[1], V. SHAH[2], T. JOHNS[1], M. SUR[3,1];
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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 $^{Ca2+}$ signaling. However the contribution of astrocytes *in vivo* to complex behaviors and cognition remains unresolved. During motor learning, the primary motor cortex (M1) is functionally and structurally reorganized, manifest in changes of neuronal activity and dendritic spine turnover. We hypothesize that astrocytes modulate learning-associated neuronal network reorganization by influencing synaptic strength through glutamate clearance and $^{Ca2+}$ signaling. Here we investigated the role of cortical astrocytes in a motor learning task *in vivo*, where mice were rewarded for pushing a lever following an auditory cue. Using the engineered human muscarinic G protein-coupled receptor DREADD-hM3Dq activated by low doses of clozapine-N-oxide (CNO), we found that modulation of astrocyte $^{Ca2+}$ activity perturbed task performance, causing decreased responses rate and increased delay. Using a transgenic mouse line in which the expression of the glutamate transporter GLT1 was inhibited locally in M1, we found that decreasing astrocyte glutamate clearance prevented learning of a stereotypical motor trajectory while increasing response rate. Using genetically encoded $^{Ca2+}$ indicators and high-resolution two-photon imaging, we imaged neuron activity during execution of the motor task following training with astrocyte manipulation. Perturbing $^{Ca2+}$ activity and glutamate clearance both disrupted M1 neurons' capability to encode the motor command, as in both cases neuron populations showed drastically weakened performance when decoding for lever trajectory. Perturbation of astrocyte $^{Ca2+}$ activity was found to create a higher level of correlated noise in neural activity and to hamper neurons' ability to encode for lever trajectory. In contrast, decreased glutamate clearance by astrocytes increased neuronal activity and prevented the emergence of highly motion relevant neurons in the circuit, potentially by decreasing their dynamic range. These findings demonstrate specific contributions by astrocytes to the creation of

neuronal ensembles during motor learning, and their representation and encoding of learned trajectories.

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Poster

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Topic: E.04. Voluntary Movements

Support: NIH Grant 1DP2HD087952-01
Mong Cornell Neurotech Fellowship
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Klingenstien Fellowship

Title: Cortical contribution to lingual kinematics as the tongue reaches for, and misses, targets

Authors: *T. BOLLU[1], S. C. WHITEHEAD[2], B. KARDON[1], J. REDD[3], M. LIU[1], J. H. GOLDBERG[1];
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Abstract: Many animals, including humans and rodents, have prehensile tongues that act external to the oral cavity to contact objects such as food, water and conspecifics (Kier, 1985;Hiiemae, 2003). During natural behaviors such as licking, eating and grooming, tongues must precisely contact unseen targets. Yet from the motor control perspective, it remains unknown if animals 'reach' with their tongues. For example, when a mouse licks at an unseen water spout, does its tongue, like a hand, make an initial guess and, after a miss, produce corrective submovements to zero in on the spout?
Identifying motor control principles requires precise quantification of moment-to-moment movement kinematics, but lingual kinematics are difficult to resolve because tongues are complicated, deformable effectors that move extremely fast (Kier, 1985; Hiiemae, 2003). Even in tractable model systems such as rodents, licking is usually measured as a binary register of tongue-spout contact (Guo, 2014; Komiyama, 2010; Li, 2015; Goard, 2016;Williams, 2018;Chen, 2019), with EMGs (Travers, 1997), or with single plane imaging (Welsh, 1995 ;Gaffield, 2017). Recently, neural mechanisms of movement initiation, planning, and decision making have been clarified in head-fixed mouse preparations compatible with ascendant neural recording and manipulation technologies (Guo, 2014 ;Komiyama, 2010 ;Goard, 2016 ;Li, 2015 ;Gaffield, 2017; Svoboda, 2018; Crochet, 2019). Yet precise tongue kinematics during licking remain unknown.
Here, we combine kilohertz frame-rate imaging and a deep-learning based artificial neural

network (U-Net) to resolve tongue kinematics in mice performing a cued lick task. Cue-evoked licks exhibit previously unobserved, fine-scale movements which, like a hand searching for an unseen object, were produced after misses and were directionally biased towards remembered locations. Photoinhibition of anterolateral motor cortex (ALM) abolished these fine-scale adjustments, resulting in stereotyped, hypometric licks that missed the spout. Our results show that cortical activity is required for online corrections during licking and reveal novel, limb-like dynamics of the mouse tongue as it reaches for, and misses, targets.

Disclosures: **T. Bollu:** None. **S.C. Whitehead:** None. **B. Kardon:** None. **J. Redd:** None. **M. Liu:** None. **J.H. Goldberg:** None.

Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

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Topic: E.04. Voluntary Movements

Support: NIH Director's New Innovator Award (NIH 2015 DP2 HD)
Pew Scholar
NSF Graduate Research Fellowship

Title: Kinematics of the mouse tongue as it searches for a water spout

Authors: ***B. ITO**, T. BOLLU, J. GOLDBERG;
Cornell Univ., Ithaca, NY

Abstract: Reaches to unseen targets exhibit complicated trajectories, including corrective submovements that are produced after initial misses. Biasing a submovement towards a target requires an online estimate of current hand position as well as target location. However, the neural mechanisms of submovement production and aiming remain unclear. Here, we combine kilohertz frame-rate imaging and machine vision to track 3D tongue kinematics as head fixed mice perform a novel directional lick task. Mice are trained to guess the location of a water spout among three distinct positions (left, center, right) on a trial-by-trial basis. A single rule specifies spout location: it cannot be in the location most recently rewarded. On trials with a lucky guess, cue-evoked licks are immediately followed by stereotyped water-retrieval licks to the just-contacted water spout, suggesting an immediate update of the lick plan by spout contact. Yet, on trials when an initial tongue protrusion missed the spout, mice produce within-lick adjustments resembling corrective submovements previously observed in primate reach studies. The demonstration that tongue kinematics during licking can resemble hand kinematics during reaching opens up opportunities for the study of motor control in head-fixed mice, an experimentally tractable preparation.

Disclosures: **B. Ito:** None. **T. Bollu:** None. **J. Goldberg:** None.

Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

Location: Hall A

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Program #/Poster #: 583.12/M41

Topic: D.08. Visual Sensory-motor Processing

Support: KAKENHI(19K06948)
KAKENHI(16H02061)
KAKENHI(19J21544)

Title: Distinct roles of primary, secondary visual cortex and posterior parietal cortex in visually-guided decision-making

Authors: ***Y. OSAKO**[1], T. OHNUKI[1], H. MANABE[4], Y. SAKURAI[2], J. HIROKAWA[3]; [1]Grad. Sch. of Brain Sci., Doshisha Univ., Kyotanabe, Japan; [2]Doshisha Univ., Kyotanabe-Shi, Japan; [3]Lab. of Neural Information, Doshisha Univ., Kyoto, Japan; [4]Grad., Sch., of Brain Science, Doshisha Univ., Kyoto, Japan

Abstract: Previous studies demonstrated that primary visual cortex (V1) and posterior parietal cortex (PPC) are involved in visually-guided decision making, including processing of visual sensory inputs, accumulation of evidences and transformation of visual sensory signals into accurate motor plans. Recent studies argued that secondary visual cortex (V2) is also involved in visually-guided decision making. However, distinct roles of these areas in visually-guided decision making remain unclear. In our previous study, we established a quantitative behavioral paradigm in rodent to evaluate subjective decision threshold for accurate visual detection performance. Here we investigated the role of V1, V2 and PPC for subjective decision threshold during our visual detection task. Electrophysiological recording revealed that V1, V2 and PPC neurons exhibited heterogeneous responses spanning stimulus and movement(response). While V1 and V2 population was predominantly selective for visual stimulus rather than visual detection performance, PPC population was selective for both visual stimulus and visual detection performance in equal proportion. Only PPC subpopulation exhibited predominantly visual response in self-initiated correct choice, while V1 and V2 subpopulation exhibited no differences between self- and forced-initiated correct choices. Interestingly, V1 subpopulation predominantly showed second peak at around 300ms after stimulus onset in detected performance, while V2 subpopulation showed it irrespective of detected performance. PPC subpopulation, which is selective for both visual and detected performance, showed motor-related response in only self-initiated movement, but not in forced movement. Our data indicated that V1 and V2 processed predominantly visual features, while PPC processed visual information and motor command. This has led a speculation that PPC is a potential candidate for

visuomotor transformation especially for self-initiated motor, suggesting that PPC subpopulation represents subjective decision threshold for self-initiated motor command.

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Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

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CONACyT Scholarship for Paola Rodríguez Moreno (CV 934973)

Title: Functional characterization of motor cortex neurons during voluntary movement execution in the rat

Authors: P. RODRIGUEZ-MORENO[1], G. SANTANA-CHAVEZ[1], R. OLIVARES-MORENO[1], M. LOPEZ-HIDALGO[2], *G. ROJAS-PILONI[1];
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Abstract: Motor cortex participates in the coordination of the activity of subcortical systems related to muscle control, playing a fundamental role in the coordination of movements and posture. In particular, layer 5 neurons connect with several subcortical structures by means of the pyramidal system contributing in various phases of the movement, such as the planning, execution and termination of movements. Pyramidal tract neurons are organized in partially segregated subgroups according to their projection site; however, it is still unknown how each subgroup participates in the information processing during voluntary movements. Here, a method has been developed to allowing us to identify and study the neuronal activity before, during and after the execution of a voluntary movement. Wistar rats (250-300 g at the time of registration) were used for the experiments. The animals were trained from postnatal day 24 until 2 and a half months, to execute a lever movement in response to a light stimulus in head-fixed conditions. Using this protocol, we recorded 63 putative neurons from layer 5 of the motor cortex (recording depths 600-1700 μm) were performed during different phases of movement. In this way, different subclasses of putative neurons of layer 5 of the motor cortex were found, which exhibit activity related to different phases of a movement and which were classified as

preparation, initiation, execution and termination. We conclude that the neurons of layer 5 related to motor control are functionally segregated.

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Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

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Topic: E.04. Voluntary Movements

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NSF 1904444-1042-C
NIH R01EB022903

Title: Dendritic resonance in a detailed model of pyramidal tract neuron of mouse primary motor cortex

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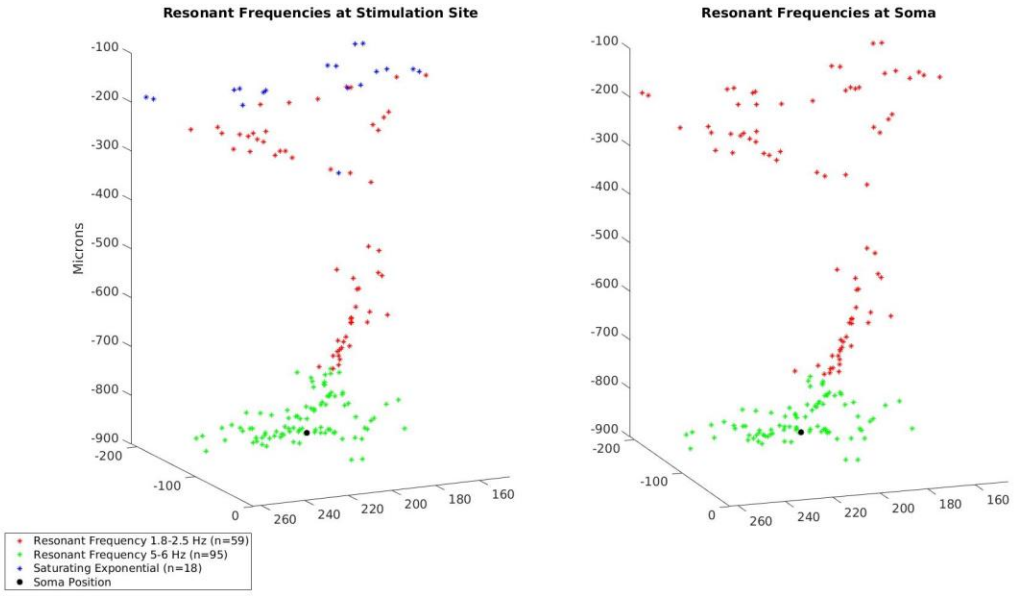
Abstract: Dendritic computation, though poorly understood, presents one of the strongest candidates for distinguishing complex biological neurons from simple integrate-and-fire analogs and still simpler units of artificial neural networks. We simulated frequency responses to subthreshold sinusoidal inputs of 0.5-20 Hz distributed across M1 apical and basilar dendritic arbors of pyramidal tract (PT) type neuron from mouse primary motor cortex (M1). Voltage recordings from the stimulated dendrites yielded three distinct groups of impedance profiles: those with broad peaks at 5-6 Hz in the basal dendrites and the apical trunk (perisomatic), those with narrow resonant peaks at 1.8-2.5 Hz for apical dendrites, and those with no discernible peaks for apical obliques. However, voltage recordings from the soma during stimulation of the saturating apical tufts showed transfer impedance profiles with resonant peaks at 1.8-2.5 Hz. At the soma, stimulation from apical dendrites showed strong positive correlation between peak impedance and frequency, while the perisomatic group had a relatively weak negative correlation between the two. The two groups both showed an inverted sigmoid relationship between peak impedance and distance from the soma, with highest impedance for proximal dendrites and a drop-off between 50-100 microns. Our findings suggest that the different populations of dendritic sections act as selectivity filters with distinct frequency response characteristics. Since synapses from long and short range inputs are spatially organized across the dendritic arbor of

PT cells, we hypothesize that these differences in dendritic resonance will play an important role in the behavior of the network and intend to investigate this further in a detailed network model.



Disclosures: **C. Kelley:** None. **S. Dura-Bernal:** None. **S. Neymotin:** None. **W.W. Lytton:** None.

Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 583.15/M44

Topic: E.04. Voluntary Movements

Support: NIH U01EB017695
NYS DOH01-C32250GG-3450000
NSF 1904444-1042-C

Title: Response to simultaneous long-range inputs and oscillatory inputs in a multiscale model of M1 microcircuits

Authors: *S. DURA-BERNAL[1], S. A. NEYMOTIN[2], B. A. SUTER[3], C. KELLEY[4], R. TEKIN[5], G. M. SHEPHERD[6], W. W. LYTTON[7];
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Abstract: We developed 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. Our model includes most major long-range inputs, primarily arising from posterior nucleus (PO) and ventrolateral thalamus (VL), and contralateral M1, primary somatosensory (S1), secondary somatosensory (S2), secondary motor (M2), and orbital (OC) cortices. We used the model to study the M1 circuit responses to simultaneous long-range inputs from different regions. We compared responses to short pulses from individual regions to combined pulses from two or more regions at varying time lags to investigate dynamical pathway interactions and information flow within the M1 microcircuit. Preliminary results showed M1 response to S2 and M2 inputs depends strongly on the order of, and interval between inputs, and the level of Ih current in pyramidal-tract corticospinal (PT) neurons (one important effect of neuromodulation by norepinephrine). We also studied oscillatory inputs with a variety of dominant frequencies seen in cortex. We computed frequency preference (resonance) of multiple populations and of different dendritic regions within individual neurons. Preliminary results indicated that IT5A and PT5B response to IT2/3 stimulation depends on frequency, phase and PT Ih level. Our results support the hypothesis that the brain encodes multiple parallel information pathways, multiplexing within and across frequencies, by filtering oscillatory synaptic inputs at the circuit and cellular level.For each of the conditions above, we computed and correlated measures of neural activity responses at multiple spatiotemporal scales: single-neuron voltage traces, single-neuron and population spiking activity, local field potentials (LFP), primary currents contributing to electro- and magnetoencephalogram (EEG/MEG) signals, and information transfer measures. Interactions observed within scale include synchronous firing of neuronal ensembles with LFP phase-amplitude coupling; interactions across scales included dendritic frequency resonance filtering synaptic inputs, and coupling of cell spiking with large-scale LFP/EEG/MEG oscillations. Analyzing correlations within and across scales identified mechanisms of multi-plexed neural signaling, and predicted observables that can be pursued experimentally.

Disclosures: S. Dura-Bernal: None. **S.A. Neymotin:** None. **B.A. Suter:** None. **C. Kelley:** None. **R. Tekin:** None. **G.M. Shepherd:** None. **W.W. Lytton:** None.

Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 583.16/N1

Topic: E.04. Voluntary Movements

Support: Whitehall Foundation Research Grant 2017-05-71

Title: Single unit characterization of cortical sensorimotor transformations in a whisker detection task

Authors: *Z. ZHANG[1], B. ZAREIAN[2], E. ZAGHA[2];
[1]Neurosci. Grad. Program, [2]Dept. of Psychology, UC Riverside, Riverside, CA

Abstract: How are neuronal signals transformed across cortex to convert sensory information into decisions and motor actions? Here, we assess single unit representations in different cortical areas during a passive whisker detection task. In this task, mice learn to lick a water port in response to whisker deflections in one whisker field (target) and ignore identical stimuli in the opposite (distractor) whisker field. Concurrent studies in our lab have identified several cortical regions active during the sensorimotor transformation including whisker primary somatosensory cortex (S1), whisker primary motor cortex (wM1) and anterior lateral motor cortex (ALM). We recorded single unit activities from these cortical regions during task performance and analyzed diverse neuronal firing properties including stimulus encoding, response latency, transient versus sustained firing, sensory versus motor temporal alignment and choice probability. Most S1 neurons were transiently active, aligned to the stimulus onset at short latency, and showed low choice probability, consistent with pure sensory coding. Individual S1 neurons displayed a wide range of stimulus encoding magnitudes, with a small portion of neurons encoding stimulus probability values that approached behavioral performance. In contrast, most ALM neurons were active at long latency from stimulus onset and then remained active until the response time, aligned to response initiation, and showed high choice probability, consistent with pure motor coding. Our results suggest that S1 and ALM neurons represent two ends of the cortical sensorimotor transformation spectrum. Single units in wM1, alternatively, showed a mixture of sensory, motor and sensorimotor representation. We discuss why this mixed population may be a critical node in transforming cortical signals in our whisker detection task.

Disclosures: **Z. Zhang:** None. **B. Zareian:** None. **E. Zagha:** None.

Poster

583. Cortical Planning and Execution: Neurophysiology in Rodents and Others II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 583.17/N2

Topic: E.04. Voluntary Movements

Support: Whitehall Foundation Research Grant 2017-05-71

Title: Visualizing cortical sensorimotor propagation for selective detection

Authors: *K. ARULJOTHI[1], K. MARRERO[2], E. ZAGHA[1];
[1]Psychology, [2]Neurosci., Univ. of California, Riverside, Riverside, CA

Abstract: Widefield Ca^{2+} imaging enables us to observe neural activity simultaneously across multiple cortical regions. We apply this technique to mice performing a selective detection task, in which mice learn to respond to rapid stimuli in the target whisker field and ignore identical stimuli in the opposite (distractor) whisker field. Comparing activity between cortical hemispheres enables us to study both enhanced (target-aligned) and suppressed (distractor-aligned) sensorimotor transformations throughout dorsal cortex. For both hit and correct rejection trials we observe post-stimulus signals emerging first in somatosensory cortex (contralateral to the deflected whisker field). Only on hit trials do we observe subsequent propagation to frontal areas, including both the rostral portion of the whisker representation of primary motor cortex and anterior lateral motor cortex (ALM). Propagation to frontal cortex occurred prior to the response, and therefore may represent part of the motor command. During the response epoch we observe widespread Ca^{2+} signals throughout dorsal cortex. On correct rejection trials, we observe Ca^{2+} signals that did not propagate to frontal areas but remained confined to primary somatosensory cortex. Using signal detection theory, we quantify sensory representation for target and distractor stimuli. Sensory signals are comparably strong for both stimuli, suggesting that stimulus encoding is not gated out before it reaches the sensory cortex. Thus, our data illustrate a cortical correlate of sensory selection as the regulated propagation of sensory signals from primary sensory to motor regions.

Disclosures: K. Aruljothi: None. **K. Marrero:** None. **E. Zagha:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.01/N3

Topic: E.05. Brain-Machine Interface

Support: DoD W81XWH-16-1-0503 (PM, RJN)

Title: Optimal post-injury time window to apply activity-dependent stimulation to drive functional recovery after traumatic brain injury in the rat

Authors: *H. M. HUDSON[1], D. J. GUGGENMOS[1], N. VITALE[3], M. AZIN[3], P. MOHSENI[3], R. J. NUDO[1,2];
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Abstract: Traumatic brain injury (TBI) is a significant contributor to death and disability worldwide. Approximately 1.7 million people in the United States sustain a TBI annually. Forty-three percent of patients discharged from acute hospitalization with TBI develop some form of long-term TBI-related disability, leading to reduced quality of life, prolonged medical

complications and significant health care expenses. Injury to the cerebral cortex, as might occur from TBI, can result in substantial cell loss and widespread disruption of the sensorimotor network, leading to chronic motor deficits. Few treatment options exist for those with chronic disabilities following acquired brain injuries. Our previous research has shown that activity-dependent stimulation (ADS), used to create an artificial communication link between spared cortical areas, is effective in restoring functional use of the forelimb when applied immediately following a cortical TBI to primary motor cortex (M1) in rats. From a clinical perspective, the immediate implementation of ADS following cortical injury may not be feasible as surgical implantation of the device in a patient would need to be delayed days to weeks allowing for the patient to become medically stable and post-TBI edema to be resolved. The goal of this study was to determine the optimal post-injury time window to apply ADS treatment and achieve functional recovery following a TBI. We hypothesized that delaying the initiation of ADS by 1, 2 or 3 weeks after an M1 injury will lead to improved skilled reaching performance compared to non-stimulated controls. In a rodent model of TBI, we used a custom wireless microdevice to create an artificial communication link between spared cortical areas (premotor cortex, PM; primary somatosensory cortex, S1), forming a closed loop brain-machine-brain interface. At the specified post-injury delay (1, 2 or 3 weeks), the closed-loop operation of the microdevice was turned on. PM neural activity was recorded, and action potentials were discriminated in real time and used to trigger stimulation pulses in S1 for 24 hours per day over a 4-week treatment period. Behavioral recovery was assessed weekly using a skilled reaching task. Preliminary results indicate that the application of ADS, regardless of treatment delay, leads to significant improvement in skilled reaching performance compared to non-stimulated controls. The results demonstrate that delaying the application of ADS does not impair the ability to bridge communication between spared cortical areas in the sensorimotor network and can drive functional behavioral recovery following a TBI.

Disclosures: H.M. Hudson: None. **D.J. Guggenmos:** None. **R.J. Nudo:** None. **N. Vitale:** None. **M. Azin:** None. **P. Mohseni:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.02/N4

Topic: E.05. Brain-Machine Interface

Title: Non invasive kinesthetic feedback in a bidirectional hand system for upper limb amputees

Authors: *G. DOMINIJANNI[1], G. VALLE[2,1], E. D'ANNA[1], S. MICERA[1,2];
[1]Ctr. for Neuroprosthetics and Inst. of Bioengineering, École Polytechnique Fédérale de

Lausanne (EPFL), Lausanne, Switzerland; [2]The BioRobotics Inst., Scuola Superiore Sant'Anna, Pisa, Italy

Abstract: Rich sensory feedback restoration is proved to be the key for better and more intuitive control of current myoelectric prostheses. In light of this, a stimulation system for muscle vibration was developed to provide homologous and somatotopic kinesthetic feedback non-invasively to transradial amputees. Testing protocols were then designed to understand the capabilities of the developed device in eliciting hand related illusory movement sensations as well as to investigate the possibility of properly controlling the illusion created. The results obtained with both healthy subjects and amputees suggested that the developed vibratory stimulation system could be exploited to provide kinesthetic sensory feedback in a closed-loop configuration to improve motor control of the prosthetic hand. In this perspective, a one degree of freedom robotic hand was endowed with the vibratory stimulation system for proprioception of hand position and movement restoration. In order to evaluate the functionality of the delivered feedback in conjunction with the bidirectional hand system, a set of experiments with the system in open-loop and closed-loop configuration was carried out. Open-loop experiments were designed to quantify only the performances of the vibratory stimulation system when used to provide kinesthetic feedback, without the influence of the additional burden of robotic hand control. The closed-loop experiments instead involved the overall bidirectional hand system. Open-loop experiments showed how the amputee was able to discriminate hand closing and opening movement, as well as rest condition. In particular, overall correct movement identification percentage was as high as 88.9%. Moreover, all the movements were identified above chance level with 95% confidence interval. Object size recognition task was performed considering two cylinders of different diameters. The overall correct classification performance achieved in the object size recognition experiment was 87.5% and both objects were correctly identified above chance level. The same object recognition experiment was carried out also in closed-loop configuration and high overall performance was achieved by the patient (87.5% correct classification) with both objects classified above chance level.

Disclosures: G. Dominijanni: None. **G. Valle:** None. **E. D'Anna:** None. **S. Micera:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.03/N5

Topic: E.05. Brain-Machine Interface

Support: FRQNT
Craig H. Neilsen Foundation
IVADO

Title: Neuroprosthetic stimulation optimized by learning control algorithms

Authors: *M. BONIZZATO, S. COTE, S. LAFERRIERE, S. QUESSY, G. LAJOIE, M. MARTINEZ, N. DANCAUSE;
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Abstract: We are developing neuroprosthetic systems for motor control that are based on intracortical microstimulation (ICMS). In rats with spinal cord injury (SCI) we demonstrated that targeted and timed ICMS immediately alleviates locomotor deficits. Here, we tackled the problem of controlling multi-dimensional neurostimulation intervention.
In practice, in ICMS as other functional electrical stimulation applications, stimulus parameters are often arbitrary and the strategies for optimizing these stimulations poorly developed. Moreover, the motor cortex (M1) organization widely varies from one individual to another and even over time for the same subject. We propose that learning algorithms could be used to quickly optimize the stimulation parameters of an implant according to the specific effects evoked by its electrodes and to be able to rapidly adapt these parameters according to the changes that may occur in the brain, for example after injury. This would maximize the effectiveness and durability of motor neuroprostheses.
We implanted n=4 rats with 32-channel arrays in the hindlimb M1 and n=2 non-human primates (NHP) with 96-channel cortical arrays in the forelimb M1. Under ketamine anesthesia and in resting awake subjects, ICMS through different electrodes generates a variety of motor outputs. We used a Bayesian learning algorithm based on Gaussian processes to explore the space of stimulation parameters. In a first experiment, the algorithm was used to determine which spatial location for stimulus delivery within M1 held the strongest activation of a target muscle. Over a total of 2 to 3 muscles per subject and 10 repetitions per muscle, the algorithm over-performed random search in determining the optimal stimulation site.
We further demonstrated that the algorithm can be applied to online optimization of cortical neuroprosthetic stimulation. In n=3 rats with SCI, the learning routine optimized stimulation parameters to maximize leg clearance and alleviated leg dragging. The algorithm found optimal cortical locations for stimulus delivery in less than half a minute and during active usage of the neuroprosthesis, largely outperforming the capacity of a human operator.
The proposed algorithm optimized ICMS delivery in the space of a minute, across complex motor representations and during neuroprosthetic usage. Our framework could be extended to other neurostimulation treatments to maximize their therapeutic benefits. Furthermore, intelligent algorithmic approaches to “motor mapping” can provide new optimized tools to support studies in neural control of movement, skilled motor learning and effects of neurological damage and rehabilitation.

Disclosures: M. Bonizzato: None. **S. Cote:** None. **S. Laferriere:** None. **S. Quessy:** None. **G. Lajoie:** None. **M. Martinez:** None. **N. Dancause:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.04/N6

Topic: E.05. Brain-Machine Interface

Support: NSF IIS-1302339
NIH F99NS105210-01

Title: A neural-machine interface for control of a lower-limb prosthesis

Authors: *J. A. BRANTLEY[1], J. L. CONTRERAS-VIDAL[2];
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Abstract: Limb amputation is a major cause of physical disability that causes activities of daily living to become difficult or impossible for the amputee. Current lower-limb prostheses provide limited control and result in reduced mobility for the amputee. Recent advancements in powered lower limb prostheses allow for more intelligent control and better locomotion functions (3). The most advanced strategy employs user intent detection to combine volitional and autonomous control during locomotion. The incorporation of neural signals, specifically muscle and brain, may offer a viable method for improved volitional control by directly interpreting signals from muscle (measured through electromyography—EMG) and cortical brain activations (measured through electroencephalography—EEG). In this study, we employ a multimodal neuroimaging approach to: (1) identify neural correlates of movement during isolated limb movements and walking in the amputee population, and (2) demonstrate the feasibility of control of a powered LL prosthesis using neural signal from EEG and EMG. Transfemoral amputees were recruited to perform a series of isolated limb movements of the intact and phantom knee and ankle while undergoing a functional magnetic resonance imaging (fMRI) scans. The subjects subsequently repeated the experiment while instrumented with EEG, EMG, and motion capture. fMRI data were used to extract regions of interest during individual limb movements, and a systematic EEG processing approach was implemented to reduce artifacts (e.g., eye blinks/movements, muscle artifacts) and estimate the underlying source activity. We investigate the temporal and spectral dynamics associated with activation of the phantom limb as compared to the intact limb. Secondly, we investigate the ability to leverage EEG signals for control of a lower limb prosthesis and how this may supplement control schemes utilizing neural signals from the muscles of the residual limb. This work contributes to a greater understanding of the neural dynamics associated with phantom limb movements in lower limb amputees and presents a strategy for BMI control of powered prostheses. This research is partly supported by NSF award IIS-1302339 and an NIH F99 Predoctoral Fellowship (1F99NS105210-01) to JAB

Disclosures: J.A. Brantley: None. **J.L. Contreras-Vidal:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.05/N7

Topic: E.05. Brain-Machine Interface

Support: James S. McDonnell Foundation Grant 220023046
Center for Visual & Neurocognitive Rehabilitation Pilot Grant 1I50RX002358-01

Title: Repetitive anodal transcranial direct current stimulation hastens isoflurane-induced emergence and recovery and enhances memory in healthy rats

Authors: M. T. MANSOURI, *P. S. GARCIA;
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Abstract: Introduction: Rapid and smooth recovery from general anesthesia is a goal for clinical anesthesiologists. Recently intense research interest has focused on the neural mechanisms involved in emergence from unconsciousness. Thus far, there has been no effective clinical strategy proven to hasten recovery from surgical anesthesia. One promising approach is the use of non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) to stabilize neural activity around a physiologic setpoint. To date, use of this technique for the relief of symptoms caused by neuropsychiatric disorders and the enhancement of cognitive performance has led to promising results. **Objective:** In this study, we hypothesized that repetitive anodal tDCS can hasten post-anesthesia emergence and recovery behaviors. **Methods:** Age-matched, adult male rats (n=15; 450-525 g) were divided into two groups; the anodal tDCS and sham groups. Four days after the tDCS socket implantation over the right motor cortex (AP: +1.5mm, ML: +2mm), repetitive anodal direct electrical current of 0.2 mA intensity applied for 20 min/day for 10 consecutive days in tDCS group, while sham stimulation was applied to sham group. Minimum alveolar concentration (MAC) to prevent movement, as well as emergence and recovery behaviors following 2-hour isoflurane anesthesia were evaluated 24 hours after the last tDCS session. Cognitive performance was assessed by novel object recognition and spontaneous alternation Y-maze tests 48 h after the last tDCS session. Locomotion was also measured using Oxymax indirect calorimetry system. **Results:** The concentration of isoflurane necessary to suppress movement to tail-pinch was not affected by tDCS, although tDCS-treated animals righted themselves after anesthesia sooner than sham-treated group. Recovery behaviors such as attempts to remove adhesive tape affixed to the forepaw (sticky-dot test) were also hastened in tDCS-treated rats as compared to sham. Treatment with tDCS also exhibited positive effects on both novel object recognition and Y-maze tests, without affecting locomotor performance, indicating a potential benefit on working memory from the intervention. **Conclusions:** Taken together, our findings propose that anodal

tDCS over the motor cortex might be useful to hasten recovery from the anesthesia in patients who take the isoflurane during the surgery.

Disclosures: M.T. Mansouri: None. **P.S. Garcia:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

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Program #/Poster #: 584.06/N8

Topic: E.05. Brain-Machine Interface

Support: NIH Grant MH111874

Title: Dose and montage effects of transcranial direct current stimulation on motor sequence learning

Authors: *G. SCHLAUG[1], A. B. SHINDE[2];
[1]Neurol., Beth Israel Deaconess Med. Center/HMS, Boston, MA; [2]Neurol., Beth Israel Deaconess Med. Center/Harvard Med., Boston, MA

Abstract: Research investigating the use of noninvasive electrical stimulation has provided compelling evidence that such stimulation can modulate behavior and cognition, and even facilitate recovery of function after a focal brain injury. Our understanding of stimulation variables such as *current strength* and *electrode montage* has to be further explored. We are conducting a series of studies to characterize brain and behavioral responses to tDCS varying dose and electrode montage. In this study, we used three different dose levels (Sham-0.1mA, 2mA and 4mA (Corresponding current densities under Anodal electrode: 0.007 mA/cm^2, 0.156 mA/cm^2, and 0.318 mA/cm^2) and two different electrode montages (unihemispheric or bihemispheric) to examine effects on a finger sequencing task. Anodal electrode diameter was 4 cm placed over the right motor region (C4) while the cathodal electrode was 5 cm diameter and it was either placed over the left supraorbital region (unihemispheric montage) or over the left motor region (C3; bihemispheric montage). C3 and C4 correspond to the precentral gyrus hand motor knob region. Each stimulation study was of 10 min duration including initial ramp up and final ramp down signal. 20 healthy Right-Handed subjects participated in the study. Each visit was separated by at least 24 hours and subjects performed a finger sequence learning task consisting of a randomly chosen sequence of 7 digits with each hand separately before and immediately after the stimulation. Subjects performed finger sequence learning task for 30 sec at a time, the task was performed five times with each hand with 30 sec rest between two tasks. Repeated measure ANOVA for unihemispheric electrode montage with all three stimulation conditions showed significant difference in left hand pre-post performance. There was no significant effect on the performance of the right hand with unihemispheric stimulation. Post

unihemispheric stimulation, both left and right hand showed improvement in the task performance with a clear trend between the stimulation dose and percentage change. Bi-hemispheric 2mA and 4 mA stimulation showed improvement in performance for left as well as right hand; improvement in performance of left hand was more than the improvement of right-hand performance. Pairwise comparisons confirmed the causal relationship between the anodal stimulation of the peri-rolandic region during the motor learning consolidation phase and the improved motor sequence performance after stimulation.

Disclosures: G. Schlaug: 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.; R01MH111874-01. **A.B. Shinde:** 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.; R01MH111874-01.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.07/N9

Topic: E.05. Brain-Machine Interface

Support: NIH 1R01MH111874-01

Title: Transcranial direct current stimulation increases regional cerebral blood flow in targeted and network brain regions

Authors: *A. B. SHINDE, F. MUNSCH, D. ALSOP, G. SCHLAUG;
Neurol., Beth Israel Deaconess Med. Ctr. and Harvard M, Boston, MA

Abstract: Noninvasive transcranial direct current stimulation(tDCS) of targeted brain regions leads to an increase or decrease in cortical excitability in the stimulated region. How tDCS drives these physiological and associated behavioral effects remains speculative at this point. In the current experimental setup, we investigate local and network relationships between tDCS stimulation and cerebral blood flow(CBF) change. This is achieved with two intertwined sets of experiments. First, increasing stimulation current to study dose effects (sham, 2mA, and 4mA) and second, varying placement of the cathodal electrode (Unihemispheric-FP1and Bihemispheric -C3) to study montage effects with Anodal electrode fixed on the right primary motor area(C4). Each stimulation session was of 10 min duration with initial ramp up and final ramp down over 30s. A 3T GE MRI scanner, acquiring non-invasive blood flow images using ASL fMRI, and an MR compatible NeuroConn DCMC stimulator allowed us to simultaneously perform brain

stimulation and MR acquisitions. The ASL sequence lasted 24 min (resulting in 160 acquisitions) while tDCS was delivered in the middle of the scanning session. Fifteen healthy Right-Handed subjects participated in the study so far undergoing 6 imaging and 6 behavioral assessments. The resulting MR images were analyzed with SPM12 and its toolbox CAT12. A significant change ($p < 0.05$ unc) in cerebral blood flow between ON and OFF conditions was seen for the group under the anodal electrode for unihemispheric tDCS of 2mA. In contrast, the 4mA unihemispheric condition showed blood flow changes in the precentral gyrus in both hemispheres. Bihemispheric stimulations caused significant changes ($p<0.05$ unc) in blood flow changes under both anode and cathode electrode for the 2mA and 4mA condition, with the 4mA condition driving blood flow changes in larger brain areas including frontomesial regions compared to changes in the 2mA condition. In conclusion, ASL-CBF changes, induced by tDCS can be used as a surrogate marker of regional and remote (network) neuronal effect, with differential effects caused by varying parameters of the stimulation.

Disclosures: **A.B. Shinde:** None. **F. Munsch:** None. **D. Alsop:** None. **G. Schlaug:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

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Program #/Poster #: 584.08/N10

Topic: E.05. Brain-Machine Interface

Support: NIH Grant R41DC015142

Title: Brain computer interface operation of a commercial augmentative and alternative communication device

Authors: ***J. E. HUGGINS**[1], R. T. CROSS[2], M. A. GARCIA VERDUGO[1], C. G. WOODWORTH[3], K. HILL[3];
[1]Physical Med. and Rehabil., Univ. of Michigan, Ann Arbor, MI; [2]Prentke Romich Co., Wooster, OH; [3]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Brain-computer interfaces (BCIs) are often intended for use as augmentative and alternative communication (AAC) devices. But to be successful, BCIs must incorporate the linguistically robust AAC user interfaces resulting from 50 years of AAC research. BCIs can thus most efficiently serve people with complex communication needs by interfacing to commercial AAC technology instead of trying to recreate an AAC user interface in the BCI. This NIH-funded project was intended to provide a BCI input accessory to a commercial AAC product line.
A non-invasive P300-based BCI design [1] was configured as an input device to the AAC system of an industry partner. Using the Microsoft User Interface Adaptation framework, the AAC

system publishes the size and location of every key on its on-screen keyboard. The BCI then matches stimuli to the size and shape of the AAC system keys to provide BCI access to on-screen keyboards and icon displays of up to 144 locations. The stimuli update after each selection to match the selections on the AAC user interface.
The AAC-BCI was tested with 8 people with cerebral palsy who use an AAC device for everyday communication. Participants (2 female; 6 male) were aged 13 to 61 years. The custom user interface from each participant's own communication device was loaded into the AAC-BCI prototype to provide familiar screens and content. These interfaces included single-hit and multiple-hit stored vocabulary using icons and spelling/word prediction.
The AAC-BCI was calibrated for 7 of the 8 participants. For the remaining user, the study was interrupted when the gel-based EEG cap twisted under the weight of the head-mounted typing stick typically used for communication. The participants found the communication potential exciting, but wanted improved interface responsiveness. BCI accuracy did not vary based on the number of active locations on the AAC display. However, issues were identified with the gel electrode caps, which were slow to set up and catch on user headrests.
Future work will include using dry electrodes and testing a P300-certainty algorithm, both for accuracy of typing and to provide an automatic pause feature.
[1] Farwell, L. A. Donchin, E. Talking off the top of your head:. Elect clin neuro,70(6):510-523, 1988.

Disclosures: **J.E. Huggins:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH grant R41DC015142. **R.T. Cross:** A. Employment/Salary (full or part-time):; Prentke Romich Company. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH grant R41DC015142. **M.A. Garcia Verdugo:** None. **C.G. Woodworth:** None. **K. Hill:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH grant R41DC015142.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.09/N11

Topic: E.05. Brain-Machine Interface

Support: R01 DC009834-09S1

Title: Neurofeedback (NFB) using brain computer interface (BCI) software for training reading-related attention in mild Alzheimer's disease (AD)

Authors: D. KLEE, D. MCLAUGHLIN, T. MEMMOTT, M. FRIED-OKEN, *B. S. OKEN; Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Prior BCI research has suggested NFB may improve performance. The goal of this study was to develop NFB to improve reading-related cognitive processes in people with AD. In addition to memory deficits, AD is usually associated with functional impairments in language and reading. This abstract describes the outcome measures and the generation of BCI NFB signals in a group of healthy younger and older adults.

NFB training used a P300 speller and rapid serial visual presentation (RSVP) of letters developed with BciPy software and a dry-electrode cap. Calibration consisted of 100 trials. Each trial presented a target letter and then 10 letters serially including the target letter at a rate of 4 Hz. Machine learning was trained on 500 ms of EEG data following target and non-target letters using a regularized discriminant classifier following dimension reduction using a principal components analysis. The best parameters for the classification were obtained using a 10-fold leave-one-out cross-validation. The session AUC is used as a BCI outcome measure.

Currently, NFB uses steady state VEP amplitudes for attentional feedback. NFB was presented after each trial based on estimated SSVEP amplitude using 3.4 - 4.6 Hz power for each trial. The feedback was presented as 5 horizontally oriented rectangles ranging from red to green. The trial feedback was presented for 2 s as a highlighted border around 1 rectangle. SSVEP amplitude thresholds for the 5 levels were individualized for each subject based on a prior calibration. We provided more positive than negative feedback and selected category 1 as the lowest 15^{th} percentile up to category 5 as the top 30^{th} percentile. Primary cognitive outcome measures assessed reading processing speed, attention (letter cancellation task), and working memory skills (letter span task; WAIS digit span).

Four healthy participants (age range 23-71 years) signed informed consent, completed cognitive outcomes measures, and completed the RSVP BCI task with neurofeedback. Participants completed 2 letter cancellation tasks: harder condition in 32.5 ± 3.7 s and easier condition in 27.3 ± 4.0 s. Participants responded to an average of 78.5 ± 14.5 items correctly on the sentence fluency task. Participants' letter spans averaged 5.85 ± 1.5 letters in the forward condition and 4 ± 1.8 letters in length in the backward condition. On the BCI task, participants achieved a mean correct classification rate (AUC) of 0.71 $\pm$ 0.09. For individualized neurofeedback, we were able to successfully deliver feedback at the 5 levels in approximate target distributions. Following development of the NFB, we have begun the 6-week NFB implementation phase of the experiment.

Disclosures: B.S. Oken: None. **D. Klee:** None. **D. McLaughlin:** None. **M. Fried-Oken:** None. **T. Memmott:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.10/N12

Topic: E.05. Brain-Machine Interface

Support: Horizon 2020, ERC Consolidator Grant Feel Your Reach 681231

Title: Artificial somatosensory kinaesthetic feedback of arm movements

Authors: *L. HEHENBERGER, A. I. SBURLEA, R. J. KOBLER, G. R. MUELLER-PUTZ; Inst. of Neural Engin., Graz Univ. of Technol., Graz, Austria

Abstract: Afflictions like spinal cord injury potentially interrupt both efferent and afferent pathways. The main focus of neuroprosthesis research naturally lies on restoring the forward part of the feedback loop, i.e. control, while the loop is usually closed via visual feedback. In pursuit of making neuroprostheses increasingly intuitive to use, artificial somatosensory feedback should be a prominently featured topic.

We are exploring non-invasive vibrotactile stimulation to give artificial kinaesthetic feedback to a person controlling a robotic arm. In the current setup, tactors driven by a custom device are arranged in a sparse grid attached to a custom shirt in the area of the shoulder blade, and their intensities are modulated such that the stimulation is perceived as a smoothly moving sensation. This perception is based on tactile illusions arising due to the low spatial resolution of the tactile sense. We have performed tests to identify correct settings for a number of parameters to produce such moving sensations with our custom setup. Most importantly, we conducted a behavioural experiment to identify how to correctly manipulate tactor intensities in order to evoke specific apparent movement sequences across the grid, and found that a power relation between the intensities and the desired stimulation location (relative to the active tactors) at any time point leads to the best result.

Subsequently, we conducted a study to investigate the impact of vibrotactile feedback on movement parameters in electroencephalography. Participants performed unidirectional arm movements in 3 different directions on a planar surface with either real-time vibrotactile feedback of the movement, static vibrotactile stimulation or no vibrotactile input. Average peak amplitudes of motor-related cortical potentials were found to be higher in the feedback condition, and lowest in the condition with static stimulation. We present classification results with respect to the movement directions and conditions.

Disclosures: L. Hehenberger: None. **A.I. Sburlea:** None. **R.J. Kobler:** None. **G.R. Mueller-Putz:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.11/N13

Topic: E.05. Brain-Machine Interface

Support: Ambizione Fellowship (167912) to Marco Capogrosso
Wyss Center Grant in Geneva (WCP 008)
Catalyst Fund Grant, from Bertarelli Foundation (N8C1709)

Title: Neurotechnologies for the restoration of three-dimensional arm movements after cervical spinal cord injury

Authors: *B. BARRA[1], S. CONTI[1], M. G. PERICH[2], K. Z. ZHUANG[1], G. SCHIAVONE[3], N. GREINER[1], M. KAESER[1], E. M. ROUILLER[1], S. P. LACOUR[3], T. MILEKOVIC[2], J. BLOCH[5], G. COURTINE[4], M. CAPOGROSSO[1];
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Abstract: Half of spinal cord injuries (SCI) result in reduced mobility in both the upper limbs and lower limbs. In particular, loss of upper limb functions can dramatically impair the social and professional lives of patients, making recovery of these functions a top priority. Several studies employing functional electrical stimulation of the arm muscles have been able to produce grasping gestures in people with tetraplegia. However, this strategy is insufficient to generate the forces necessary to produce three-dimensional natural reaching movements, thus hindering its application in real-life scenarios. Epidural electrical stimulation (EES) applied over the dorsal spinal cord engages motoneurons through the recruitment of large sensory afferents, thus producing large forces while concurrently improving functional muscle control. Here, we detail the technological framework allowing the restoration of reaching and grasping movements in a nonhuman primate model of incomplete SCI by delivering brain-controlled EES to the cervical spinal cord. We designed and validated a soft spinal implant that targets the posterior roots of cervical segments in macaque monkeys. After training to perform a three-dimensional reaching and grasping tasks, the spinal implant was inserted together with intramuscular electrodes into selected arm muscles to record electromyographic (EMG) activity and intracortical multi-electrode arrays to record the spiking activity of neurons in the primary moor cortex, dorsal premotor cortex and somatosensory cortex. We evaluated the chronic stability, efficacy and selectivity of our spinal implant to elicit activation of synergistic muscles. We then implemented

a real-time control framework that extracted movement-related intentions from intra-cortical recordings of primary motor and dorsal pre-motor cortex and linked them to the delivery of electrical stimulation at different spinal locations. Finally, we performed a partial hemisection of the spinal cord at the C6 level and evaluated the effects of alternated EES bursts timed with reaching (arm extension) and grasp (hand flexion) on arm/hand kinematics.

Disclosures: B. Barra: None. **S. Conti:** None. **M.G. Perich:** None. **K.Z. Zhuang:** None. **G. Schiavone:** None. **N. Greiner:** None. **M. Kaeser:** None. **E.M. Rouiller:** None. **S.P. Lacour:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Holds various patents in relation to the present work., Founder and shareholder of GTX medical.. **T. Milekovic:** None. **J. Bloch:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Holds various patents in relation to the present work., Founder and shareholder of GTX medical. **G. Courtine:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Holds various patents in relation to the present work., Founder and shareholder of GTX medical. **M. Capogrosso:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Holds various patents in relation to the present work..

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.12/N14

Topic: E.05. Brain-Machine Interface

Support: The Whitaker Foundation
Wyss Center for Bio and Neuroengineering in Geneva
Swiss National Science Foundation

Title: Dynamical encoding of swing and stance phases as orthogonal states in hindlimb motor cortex

Authors: *L. S. URBAN, I. SEÁÑEZ, S. ANIL, C. HITZ, S. SUN, N. MACELLARI, G. COURTINE;
EPFL, Geneve, Switzerland

Abstract: While the forelimb region of primary motor cortex has been extensively studied, less is known about the neural dynamics of the hindlimb region. This is a problem, first, because these brain regions likely share functional characteristics, since both interact with distant spinal circuits to control the major limbs of the body. Basic functional properties may be obscured by

the sophistication of forelimb movements, and may be better observed with the limited repertoire of hindlimb movements. Second, hindlimb motor cortex activity could serve as a control signal in a brain-spine interface for adjusting stimulation parameters in real-time throughout the gait cycle to assist in the recovery of walking for paraplegic patients.
Here we apply dynamical system analysis to show that hindlimb motor cortex encodes the swing and stance phases of the gait cycle as two distinct states. Neural activity was recorded during walking from chronic implanted arrays (Utah) in the nonhuman primate. These neural signals were projected onto a dynamical system space optimized for a harmonic oscillator. These dynamics were chosen to match the oscillatory patterns of leg movements during walking and to mimic physical models used in bipedal robotics. Our results were derived from continuous recording sessions with many gait cycles and rest periods.
Our work shows that the dominant oscillating patterns in the hindlimb motor cortex strongly correlate with movement during walking. The 3D structure of the dynamics shows two orthogonal brain states that correlate with the swing and stance phases respectively. This means swing and stance are encoded by two distinct patterns of neural activity that do not overlap in time. Each pattern fades in and out before transitioning to the next, as opposed to smoothly transitioning between the two. Therefore the brain enters a unique state during the swing phase, then switches states during the stance phase. Results also show that the swing phase is encoded in a localized region of hindlimb primary motor cortex, while the stance phase is more distributed.
These results show that although walking is an oscillatory movement, the brain encodes swing and stance as independent states, and suggests that their neural properties should be studied separately. The robustness of this signal suggests this is an important property of the hindlimb motor cortex, and has potential for decoding in the brain-spine interface.

Disclosures: **L.S. Urban:** None. **I. Seáñez:** None. **S. Anil:** None. **C. Hitz:** None. **S. Sun:** None. **N. Macellari:** None. **G. Courtine:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.13/N15

Topic: E.05. Brain-Machine Interface

Support: Ambizione Fellowship (167912) to Marco Capogrosso
Wyss Center Grant in Geneva (WCP 008)
Catalyst Fund Grant, from Bertarelli Foundation (N8C1709)

Title: Experimental framework for the assessment of the efficacy of spinal cord stimulation to restore voluntary arm movement in monkeys after spinal cord injury

Authors: *S. CONTI[1], B. BARRA[1], M. G. PERICH[2], K. Z. ZHUANG[1], G. SCHIAVONE[3], N. GREINER[3], M. KAESER[1], E. ROUILLER[1], S. P. LACOUR[3], T. MILEKOVIC[2], J. BLOCH[4], G. COURTINE[3], M. CAPOGROSSO[1];
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Abstract: Recovery of arm and hand movement is a high priority for people with cervical spinal cord injury (SCI). Several studies employing electrical stimulation of hand muscles showed promising results in restoring grasping abilities in paralyzed people. However, direct muscle stimulation induces rapid muscle fatigue, limiting the applicability for functional three-dimensional arm reaching movements that are critical for activities of daily living. In contrast, epidural electrical stimulation (EES) of the spinal cord can elicit large muscle forces with reduced fatigue by recruiting motoneurons pre-synaptically through the activation of proprioceptive afferents. Indeed, this technology has already shown remarkable results in improving voluntary motor control of the legs in people with incomplete and complete spinal cord injuries. Here we present an experimental framework for the investigation of the behavioural effects and the therapeutic potential of cervical spinal EES on the restoration of voluntary arm function after unilateral SCI in monkeys. We designed and implemented a robotic framework allowing the evaluation of natural three-dimensional arm reaching performances in macaque monkeys. We then trained macaque monkeys to perform a reach, grasp and pull task using our set up. We simultaneously recorded full-limb kinematics, neural activity along with EMG signals from proximal and distal arm muscles. The monkeys were then implanted with an epidural spinal implant tailored to the C6 to T1 dorsal roots. We then performed a partial hemisection of the spinal cord at the C6 level that led to incomplete paralysis of the left arm. Specifically, while forearm and elbow extensors muscles were compromised, the macaques were able to voluntarily activate proximal shoulder and biceps muscles. We then tested the efficacy of targeted spatiotemporal EES protocols to restore movements of the arm as well as control of the paralyzed muscles as early as 6 days after injury. Similarly to what has been shown in locomotion, our preliminary results seem to indicate the critical role of voluntary motor intention in the recovery of arm motor function using EES.

Disclosures: S. Conti: None. **B. Barra:** None. **M.G. Perich:** None. **K.Z. Zhuang:** None. **G. Schiavone:** None. **N. Greiner:** None. **M. Kaeser:** None. **E. Rouiller:** None. **S.P. Lacour:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder and shareholder of GTX medical., Holds various patents in relation to the present work. **T. Milekovic:** None. **J. Bloch:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder and shareholder of GTX medical., Holds various patents in relation to the present work. **G. Courtine:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder and shareholder of GTX medical., Holds various patents in relation to the present work. **M. Capogrosso:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual

property rights/patent holder, excluding diversified mutual funds); Holds various patents in relation to the present work.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.14/N16

Topic: E.05. Brain-Machine Interface

Support: Whitaker Foundation International Scholars Program to I.S.
Wyss Center for Bio and Neuroengineering in Geneva
Swiss National Science Foundation
National Centre of Competence in Research in Robotics
Sinergia program (CRSII3_160696)
Bertarelli Foundation
Marie Curie COFUND EPFL Fellows program

Title: Exploring the neural basis underlying locomotor activities and leg reaching in macaque motor, premotor, and sensory cortex

Authors: *I. SEÁÑEZ[1], S. BORGOGNON[2,1], N. MACELLARI[1], A. HICKEY[1], C. HITZ[1], R. ORNELAS KOBAYASHI[1], L. S. URBAN[1], H. LORACH[1], M. G. PERICH[3], T. MILEKOVIC[4], M. CAPOGROSSO[2], E. ROUILLER[2], J. BLOCH[5], G. COURTINE[1];
[1]Swiss Federal Inst. of Technol. (EPFL), Lausanne, Switzerland; [2]Univ. of Fribourg, Fribourg, Switzerland; [3]Dept of Fundamental Neurosciences, Fac. of Med., [4]Univ. of Geneva, Geneve, Switzerland; [5]Lausanne Univ. Hosp. (CHUV), Lausanne, Switzerland

Abstract: Cortical activity is believed to coordinate the adjustment of leg movements associated with volitional modifications of gait, such as walking along ladders, avoiding obstacles, or climbing up staircases. However, previous studies have primarily been conducted over motorized treadmills, a relatively simple and automated locomotor task. Consequently, cortical dynamics underlying the production of basic and skilled locomotion remains unclear. To address this question, we trained *Macaca fascicularis* monkeys to walk on a moving treadmill at different speeds, along corridors, uneven ladders, obstacles, and stairs. We also trained them to perform a center-out reach and grasp task with the leg. Finally, we introduced a novel, untrained task requiring object avoidance during stepping. Three animals were implanted with 48-channel intracortical arrays in the leg motor (M1) and premotor (PMd) cortices to record multi-unit activity, in conjunction with 14 pairs of electrodes in leg muscles to record electromyographic (EMG) activity. One animal was additionally implanted with a 64-channel array in the leg sensory (S1) cortex. Neural and EMG signals were transmitted wirelessly. Kinematics of the hindlimb were recorded using a high-definition video camera system and tracked via transfer

learning with DeepLabCut. In this work, we document the neural dynamics of motor, premotor, and sensory cortex activity during rhythmic and volitional control of locomotion. We describe the neural correlates of these sensorimotor areas during specific tasks and how these generalize to the other tasks by using a neural decoder to predict kinematic events from neural recordings within and across tasks. Finally, we study the neural population mechanisms of these areas during the learning of a novel locomotor task. These results will guide the design of additional experiments that aim to link cortical activity to the execution of leg movements.

Disclosures: I. Seáñez: None. **S. Borgognon:** None. **N. Macellari:** None. **A. Hickey:** None. **C. Hitz:** None. **R. Ornelas Kobayashi:** None. **L.S. Urban:** None. **H. Lorach:** None. **M.G. Perich:** None. **T. Milekovic:** None. **M. Capogrosso:** None. **E. Rouiller:** None. **J. Bloch:** None. **G. Courtine:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.15/N17

Topic: E.05. Brain-Machine Interface

Support: NIH NIBIB 1P41EB018783

Title: The music box: A steady-state visual evoked potentials (SSVEP)-based brain-computer interface (BCI) for people with complex communication disorders

Authors: O. ZHOU[1], J. J. S. NORTON[1,2], C. S. CARMACK[1], J. CARTER[1], *K. GOSMANOVA[1], J. R. WOLPAW[1,2], T. M. VAUGHAN[1,2];
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Abstract: Nearly 4 million children and adults in the US with complex communication disorders (CCD) experience life-long educational, vocational, medical, and social challenges (Light and McNaughton, AAC 2015). Visual scene displays (VSDs) allow users with CCDs to make selections within a broader context, (e.g., selecting the image of a TV in a living room scene to activate an actual TV). VSDs can be an effective communication tool for people who have never learned to speak or control a computer, and for those with acquired apraxia or aphasia (Beukelman et.al, AAC 2007). Here, we describe Music Box, a VSD interface controlled using steady-state visual evoked potentials (SSVEPs). The Music Box elicits an SSVEP by alternating between light and dark grey squares at 7.5 Hz (PsychToolBox), and recording EEG signals from 8 scalp locations using BCI2000. The amplitude of the SSVEP elicited by the stimulus is analyzed in real time by canonical correlation analysis. The participant receives visual feedback via a semi-transparent overlay. The size of the overlay is proportional to the SSVEP amplitude.

When the amplitude of the SSVEP exceeds a predetermined threshold, the overlay turns from red to green and music plays. The overlay remains green and the music continues to play as long as the amplitude of the participants' SSVEP is above threshold. Thresholds are adjusted manually to challenge individuals to do better. Four healthy participants each performed sixty 30-sec trials during a 90-min session. SSVEP amplitude exceeded the threshold (i.e., music played) in 88.1(0.1SD)% of the trials; time to reach threshold averaged 1.5(1.1SD) seconds. The spectral power of EEG in the 7.5 Hz band (and its harmonics) increased the longer the participant gazed at the screen. These initial results show that SSVEP-based BCIs can be used to control VSDs. Ongoing studies in our laboratory are examining the impact of stimulus contrast, threshold value, and trial length on participants' performance. We then plan to test the system with people who have CCDs; the goal is to enhance their ability to interact with and control their environments.

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Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.16/N18

Topic: E.05. Brain-Machine Interface

Support: NIH P41EB018783

Title: Brain Storm: A gamified steady-state visual evoked potential (SSVEP)-based brain-computer interface (BCI) for children

Authors: J. MULLINS[1], ***J. J. S. NORTON**[2,3], T. BRETL[1];
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Abstract: There is very little previous research on the development of BCIs for children. Some of that research suggests that children are not able to control SSVEP-based BCIs. A lack of adequate engagement is one possible explanation for these results. Motivated by previous research that uses gamification as an engagement tool, we incorporated gaming elements—narrative, improved graphics and audio, scoring, and prize selection—into Brain Storm, a gamified SSVEP-based BCI. Twenty-two children (9-11 years old) completed experiments with three phases: a calibration phase (CP) and two experimental phases (EPs). During the CP, participants were asked to attend to one of three targets (each flashing at a unique frequency) for five seconds. The CP data from 15 trials were then used to set parameters of an online SSVEP classifier. During the EPs, participants were asked to use two different SSVEP-based BCIs—Brain Storm and a control interface (previously reported in Norton et al., J Neuroeng, Vol 15,

2018)—to select targets (nearly identical to those used in the CP) as quickly and accurately as possible. Half of the participants used Brain Storm first; the other half used the control interface first. For each interface, there were four rounds of target selection with 15 targets/round. At the end of the four rounds, the participants were allowed to select as many targets as they wanted during a bonus round. We compared the two interfaces based on participants' performance (accuracy, latency, and bitrate) and engagement (number of targets selected in the bonus round). The children selected targets with a similar accuracy (78% versus 83%), latency (2.13 versus 2.17 seconds), and bitrate (0.53 versus 0.51 bits/second) when using Brain Storm as compared to the control interface. During the bonus round, however, children voluntarily selected more targets with Brain Storm (56.18 targets) than with the control interface (19.18 targets). Our data show that 9-11-year-old children can use both of the SSVEP-based BCIs tested here for target selection. Furthermore, gamification increased the engagement of children with these systems.

Disclosures: **J. Mullins:** None. **J.J.S. Norton:** None. **T. Bretl:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.17/N19

Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant 5099400

Title: Investigating modularity and functional outcomes of rehabilitation of rats with complete T9/10 SCI through viral brain-derived neurotrophic factor, epidural stimulation and pelvic-based robot training

Authors: *A. P. BORISYUK, S. F. GISZTER;
Dept Neurobiol & Anat, Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: It is believed that some interneuronal circuits in the spinal cord that synapse directly onto motor neurons may be organized so as to control muscles modularly, i.e., as groups, rather than individually. Electromyogram (EMG) recordings can serve as a proxy for detecting the modular structure of these interneuronal circuits and their firing patterns as premotor drives, allowing inferences of modular spinal circuit changes after a spinal cord injury (SCI) and rehabilitation. Previous research in our lab demonstrated enhancement in functional outcomes in rats with complete T9/10 SCI after a combined rehabilitation of viral brain-derived neurotrophic factor (BDNF) and passive ankle-based robot training. Combining epidural stimulation (ES) with the ankle-based rehabilitation further enhanced functional outcomes. Interestingly, the combined rehabilitation at the ankle didn't result in improvement in functional outcomes to levels as high as did viral BDNF treatment with pelvic-based weight-supported treadmill training alone (i.e.,

without ES). Further, relative to the viral BDNF effects, our prior work has demonstrated the possibility of a critical period in the initial two weeks of training where ES likely has its effects on preventing some spasticity viral side effects on motor function in the experiments using pelvic centered rehab. Modularity analysis of the hindlimb muscles in the ankle based and in pelvic-based training combined with viral treatments is unexplored. The current study aims to measure the changes in modularity and improvement in functional outcomes in rats with complete SCI though rehabilitation combining viral BDNF, ES and the pelvic-based training - a combination which so far generates the best outcomes. We hypothesize that modularity analysis of the hindlimb muscles should help reveal the patterns of change during an initial period of reorganization of spinal circuit and then a subsequent stabilization. Improvement in weight-supported stepping is expected throughout therapy in most of these rats.

Disclosures: A.P. Borisyuk: None. **S.F. Giszter:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.18/N20

Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant AG031769

Title: Magnification of visual feedback alters modulation of motor neuron pool in older adults

Authors: *S. PARK[1], M. KWON[3], E. A. CHRISTOU[2];
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Abstract: Magnification of visual feedback impairs force control in older adults by increasing the power in low-frequency oscillations in force. However, it is unclear how the impaired visual information processing in older adults alters the modulation of the motor neuron pool that increases the low-frequency oscillations in the force output with magnified visual feedback. To address this, eleven healthy young adults (21.82 ± 3.52 years, 6 females) and 11 healthy older adults (78.27 ± 5.59 years, 7 females) performed an isometric ankle dorsiflexion task at 15% maximal voluntary contraction with magnified visual feedback (1.2°). We recorded the force output and multiple motor unit activity from the tibialis anterior muscle and quantified the following outcomes: 1) force variability using the standard deviation (SD) and coefficient variation (CV) of force and 2) power spectrum of force and multiple motor unit activity. Older adults exhibited greater force variability compared with young adults (SD: $P = 0.045$; CV: $P = 0.01$). The greater force variability was associated with greater power in the <0.3 Hz oscillations in force (SD: $R^2 = 0.30$; CV: $R^2 = 0.36$). The power in the <0.3 Hz oscillations in force were

positively related to power <0.3 Hz in multiple motor unit activity ($R^2 = 0.42$). These results provide novel evidence that magnification of visual feedback alters the modulation of the motor neuron pool with detrimental consequences to force control in older adults.

Disclosures: S. Park: None. **M. Kwon:** None. **E.A. Christou:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.19/N21

Topic: E.05. Brain-Machine Interface

Support: FINEP 01.12.0514.00 (FINEP and MCTIC)
CNPq (Siconv #704134/2009) (INCT Program from CNPq and MCTIC)

Title: Validation of an assistive-oriented and rehabilitative-oriented brain-machine interface paradigm for locomotion restoration in a group of patients with chronic complete spinal cord injury

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Abstract: Brain-machine interfaces (BMIs) offer the promise of new therapeutic approaches for millions of people worldwide who suffer from a range of neurological disorders. Here, we describe two non-invasive BMI control strategies, aimed at restoring locomotion in paraplegic patients suffering from chronic spinal cord injuries (SCI) but used for different needs: 1) We suggest the hybrid state machine (HSM) protocol, to maximize the decoding robustness for assistive devices and 2) The single legs control (SLC) method to promote control intuitiveness using lower-limb motor imagery for rehabilitation purposes.
We validated the two paradigms with 12 motor-complete SCI patients (11 AIS A, 1 AIS B) in a setup where the BMI signal was used to control the locomotion of a virtual avatar or a robotic-gait training device.
For the HSM protocol, subjects used arms motor imageries (captured via 16 channel EEG recording) to select specific actions in a state machine (walk, stop, etc.), followed by EMG

activation to confirm the selection. For the SLC paradigm, they used leg motor imageries to trigger the stepping of the corresponding limb.
We report patients' performance for 498 BMI blocks (a block was 6 minutes long) with the HSM protocol for 8 patients and 147 BMI blocks with the SLC method for 4 patients. Control performance was significantly above chance level (t-test, $p < .05$), for all patients trained with the HSM and 3 out the 4 patients using the SLC protocol. Notably, two patients, trained with the HSM reached above 95% accuracy and a cumulated 83 BMI blocks (> 1000 consecutive BMI instructions) without a single mistake.
We also compared for 8 patients, the BMI training performance for 154 blocks of leg motor imagery (LMI) and 295 blocks of arm motor imagery (AMI). In both cases, patients were randomly instructed to imaging move their left or right limb for 3 seconds, 40 times per block. Patients were significantly better than chance level for both paradigms, with significantly higher scores for AMI (75.8 +- 7.3 %, mean +- SEM) compared to LMI (74.1+- 4.9 %) (t-test, $p = .012$). The ability to perform the LMI was independent of both the lesion height and the time since the lesion (coefficient of correlation, $r < 0.02$, $p > .1$), suggesting that our protocol is not restricted to a subset of patients with SCI.
We propose that the two strategies could target different contexts of the rehabilitation process and yet being complementary; the HSM for assistive devices in real-world activities where high levels of accuracy are demanded, whereas the SLC for clinical environments to promote neurological recovery with SCI patient by stimulating cortical plasticity and engaging patients in performing leg motor imagery.

Disclosures: **S. Shokur:** None. **D. Schwarz:** None. **D.S.F. Campos:** None. **A.C. Donati:** None. **G. Bao:** None. **N.M.P.C. Rios:** None. **A. Lin:** None. **A. Takigami:** None. **M.A. Aratanha:** None. **S.Y. Yamauti:** None. **S.S. Joshi:** None. **R.C. Moioli:** None. **F.L. Brasil:** None. **E. Morya:** None. **M.A. Nicolelis:** None.

Poster

584. Brain-Computer Interface: Rehabilitation

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ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: E.05. Brain-Machine Interface

Support: Eurostars Comalert

Title: Effects of a vibri-tactile brain-computer interface paradigm on the coma recovery scale-revised in patients with disorders of consciousness

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Abstract: Persons diagnosed with disorders of consciousness (DOC) typically suffer from motor disabilities, and although their cognitive abilities might be intact, they are difficult to assess. Recent research has shown that the non-invasive brain-computer interface (BCI) technology can help to assess these patients' cognitive abilities and command following. In the study presented here, twenty DOC patients participated and performed 10 vibro-tactile P300 BCI sessions over 10 days with 8-12 runs on each day. Patients were in a stable chronic stage, 11 were diagnosed with a minimally conscious state (MCS) and 9 with unresponsive wakefulness syndrome (UWS) based on the Coma Recovery Scale-Revised (CRS-R). Changes of the BCI classification accuracy were investigated over the 10 days, and the changes of the CRS-R score before and after 10 vibro-tactile P300 sessions. Patients had vibro-tactile stimulators fixed on both writs and one foot, and were instructed to mentally count either the stimuli on the left or right wrist, which induces the P300 for the target wrist only. The grand average accuracy of the BCI paradigm in the first session for all patients was 40 %, in the best session the grand average accuracy was 88 % and the median accuracy of all sessions was 21 %. In the first run 10 patients had a classification accuracy above chance level (>23 %). In the best run every patient reached an accuracy ≥ 60 %. Twelve out of twenty patients showed an improvement of 1 to 7 points in the CRS-R score after the VT3 BCI sessions. 6 patients did not show change in the CRS-R score and 2 patients showed a decline in the score for 1 point. This study shows the importance of repeating the EEG measures when DOC patients are assessed to increase the chance of detecting the abilities of the command-following. The improvement of the CRS-R score after the 10 vibro-tactile sessions is an important fact for future studies to test the training effects and the signs of motor recovery with DOC patients with a larger group of patients and the vibro-tactile BCI setup.

Disclosures: **N. Murovec:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **A. Heilinger:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **R. Xu:** A. Employment/Salary (full or part-time):; g.tec Guger Technologies OG. **R. Spataro:** None. **V. La Bella:** None. **Y. Miao:** None. **J. Jin:** None. **G. Edlinger:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); g.tec neurotechnology GmbH. **C. Guger:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); g.tec neurotechnology GmbH.

Poster

584. Brain-Computer Interface: Rehabilitation

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 584.21/N23

Topic: E.05. Brain-Machine Interface

Support: WT 104128/Z/14/Z
ERC 715022 EmbodiedTech

Title: Brain plasticity following intensive robotic 'Third Thumb' usage for hand augmentation

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Abstract: Interest is growing in augmentative technologies that extend the physical and cognitive abilities of able-bodied individuals. These new devices introduce various theoretical and practical challenges for how the brain should adapt to representing a new robotic body-part. Supernumerary robotic fingers, such as the 'Third Thumb', allow the user to single-handedly perform normally bimanual tasks. Strapped to the ulnar side of the right hand, the Third Thumb is controlled via pressure sensors under the users' big toes, providing two degrees of freedom for operating a 2nd opposable thumb. Here, using the human somatosensory cortex as a model, we investigate neural correlates of Third Thumb usage. We trained 18 healthy able-bodied participants to use the Third Thumb over the course of five days, including spontaneous usage (tracked using pressure signals, used to operate the device) and customised daily training sessions. During training, participants completed a set of typical bimanual daily life tasks, using their (right) augmented hand. A separate control group (n=10) wore the Third Thumb and underwent daily training sessions, but did not operate the Third Thumb. Multiple measures of Third Thumb dexterity and hand-robot coordination showed significant improvement in motor control over the five days of usage. We used pre- to post- comparison measures to assess brain and behavioural outcomes of Third Thumb usage on body representation. Questionnaires for explicit sense of body ownership revealed increased embodiment over the Third Thumb specifically in the users' group. fMRI neuroimaging (focusing on multivoxel representational similarity across the biological digits) revealed increased similarity after Third Thumb usage, both for the augmented hand digits, and between the toes and the augmented hand digits. Preliminary results for hand-digit individuation revealed trends towards increased enslavement following Third Thumb usage. By studying the neural correlates of hand augmentation, we introduce a novel model for examining the adult brain's ability to dynamically update body representations based on new experiences with technology. We conclude that even short experience with wearable motor augmentation impacts fundamental aspect of hand and body representation.

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Poster

584. Brain-Computer Interface: Rehabilitation

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Topic: E.05. Brain-Machine Interface

Support: NIH Grant NS102259

Title: Efficacy and long-term stability of a high-density intramuscular electrode system for functional electrical stimulation

Authors: N. L. HOLLY[1], B. A. HASSE[1], L. COX[2], D. M. MARGOLIS[3], K. M. GOTHARD[4], *A. J. FUGLEVAND[1];
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Abstract: Functional electrical stimulation (FES) involves artificial electrical stimulation of muscles to elicit movement in paralyzed limbs. We are developing a method that uses electromyographic and kinematic signals recorded in able-bodied subjects to train machine-learning algorithms to control FES in paralyzed individuals. For this system to work, we need access to most of the muscles controlling a limb with implanted intramuscular electrodes. As such, we require an electrode system that: 1) minimizes electrode migration, 2) is biocompatible, 3) has small leads needed to accommodate large numbers of electrodes, and 4) is efficient to implant within one surgical session. With such requirements in mind, we developed an electrode system and tested it in a chronic implant of 60 electrodes in 30 upper-limb muscles of a rhesus macaque. Electrode leads were made of Teflon-coated multi-stranded stainless steel wire (0.3 mm outside diameter). During surgery, the color-coded leads were tunneled below the skin from a skull-mounted connector to incisions made over target muscles. Leads were then cut to length, insulation from the tip of the leads was removed with a thermal wire stripper, and gold anchors (~ 1 x 4 mm) were crimped onto the leads. The anchor was loaded into a 14-guage needle with the lead exiting the needle in a slot cut along its shaft. The needle was inserted into the muscle and stimulation was delivered through the tip of the needle that was otherwise insulated. The position of the needle was adjusted until strong contractions were evoked. The anchor was then deployed with a plunger and the needle removed. Anchor placement was then verified by stimulating through the lead and the threshold current was determined visually. The entire surgery lasted 9 hours. There were no post-operative complications and no electrode rejection. All 60 electrodes were functional at 8 weeks. At 5 and 8 weeks post surgery, the animal was anesthetized, secured upright in an infant car seat, and the hand fixed to a 6 degree-of-freedom force/torque transducer. Contractile responses to 1-s pulse trains, incrementing in 1 mA steps,

were measured for each electrode. Average (± SD) thresholds were 3.0 ± 2.2 mA and 2.8 ± 2.3 mA at 5 and 8 weeks, respectively. These values were slightly higher than that measured visually during surgery (1.5 ± 0.7 mA). While preliminary, these results indicate that such anchor electrodes might provide a long-lasting implant that could be used in future FES systems.

Disclosures: N.L. Holly: None. **B.A. Hasse:** None. **L. Cox:** None. **D.M. Margolis:** None. **K.M. Gothard:** None. **A.J. Fuglevand:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.01/N25

Topic: E.09. Motor Neurons and Muscle

Support: CONACYT 178544.

Title: The effect of dry needling therapy on gene expression in a model of muscle spasticity

Authors: *E. E. GARCIA-VENCES[1], J. CEBALLOS ZAVALA[1], J. FIGUEROA VARELO[1], E. DE LA CRUZ CASTILLO[1], S. CALVO CARRION[2], P. HERRERO GALLEGO[2], A. IBARRA[1];
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Abstract: The spinal cord injury (SCI) is an adverse condition that involve different consequences like muscle spasticity with many repercussions in patients as muscle atrophy and pain. These signs and symptoms are triggered by the activation of molecular mechanisms that promotes the release of acetylcholine into neuromuscular end-plate as a consequence of denervation after SCI, that leads to increasing calcium levels and therefore the depolarization of cell membrane that result in the myofibrillar destruction and the activation of inflammatory molecules as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNFα) and decrease the acetylcholinesterase (AChS) The dry needling (DN) is an innovative strategy that promotes the reduction of the sustained muscle contraction; however, the molecular mechanisms hadn´t been studied yet. For this reason, our goal was to analyze the motor and molecular changes that induce DN inside spastic gastrocnemius muscle in a chronic SCI model. Adult female Sprague-Dawley rats (13-14 weeks old, 200-220 g) were anesthetized and its spinal cords were exposed by laminectomy at T9. Rats were subjected to spinal cord transection (SCT) (n=20). Twenty days after SCT the animals were randomly allocated into five groups: 1. Sham surgery, n=4, 2. SCT without DN, n=10; 3. SCT + DN, 3 days n=5 and 4. SCT + DN 7 days n=5 and the DN was applied in gastrocnemius muscles with previous localization of the trigger points at 3 hr and 7 days after (28 days after SCT). We

perform motor recovery test with BBB scale from SCT until 28 days. We assessed the gene expression of iNOS, COX-2, IL-1β, TNFα and AChS in gastrocnemius to 3 hr and 7 days after DN. Seven days after DN the animals showed a significant increased motor recovery comparing with the other groups (5.6+/- SD vs 2.1 +/- SD, U de Mann Whitney p≤0.05). In relation to gene expression at 3 hr iNOS, COX-2 and AChS were down-regulated (U de Mann Whitney p ≤0.05); however, at 7 days shift up-regulated (U de Mann Withney p ≤0.05). The other genes didn´t show a significant difference. The DN induce the up-regulation of AChS, iNOS y COX-2 at 7 days that promotes the reduction of the sustained muscle contraction, vasodilatation and protection of the muscle fiber, data support the trend to motor recovery at this time. The DN set up a focal inflammatory response that promote the decreased of chronic inflammation of trigger points in spastic muscles.

Disclosures: E.E. Garcia-Vences: None. **J. Ceballos Zavala:** None. **J. Figueroa Varelo:** None. **E. De la Cruz Castillo:** None. **A. Ibarra:** None. **S. Calvo Carrion:** None. **P. Herrero Gallego:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.02/N26

Topic: E.09. Motor Neurons and Muscle

Title: Preservation of Ia afferent synaptic inputs on regenerated motoneurons after nerve injury does not result in restoration of function

Authors: *T. M. ROTTERMAN[1], P. NARDELLI[2], V. GARCIA[3], F. J. ALVAREZ[5], T. C. COPE[4];
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Abstract: Peripheral nerve injury (PNI) results in the permanent reorganization of essential motor circuits within the spinal cord even after peripheral axon regeneration is complete. One example of this is the loss of the proprioceptor Ia afferent input from axotomized motoneurons (MNs) which ultimately results in the complete absence of the stretch reflex. Recent work from our labs has shown that this loss is due to a central neuroinflammatory response. We hypothesized that administration of the broad-spectrum antibiotic with known anti-inflammatory properties, Minocycline, would dampen overall inflammation resulting in the preservation of Ia afferent boutons and restoration of the stretch reflex. To investigate this, we completely transected the medial gastrocnemius (MG) nerve in adult rats followed by an immediate repair using fibrin glue. Rats were treated with minocycline (49mg 1x daily) or vehicle food cubes for two weeks post injury. Sham control rats treated with minocycline were also prepared. Three

months post injury, well after peripheral regeneration has occurred, we quantified the somatic and linear dendritic density of Ia synapses on retrogradely labeled MG MNs. Rats who had undergone injury with no drug showed, as expected, an 81% decrease in Ia input on the soma and a 58% drop on the proximal dendritic arbor. However, treatment with minocycline rescued this synaptic loss resulting in a 5% increase on the soma and a mild 17% loss on the dendrites compared to controls. To investigate the function of these preserved synapses we measured the stretch reflex in regenerated and control rats. Rats who had undergone a nerve injury with no drug showed absolutely no stretch reflex in response to both vibration and to a ramp-hold-release paradigm compared to sham controls. Rats who had undergone injury with drug, in which synapses were preserved, surprisingly also showed no response to muscle stretch. To investigate these findings further we performed *in vivo* intracellular recordings of MG MNs in all conditions. In injured rats with vehicle there was a significant drop in stretch evoked synaptic potentials (SSPs) compared to controls, while majority of all MG MNs in drug treated rats evoked an SSP but still did not produce a reflex. Based on current evidence the preservation of Ia afferent inputs on regenerated MNs in necessary but not sufficient to restore stretch-evoked reflexes even though SSPs can be detected in essentially all MG MNs with drug treatment. This lack of functional recovery is under further investigation to explain the discrepancy between structural synaptic preservation and presence of SSPs but no reflex.

Disclosures: T.M. Rotterman: None. **P. Nardelli:** None. **V. Garcia:** None. **F.J. Alvarez:** None. **T.C. Cope:** None.

Poster

585. Motor Neuron II

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Support: Grant-in-Aid for Young Scientists (B) 17K13069
Grant-in-Aid for Scientific Research (B) 16H05443

Title: Exercise improves contractile force and kinematical movement of paralyzed hindlimb after brain damage of mice

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Abstract: Rehabilitation is one of the therapies for recovery of lost function after neural damage. Exercise such as movement of the extremities in the patients promotes the recovery of motor function. In rodents, although several behavior experiments such as ladder waking and footprint

test are performed to assess the motor function, there are no objective measurement for the motor evaluation. In present study, we induced brain damage in mice and evaluated the effect of exercise on the motor function in a quantitative fashion using motion-capture technology. Male 8 weeks old mice were subjected to brain damage. The brain damage was produced by aspiration of left sensorimotor cortical region. Then the mice divided into exercise (Ex) and non-exercise (Non-Ex) group. Rehabilitation program was a running exercise. Mice were run on treadmill (30 min/day, 5 days/week) for 4 weeks. After the exercise, the mice were recorded the steps on the treadmill by synchronized four cameras and were analyzed three-dimensional motor functions by using kinematical analysis including motion-capture technology. The mice then were removed soleus muscle in the side of paralyzed and the contractile force was measured by the Magnus method under the KCl stimulation. There were no significant differences in gait parameters (time of gait cycle, stance phase and swing phase) and in the mass of muscles in the limbs between Ex and Non-Ex group. However, the contractile force of paralyzed soleus muscles in Ex group was shown significantly stronger than that in Non-Ex group. The soleus muscle is responsible for the ankle movable of the dorsal-plantar flexion. Therefore, the mice were further evaluated the ankle movement on the paralyzed side during the steps by using kinematically analysis. No significant difference in the range of joint movement during the steps was observed in the ankle of paralyzed side. However, the angular velocity and acceleration of the paralyzed side in Ex mice was increased shortly before takeoff the floor. From this study, hindlimb movement was evaluated quantitatively by using kinematical method. Our results suggest that exercise therapy after brain damage improve paralyzed muscles activity participate as joint movement.

Disclosures: A. Yoshikawa: None. **H. Ohtaki:** None. **M. Izumizaki:** None.

Poster

585. Motor Neuron II

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Program #/Poster #: 585.04/N28

Topic: E.09. Motor Neurons and Muscle

Support: JSPS KAKENHI 19K19827

Title: The duration and frequency of vibration modulate the recovery time of the post-vibration depression of monosynaptic Ia facilitation in humans

Authors: *M. NITO, T. YOSHIMOTO, M. JIMENJI, W. HASHIZUME, A. NAITO;
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Abstract: Effects of the tonic vibration stimulation (TVS) to a muscle on the monosynaptic Ia facilitation to the homonymous and heteronymous muscles were examined using the Hoffmann(H)-waves of the flexor carpi radialis (FCR) and the tendon(T)-waves of the biceps

brachii (BB), respectively, in fifteen healthy human volunteers. The H-wave of FCR were provoked by electrical stimulation to the median nerve trunk at the elbow. The T-wave of BB were induced by a mechanical quick tap applied to the distal tendon of BB (test T-wave) and the amplitude of the T-waves was increased significantly by electrical stimulation to the median nerve trunk (conditioned T-waves). TVS (frequency: 57, 77 and 100 Hz; duration: 2, 4, 6, 8, 10 and 20 minutes) was delivered manually to the FCR muscle belly. As a result, the amplitudes of the H-waves and the conditioned T-waves were suppressed by TVS, and the suppression lasted after removal of TVS in all the subjects. In both the H- and conditioned T-waves, the longer the duration and the higher the frequency of TVS, the longer the recovery time of the suppression. Since the amplitude of the test T-waves did not change throughout the experiment, TVS should not have affected the excitability of motoneurons. It therefore seems that the duration and frequency of TVS affect the transmission of group Ia afferent terminals mediating the facilitation to the homonymous and heteronymous motoneurons.

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Poster

585. Motor Neuron II

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Topic: E.09. Motor Neurons and Muscle

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Title: Loss of NAMPT alters function and structure of the neuromuscular junction (NMJ)

Authors: *S. LUNDT, N. ZHANG, X. WANG, L. POLO-PARADA, S. DING;
Univ. of Missouri, Columbia, MO

Abstract: Nicotinamide adenine dinucleotide (NAD^+) is one of the most abundant metabolites in the human body. The majority of NAD^+ in cells is synthesized via the NAD^+ salvage pathway, where nicotinamide phosphoribosyltransferase (NAMPT) functions as the rate-limiting enzyme. NAMPT converts nicotinamide into nicotinamide mononucleotide (NMN). In mice, conditional knockout of NAMPT in projection neurons has been shown to produce broad physiological deficits and, eventually, death. The impact of the knockout of NAMPT on the neuromuscular junction (NMJ), specifically vesicle cycling in the motor neuron or end-plate structure and contractile responses of skeletal muscles, has yet to be characterized. We found that loss of NAMPT significantly disrupts endocytosis and exocytosis of synaptic vesicles in motor neurons,

possibly impairing movement of the vesicles intracellularly. The end-plate morphology of the NMJ was significantly altered, having reduced area and thickness. When treated with NMN, the mice showed improved vesicle endocytosis and exocytosis with end-plate structure more resembling the structure observed in control mice. At low frequencies of stimulation, knockout of NAMPT produced responses of similar strength but quicker end of contraction. At moderate frequencies, Nampt$^{-/-}$ cKO mice had exaggerated contraction strength but showed no response to the highest frequency. NMN-treated Nampt$^{-/-}$ cKO mice were similar to Nampt$^{-/-}$ cKO at low frequencies, displayed reduced contraction strength at moderate frequencies but remained responsive to the highest stimulation frequency. Our results indicate that neuronal NAMPT is important for the proper function of the NMJ and that loss of NAMPT leads to both presynaptic and postsynaptic deficits.

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Poster

585. Motor Neuron II

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Program #/Poster #: 585.06/N30

Topic: E.09. Motor Neurons and Muscle

Support: JSPS KAKENHI 18H03134

Title: No influence of the menstrual cycle on ankle joint position sense and inhibitory function of primary somatosensory cortex

Authors: *K. IKARASHI[1], D. SATO[2], K. IGUCHI[1], Y. YAMAZAKI[1], K. YAMASHIRO[1]; [1]Niigata Univ. of Hlth. and Welfare, Niigata, Japan; [2]Niigata Univ. of Hlth. and Welfare, Niigata City, Japan

Abstract: Previous studies have reported that the menstrual cycle may affect sensorimotor performance, and that sex hormones, such as estradiol and progesterone, modulate cortical excitability. Accordingly, it is considered that the menstrual cycle may affect joint position sense and somatosensory cortical activity. We aimed to clarify the influence of the menstrual cycle on the ankle joint position sense and the inhibitory function of the primary somatosensory cortex. Fourteen women with regular menstrual cycle participated in the present study. Based on the basal body temperature measured during two months prior to the main experiment, we predicted the follicular, ovulation and luteal phase in the menstrual cycle of each participant. In the main experiment, in each menstrual cycle phase, we evaluated the ankle joint position sense using a joint angle modulation task, and the somatosensory inhibitory function using somatosensory paired pulse inhibition (somato-PPI) measurement. The absolute error angle, response time of the joint angle modulation task, and somato-PPI ratio were compared between each menstrual cycle

phase. The results of repeated measures ANOVA revealed no significant difference in either joint angle modulation performance or somato-PPI ratio between each menstrual cycle phase. Correlation analysis revealed a significant negative correlation between the absolute angle error in the early follicular phase and the ratio of absolute angle error in the luteal phase to that in the early follicular phase. Contrary to our hypothesis, the results of our study demonstrated that the menstrual cycle did not affect ankle joint position sense or the inhibitory function of the primary somatosensory cortex. However, the results of the correlation analysis might indicate that the change in sex hormones concentration modulates joint angle sense in the luteal phase. In conclusion, our results demonstrated that the menstrual cycle has no influence on the ankle joint position sense or inhibitory function in primary somatosensory cortex.

Disclosures: K. Ikarashi: None. **D. Sato:** None. **K. Iguchi:** None. **Y. Yamazaki:** None. **K. Yamashiro:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.07/N31

Topic: E.09. Motor Neurons and Muscle

Support: JSPS kakenhi 18H03134

Title: Influence of focal muscle fatigue on paired associative stimulation induced plasticity in the primary motor cortex

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Abstract: Previous studies have reported that muscle fatigue changes the balance between excitability and inhibitory neural activity of the primary motor cortex. Our research group and others have previously shown decreased inhibitory neural activity of the primary motor cortex (M1) during and after focal muscle fatigue. However, the effect of focal muscle fatigue on neural plasticity has remained unclear. We examined the effects of changes in M1 excitability induced by focal muscle fatigue on spike timing-dependent plasticity (STDP) using paired associative stimulation 25 (PAS 25), which induces long-term potentiation (LTP)-like effect.Ten right-handed, healthy adults participated in the present study. We measured the motor evoked potentials (MEPs) induced by transcranial magnetic stimulation (TMS) to evaluate the M1 excitability before and after PAS 25 in three experimental trials: PAS25 without fatigue, PAS25 immediately after muscle fatigue, and PAS25 after recovery. TMS was applied over the M1

hotspot of the right first dorsal interosseous muscle at the intensity required to induce MEPs with an amplitude of 1 mV. Electrical stimulation (ES) was applied to the ulnar nerve at the right wrist at the intensity of three times the sensory threshold. For the PAS protocol, paired stimulation with TMS and ES was conducted in 25-ms intervals at 0.2 Hz for a period of 20 min. We observed slightly increased MEP amplitude after PAS 25 without muscle fatigue. In addition, significantly decreased MEP amplitude was observed after focal muscle fatigue, similar to findings of previous studies. The results of repeated measures ANOVA revealed no significant change in MEP amplitude after PAS 25 after focal muscle fatigue compared to that at baseline measurement. These results indicate that muscle fatigue abolished PAS 25-induced plasticity due to homeostatic meta-plasticity, as has been previously reported. Notably, a new finding based on the results of this study is that this metaplastic effect lasts at least 30 min after muscle fatigue, as PAS 25 did not increase the MEP amplitude even when the MEP amplitude returned to baseline levels. In conclusion, focal muscle fatigue might abolish the STDP effect induced by PAS 25 irrespective of recovery of decreased MEP amplitude.

Disclosures: K. Kurihara: None. **D. Sato:** None. **K. Yamashiro:** None. **Y. Yamazaki:** None. **A. Maruyama:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.08/N32

Topic: E.09. Motor Neurons and Muscle

Support: JPSP KAKENHI JP17H06695

Title: Orexin modulates electrophysiological properties of Phox2b neurons located around trigeminal motor nucleus

Authors: *K. NAGOYA[1,2], S. NAKAMURA[2], T. TSUJIMURA[1], M. INOUE[1], T. INOUE[2]; [1]Niigata Univ., Niigata city, Japan; [2]Showa Univ., Tokyo, Japan

Abstract: Phox2b is a member of transcription factors and essential for the development of the autonomic nervous system. Previous study indicated that Phox2b-expressing neurons were located at the reticular formation dorsal to the trigeminal motor nucleus (RdV) in the rat brainstem. We recently reported that Phox2b-expressing and -nonexpressing neurons in the RdV have different physiological properties, and about half of both neurons were send their axons to the trigeminal motor nucleus. This result suggests that these neurons are also involved in the control of coordinated jaw-movements such as chewing and swallowing.
Orexin is one of the neuropeptides that are mainly derived from orexin-containing neurons in the lateral hypothalamus, and are widely distributed throughout the central and peripheral nervous

systems. Orexin have an essential role to regulate physiological functions such as feeding and wake/sleep stabilities. However, the effect of orexin on Phox2b-expressing or -nonexpressing neurons and its functional role remain unknown. In the present study, we investigated physiological changes of Phox2b-expressing neurons located at RdV by the administration of orexin.
Using brainstem slices including RdV were prepared from P2-14 Phox2b-EYFP rats, whole-cell recording were performed in Phox2b-expressing and -nonexpressing RdV neurons. We analyzed neuronal activity with the presence of orexin-A (200 nM) or orexin-B (200 nM). Furthermore, we examined effects of an orexin 1 receptor antagonist,
SB-334867, and orexin 2 receptor antagonist TCS OX2 29, on orexin-A- induced depolarization of Phox2b-expressing neurons.
The majority of Phox2b-expressing neurons (15/18) were produced membrane depolarization sometimes accompanied by spontaneous firing, whereas most of Phox2b-nonexpressing neurons (9/12) showed no depolarization changing during the application of orexin-A. Orexin-B induced depolarization in most Phox2b-expressing neurons (6/7) as well as the effect of orexin-A. Orexin-A or orexin-B- induced depolarization ranged from 5 to 20 mV. However, orexin A-induced membrane depolarization were prominently reduced with the presence of SB-334867 or TCZ OX2 29. On the other hand, all Phox2b-expressing and -nonexpressing neurons exhibited reduction of firing rate by the administration of orexin-A. Mean reduction of Phox2b-expressing and -nonexpressing neurons with the presence of orexin-A were 5.8 and 5.2 Hz, respectively. Taken together, present study suggests that orexin modulate passive membrane and firing properties of Phox2b-expressing neurons, which may affect the regulation of the jaw-movement during feeding behavior and bruxism.

Disclosures: K. Nagoya: None. **S. Nakamura:** None. **T. Tsujimura:** None. **M. Inoue:** None. **T. Inoue:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.09/N33

Topic: E.09. Motor Neurons and Muscle

Support: MED-EL Austria 404-781-7042

Title: Stimulation of a reinnervating laryngeal muscle with low frequency inhibits foreign reinnervation and promotes selective reinnervation by native motoneurons and restores function

Authors: *D. L. ZEALEAR, Y. LI, M. E. POWELL, S. HUANG;
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Abstract: Electrical stimulation of a denervated canine laryngeal muscle was shown to promote reinnervation by original over foreign motoneurons. An implantable nerve stimulation-EMG system was used to index the appropriateness of reinnervation of the vocal fold abductor (posterior cricoarytenoid, PCA) muscle by inspiratory versus foreign reflex glottal closure (RGC) motoneurons following recurrent laryngeal nerve section and repair. In the present study in 11 canines, a clinical model was used, where both nerves were sectioned and ventilation compromised due to loss of vocal fold abduction. The EMG system and a pulse generator were implanted, the latter for electrical conditioning of PCA muscles. After nerve section, animals were randomly assigned to four groups to assess the effect of different muscle stimulus paradigms on reinnervation quality and degree of functional recovery: 1)40 pps train, 2)20 pps train 3)10 pps train and 4)control-no stimulation. One msec pulses were applied with 4 sec on/4 sec off duty cycle during the post neurorrhaphy regeneration period. In bimonthly sessions, spontaneous vocal fold movement was measured endoscopically during induced hypercapnea in the anesthetized animal. Rectified integrated EMG potentials were recorded from abductor muscles and adductor (thyroarytenoid, TA) muscles. Recordings were obtained during hypercapnic respiration to index reinnervation by inspiratory motoneurons, and during superior laryngeal nerve stimulation to index reinnervation by RGC motoneurons. Exercise tolerance was measured on a treadmill in the awake animal using pulse oximetry. Results demonstrated that all stimulated groups tended to have better results (i.e. higher rank order) in all outcome measures compared to the non-stimulated control group. The rank order stayed fairly consistent across all outcome measures: 10pps > 20pps > 40pps > non-stimulated. It would appear that electrical stimulation of the denervated PCA muscle inhibited synkinetic reinnervation by RGC motoneurons and promoted selective reinnervation by its original inspiratory motoneurons. In addition, stimulation with low frequency, characteristic of the intrinsic activity of PCA inspiratory motoneurons, was more effective than high frequency in inducing correct reinnervation and improving functional recovery.

Disclosures: **D.L. Zealear:** None. **Y. Li:** None. **M.E. Powell:** None. **S. Huang:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.10/N34

Topic: E.09. Motor Neurons and Muscle

Support: NS091836
NS91836

Title: Hypoexcitability and hyperexcitability in sacral motorneurons of SOD1G93A high copy ALS mice: Disease versus compensation

Authors: *C. S. I. DRAPER[1], A. A. MAHROUS[2], S. M. ELBASIOUNY[2,3];
[1]Biomed. Sci. PhD Program, [2]Neuroscience, Cell Biology, and Physiol., [3]Biomedical, Industrial, and Human Factors Engin., Wright State Univ., Dayton, OH

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease characterized by the selective and progressive loss of motorneurons in the motor cortex, brain stem, and spinal cord. To date, many hypotheses to explain the pathogenesis of ALS has been explored, but abnormalities in motorneurons and glutamate excitotoxicity remain predominant. The current excitotoxicity theory predicts that motorneurons in ALS are excessively activated by glutamate, leading to increasing amounts of calcium entering these cells and eventually cell death. However, the current literature regarding the excitability state of motorneurons in ALS is inconsistent in which some studies have reported hyperexcitability (Pieri et al.,2003, Kuo et al., 2005, and Martin et. al., 2013) others reported hypoexcitability (Bories et. al.,2007, Delestree et al.,2014, and Martinez-Silva et al.,2018) or some reported no excitability changes (Pambo-Pambo et al. 2009 and Quinlan et al.,2011). This conflicting data on motor neuron excitability in ALS probably reflects the dynamic interaction between the underlying disease and compensatory mechanisms. Therefore, the purpose of this study was to examine spinal motorneurons' excitability in $SOD1^{G93A\text{-}High}$ mice at the time of symptom onset (i.e., postnatal day 90, P90); a stage when disease and compensatory mechanisms are at peak interaction. Interestingly, intracellular recordings from spinal motorneurons in the in-vitro whole cord preparation exhibited *concurrent* signs of hypoexcitability and hyperexcitability. Specifically, SOD motor neurons exhibited increased rheobase and input conductance (signs of hypoexcitability) but reduced afterhyperpolarization amplitude (a sign of hyperexcitability). Our study is the first to report both excitability abnormalities in the same motorneurons in ALS. Accordingly, our results indicate that hyper- and hypoexcitability are both present and interact dynamically during ALS pathogenesis.

Disclosures: C.S.I. Draper: None. **A.A. Mahrous:** None. **S.M. Elbasiouny:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.11/N35

Topic: E.09. Motor Neurons and Muscle

Support: MEXT 16K11489

Title: $Serotonin_{1b}$ receptor mediated presynaptic inhibition of jaw closing motoneurons

Authors: *K. NAKAYAMA[1], A. NAGATA[2], S. NAKAMURA[1], A. MOCHIZUKI[1], M. DANTSUJI[1], K. MAKI[2], T. INOUE[1];
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Abstract: The proprioceptive sensory inputs from neurons in the mesencephalic trigeminal nucleus (MesV) to masseter motoneurons (MMNs) play an important role in regulating masseter muscle activity during mastication. Several histological studies have shown that serotonin (5-HT) fibers densely innervate both the MesV and the trigeminal motor nucleus. However, the functional roles of 5-HT in the regulation of the excitatory synaptic inputs from MesV afferents to MMNs remain to be clarified. Thus, using the whole-cell recording technique in brainstem slice preparations from juvenile Wistar rats aged between postnatal days 8 and 12, we examined the effects of 5-HT on the excitatory synaptic inputs from MesV afferents to MMNs. Bath application of 5-HT (0.1-100 μM) reduced the peak amplitude of excitatory postsynaptic potentials evoked in MMNs by electrical stimulation of the MesV afferents (eEPSPs) in a dose-dependent manner. This inhibitory effect of 5-HT on eEPSPs was replicated with the 5-HT_{1B} receptor agonist CP-93129 (0.1 μM) but not by the 5-HT_{1A} receptor agonist 8-OH-DPAT (1 μM). Moreover, the 5-HT_{1B} receptor antagonist SB-224289 (10 μM) but not the 5-HT_{1A} receptor antagonist WAY-100635 (1 μM) antagonized the inhibitory effect of 5-HT on eEPSPs. CP-93129 increased the paired-pulse ratio and decreased the frequency of miniature excitatory postsynaptic currents (mEPSCs), while it did not alter the mEPSC amplitude. These results suggest that presynaptic 5-HT_{1B} receptors are involved in the inhibition of the excitatory synaptic inputs from MesV afferents to MMNs. Such inhibition may regulate MesV afferent activity during mastication.

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Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.12/N36

Topic: E.09. Motor Neurons and Muscle

Support: Mayo Clinic Ultrasound Research Center

Title: Quadriceps muscle motor unit activity after anterior cruciate ligament reconstruction

Authors: *A. MCPHERSON[1], N. BATES[1], C. HAIDER[1], T. HEWETT[2], N. SCHILATY[1];
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Abstract: Introduction
Quadriceps strength deficits exist after anterior cruciate ligament (ACL) injury and reconstruction (ACLR) despite rehabilitation. The mechanism for persistent strength deficits remains unclear, although reduced alpha motor neuron (α-MN) output has been suggested to reduce voluntary strength after ACLR. Therefore, the purpose of this exploratory study was to determine α-MN is different after ACLR compared to healthy controls.
Methods
Subjects (29F/24M) completed isometric knee extension tasks while surface electromyography (EMG) signals were recorded from the vastus medialis (VM) and vastus lateralis (VL). Three maximum voluntary isometric contractions (MVIC) determined peak force for 10, 25, 35, and 50% MVIC trials. After data acquisition, EMG decomposition was performed. Motor unit (MU) (de)recruitment and average firing rates (FR) were compared between groups with mixed model analyses and post-hoc Tukey all pairwise comparisons.
Results
Group, trial, and muscle were all significant effects in the mixed model for average FR and (de)recruitment thresholds ($p<0.001$). Significant differences were observed between groups for average FR, except 6 months post-ACLR and controls ($p=0.47$), and between all groups for recruitment thresholds. All trials were significantly different for average FR and recruitment thresholds, except 10% vs 25% MVIC, 10% vs 50% MVIC, and 25% vs 50% MVIC average FR. VM average FR was greater than VL, but VL recruitment was greater than VM. All groups and trials were significantly different for derecruitment threshold except controls and 12 month post-ACLR.
Conclusion
MU (de)recruitment was lowest at 6 months post-ACLR concomitant with higher average FR. This inverse relationship between average FR and MU recruitment thresholds has previously been demonstrated in healthy subjects and is now demonstrated here after ACL injury and ACLR. ACL injury and ACLR appears to have variable effects on VM and VL α-MN activity, as VM decreased (de)recruitment thresholds and increased FR whereas VL exhibited the opposite pattern. These findings suggest that quadriceps α-MN activity changes throughout rehabilitation up to 12 months post-ACLR compared to controls.

Disclosures: A. McPherson: None. **N. Bates:** None. **C. Haider:** None. **T. Hewett:** None. **N. Schilaty:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.13/N37

Topic: E.09. Motor Neurons and Muscle

Support: Lone Star Paralysis Foundation
NIH NS081063

Title: Behavioral recovery and spinal motoneuron remodeling after polyethylene glycol fusion repair of singly cut and ablated sciatic nerves

Authors: E. A. HIBBARD[1], C. GHERGHEREHCHI[2], M. MIKESH[2], G. BITTNER[2], ***D. R. SENGELAUB**[3];
[1]Indiana Univ., Bloomington, IN; [2]Univ. of Texas, Austin, TX; [3]Indiana Univ. Bloomington, Bloomington, IN

Abstract: Peripheral nerve injuries lead to the immediate loss of motor and sensory function, rapid degeneration of the distal nerve segment, neuromuscular junction loss, and muscle atrophy. Behavioral recovery is typically poor. Peripheral nerve injuries also have consequences centrally for the affected motoneurons, including somal shrinkage and retraction of dendritic arbors. The current standard of treatment for peripheral nerve injury involves microsuturing of the severed nerve segments. However, this treatment leaves axonal membranes unrepaired, and therefore Wallerian degeneration is not prevented and recovery is not improved. We have developed a novel strategy that uses a plasmalemmal fusogen, polyethylene glycol (PEG), to nonspecifically re-fuse the membranes of severed axons. This treatment allows for the immediate re-innervation of the distal muscles, prevents Wallerian degeneration, maintains muscle innervation, and improves behavioral recovery. In this study, we determined the effects of PEG-fusion repair on the central consequences of peripheral nerve injury by examining motoneurons contributing to the sciatic nerve after non-specific PEG-repair of their peripheral axons. At 2-112 days after either a single-cut or allograft repair of the sciatic nerve with PEG, the number and size of motoneurons contributing to the sciatic nerve was assessed stereologically. The location and morphology of motoneurons projecting to the anterior tibialis muscle was also assessed after retrograde labeling. Following peripheral axotomy and PEG-repair, the number and size of sciatic motoneurons was unaffected. Retrograde labeling of motoneurons revealed that following non-specific axonal fusing with PEG, retrograde transport was re-established within 2-17 days, depending on repair type. Labeled motoneurons were found not only in the appropriate L3 spinal segment, but also in the L4-L6 segments, indicating mis-pairings of proximal and distal motor axons. The morphology of PEG-repaired motoneurons was also affected, with changes in dendritic distribution from patterns typically displayed by these motor populations. Together, these findings indicate that PEG-repair after axotomy preserves spinal motoneurons, and a substantial reorganization of motoneuron morphology is induced by the non-specific repair of the severed nerve. This central reorganization may contribute to the improved behavioral recovery seen after PEG-repair, supporting the use of this novel repair methodology over currently available treatments.

Disclosures: E.A. Hibbard: None. **C. Ghergherehchi:** None. **M. Mikesh:** None. **G. Bittner:** None. **D.R. Sengelaub:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.14/N38

Topic: E.09. Motor Neurons and Muscle

Support: R01NS098509

Title: Estimate of persistent inward currents in humans during varying muscle contraction speeds

Authors: *E. H. KIM[1], R. K. POWERS[3], C. HECKMAN[2];
[2]Dept. of Physiol., [1]Northwestern Univ., Chicago, IL; [3]Dept Physiol & Biophysics, Univ. Washington, Seattle, WA

Abstract: Persistent Inward Currents (PICs) amply the spinal motoneuron outputs by prolonging their firing and it has been postulated that PICs might play an important role in balance and postural control. Unlike in animals, the level of PICs cannot be directly measured in humans. Delta-F (ΔF) is a pair-wise comparison of motor unit discharge patterns that is widely used as an indirect estimate of PICs in humans. However, a simulation study has shown that increasing muscle contraction speed decreases ΔF because of spike-threshold accommodation. Therefore, we hypothesized that as the rate of rise increases, ΔF will decrease. In this study, ΔF of the soleus and tibialis anterior (TA) were measured from young and healthy subjects while they performed voluntary isometric contractions over varying rates of rise (1-5% MVC per second) at varying %MVC levels (10-50% MVC). EMG signals were collected through High-density surface array electrodes (HD-sEMG) and were decomposed into discharge patterns of individual motor units for ΔF calculation. The results showed that in both muscles, as the effort level increases, the ΔF did not change if the rate of rise stayed constant. However, unlike the hypothesis, ΔF increased in the TA as the rate of rise increased. On the other hand, ΔF did not significantly change in the soleus, as the rate of rise increased. Our simulation experiment also showed that as the contraction speed increased, ΔF increased as well.

Disclosures: E.H. Kim: None. **R.K. Powers:** None. **C. Heckman:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.15/N39

Topic: E.09. Motor Neurons and Muscle

Title: Fatigue induced modulation of human soleus H reflex in conditions of ipsilateral common peroneal nerve stimulation

Authors: *E. V. KOLOSOVA;
Natl. Univ. of Physical Educ. and Sports of Ukraine, Kyiv, Ukraine

Abstract: It was reported that after fatiguing calf triceps muscle contraction the soleus H (Hoffmann) reflex is inhibited, probably due to the activation of the groups III and IV afferent nerves under the influence of mechanical and metabolic changes in the fatigued muscle. Other authors described soleus H-reflex depression which was caused by conditioning common peroneal nerve stimulation at rest. We supposed that investigation of inhibition, connected with conditioning peroneal nerve stimulation before and after fatiguing contraction (FC) might help to assess peculiar patterns of inhibition processes in intrasegmental systems. Ten healthy people (4 men and 6 women, 18-34 years of age, M_{age}=25.8, SD=4.9) took part in this EMG-study. The method of H-reflex of soleus muscle with tibial nerve stimulation (test H-reflex, THR) and conditioning peroneal nerve stimulation with 15 ms peroneal-tibial interstimulus interval (conditioned H-reflex, CHR) were performed using neurodiagnostic complex Nicolet Biomedical Viking Select (Viasys Healthcare, USA). Fatigue was caused by voluntary static contraction of calf triceps muscle lasting 6-9 min with the force egual to 75 % of the maximal voluntary contraction. Two-factor analysis of variance with repeated measures considering two within-subjects factors (fatigue and conditioning) was carried out in the SPSS 17.0. It was found that the fatigue factor had significant inhibitory effect on the H-reflex (F=15.634, P=0.000). The conditioning factor had similar effect (F=306.586, P=0.000). The interaction of fatigue and conditioning factors was also found (F=2.237, P=0.016). A significant result of the study was that decrease of the CHR amplitude immediately after FC was proportional to THR amplitude reduction for mean group value as well as for individual ones. This might be the evidence of existence of certain percentage (about 35 % in average) of fatigue-inhibited motoneurons; this part does not essentially depend on H-reflex amplitude before FC. Besides, predicted summarized inhibitory influence of fatigue and conditioning was calculated as 34,6 % (THR amplitude difference before and immediately after FC) adding 24,4 % (THR and CHR amplitudes difference before FC) and equaled 59,0 %. On the other hand, total inhibitory influence calculated as difference between THR amplitude before FC and CHR amplitude immediately after FC was 51,8 %. Obtained data demonstrate that two types of soleus H-reflex inhibition, namely connected with conditioning peroneal nerve stimulation and fatiguing

contraction, proceed mainly through different nervous pathways, although partial convergence of inhibition influences is possible.

Disclosures: E.V. Kolosova: None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.16/N40

Topic: E.09. Motor Neurons and Muscle

Title: An investigation into the differential effects on somatosensory functions during deafferentation

Authors: *W. CAI, F. G. HEPWORTH LLOYD, P. SARAI, S. HUGHES, P. H. STRUTTON; Dept. of Surgery and Cancer, Imperial Col. London, London, United Kingdom

Abstract: Deafferentation is the severance of sensory inputs to the central nervous system and is associated with increased motor cortical excitability to the proximal muscles of the deafferented limb and homotopic contralateral muscles. Previous work has demonstrated that partial deafferentation is sufficient to induce alterations in cortical excitability, evidenced by an increase in proximal and contralateral motor evoked potentials (MEP) accompanied by a reduction (rather than loss) of somatosensory evoked potentials during an ischaemic nerve block (INB). However, the extent to which the INB differentially affects sensory nerve function has not been investigated. In order to explore this, we performed a low-pressure INB on the right forearm in healthy volunteers for 30 mins. Transcranial magnetic stimulation was used to induce MEPs from adductor pollicis brevis and brachioradialis muscles bilaterally, whilst a truncated quantitative sensory testing paradigm was used to interrogate the sensory function distal to the INB (brush stroke for Aβ, pinprick for Aδ and heat pain for C-fibre). We observed a significant decrease in MEP amplitudes of right APB towards the end of the ischaemic period, accompanied by a significant increase in MEP amplitudes of left APB MEPs from BR bilaterally tended to increase. A significant loss of brush stroke sensation was observed in the late occlusion period. Heat pain sensation was maintained throughout the experiment. Most participants lost pinprick sensation just before cuff release. However, a minority reported an increase in pinprick sensitivity. These results suggest that selective Aβ and Aδ sensory loss may underlie the changes in cortical excitability. In participants where an exaggerated response was found to pinprick, it is possible that the preserved C-fibre transmission facilitates pinprick sensation via mechanisms such as central sensitization, resulting in the development of secondary hyperalgesia. As pain is implicated in cortical reorganization, this may be key to how cortical plasticity is shaped by somatosensory function. These results may provide insight into the development of pathological pain conditions, especially following nerve injury.

Disclosures: **W. Cai:** None. **F.G. Hepworth Lloyd:** None. **P. Sarai:** None. **S. Hughes:** None. **P.H. Strutton:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.17/N41

Topic: E.09. Motor Neurons and Muscle

Support: CONACyT (JRGP) 595412

Title: Cerebellar influence on the H-reflex of soleus muscle during acquisition of sexual experience in male rats

Authors: *J. R. GUTIERREZ[1], R. ZEMPOALTECA[2], P. CARRILLO[3], A. J. CHACON[3], R. TOLEDO-CARDENAS[4], J. FISHER[4], G. A. CORIA-AVILA[4], J. MANZO[4], L. I. GARCIA[4]; [1]Doctorado en Investigaciones Cerebrales, Xalapa, Mexico; [2]Ctr. Tlaxcala de Biología de la Conducta, Tlaxcala, Mexico; [3]Inst. de Neuroetología, Xalapa, Mexico; [4]Ctr. de Investigaciones Cerebrales, Xalapa, Mexico

Abstract: The cerebellum receives afferents signals through ascending spinal pathways that convey information about posture, balance and muscle tone. Hence, the cerebellum integrates a complex circuit underlying the neural basis of sexual behavior (SB). This wiring serves not only for the expression of SB but also for the learning of skills needed for appropriate behavioral displays during copulation. Descending signals from cerebellum modulate spinal reflex response, and studies have shown that the cerebellum is necessary for the maintenance of a motor skill, and alterations in the cerebellum or descending pathways modify spinal cord reflexes. The H-reflex (HR) as the electrical analog of the spinal stretch reflex, changes during skill acquisition. These observations support the hypothesis that the cerebellum could modify the HR response due to SB experience in male rats. In the present study, we analyzed the effect of cerebellar circuit activity (states) over the properties of soleus HR in male Wistar rats (250 and 300 gr). We used two different paradigms, sexual behavior training (4 sessions, one every two days interrupted at ejaculation) to make an efficient cerebellar circuit, and electrolyte lesion of L6a at the vermis (3.5 mA/20 s), to remove cerebellar control over the HR. Rats were divided into two groups, Naïve and Sexual experts. In each of these groups two subgroups were organized, the Control and Lesion groups, the latter with an electrolyte lesion in the cortex of L6a of the cerebellar vermis. The aim was to analyze and determine the effect of cerebellum changes on the amplitude of HR. For each animal, we did the assessment of the umbral intensity stimuli and we recorded H-waves while intensity of stimulation increases until muscular contraction begins. Results show that in both Control and Lesion groups the amplitude of the HR is higher in experts compared to naïve rats. The latency and duration of the H-wave, as well as the amplitude, duration, and

latency of the M-wave, showed no differences between groups. Our results indicate that sexual behavior experience has a disinhibitory effect on H reflex amplitude. However, further studies are needed to determine the effect of electrolyte lesion of cerebellum on the soleus HR.

Disclosures: J.R. Gutierrez: None. **R. Zempoalteca:** None. **P. Carrillo:** None. **A.J. Chacon:** None. **R. Toledo-Cardenas:** None. **J. Fisher:** None. **G.A. Coria-Avila:** None. **J. Manzo:** None. **L.I. Garcia:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.18/N42

Topic: E.09. Motor Neurons and Muscle

Support: NIDILRR

Title: Non uniform denervation of muscle fibers in botulinum toxin injected spastic muscle

Authors: S. CHANDRA[1,3], B. AFSHARIPOUR[2], W. Z. RYMER[1,3], *N. L. SURESH[1,3]; [2]Sensory Motor Performance Program, [1]Shirley Ryan Ability Lab., Chicago, IL; [3]Physical Med. and Rehabil., Northwestern Univ., Chicago, IL

Abstract: Intramuscular botulinum toxin (BT) injections are often used to mediate spasticity in post-stroke survivors, The mode of action of the toxin is via chemo denervation at the neuromuscular junction of the motor neuron from the respective fibers. We hypothesize that BT works non uniformly and selectively on different motor units among the whole motor unit population of a targeted muscle. We have recorded joint contraction force and surface electromyography (sEMG) from BT injected biceps brachii muscle during sustained isometric contractions allowing us to analyze the electromechanical delay (EMD) and (peak) amplitude distribution of the recorded sEMG, and compare them to understand the effect of BT on different size of motor units. Recordings of participants who were chronic stroke survivors was moded in both their impaired and contralateral sides 2-12 weeks after their scheduled BT injection (part of their clinical care plan)with an additional pre-injection session as reference. The force and sEMG signals were recorded during multiple isometric, non-fatiguing elbow flexion with trapezoidal force trajectory at various force ranges. EMG data were recorded using special Sensor Arrays (SA) and Single Differential (SD) electrodes from Delsys Inc. A pair of SA and SD electrodes recorded signals from long and short heads of the biceps brachii muscle. Additional electrodes were used to monitor brachioradialis and triceps brachii activity. All the data were normalized with a Maximal Voluntary Contraction (MVC) before computation of the peaks and the electromechanical delay. The (EMG) was computed as the onset of the EMG signal - onset of the force signal during the rising phase of the isometric contraction and the peaks were calculated

during the steady state contraction phase. We have found that the EMD increases by a significant amount (3x) in the BT injected side for all the subject two/four weeks after the BT injection, we have also found only larger peaks were present during this session while mean steady state contraction force (as a %MVC) and the root mean square SEMG becomes significantly low. Moreover, the higher EMD values were found during the higher contraction levels. Increased EMD value and presence of larger peaks indicate the existence of active larger motor units in the injected muscle. From 4^{th} week onward the EMD falls down and also smaller sEMG peaks starts appearing becomes comparable by the end of 12 weeks to its pre-injection recording. Any such changes were not observed in the contralateral side of the subjects. In summary, botulinum toxin may selectively affect smaller motor units subsequent to the injection in muscles that exhibit spasticity.

Disclosures: S. Chandra: None. **B. Afsharipour:** None. **W.Z. Rymer:** None. **N.L. Suresh:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.19/N43

Topic: E.09. Motor Neurons and Muscle

Support: NSERC, grant #2018-06526

Title: Sex differences in fatigue of ankle plantar flexor muscles

Authors: *M. BILODEAU, A. DUGAS, F. DUQUETTE, C. GIROUX, K. GUERTIN;
Sch. of Rehabil. Sci., Univ. of Ottawa, Ottawa, ON, Canada

Abstract: AIM: The aim of this study was to investigate differences in exercise-induced fatigue features of the plantar flexor muscles between men and women. METHODS: Seven men and eight women, all healthy and aged between 20 and 28 years, participated in the study which was approved by the relevant local research ethics boards. Measures of maximal voluntary isometric contraction (MVIC) torque, isometric twitch and doublet electrically-elicited torque and voluntary activation were taken before and immediately after fatigue, as well as at 1, 2, 5 and 10 minutes of recovery. Fatigue was induced by having participants hold a 50% MVIC torque until exhaustion. Mixed-model ANOVAs and t-tests were used to test the effects of sex and fatigue on the variables of interest. RESULTS: Time to fatigue was not different between men (142.4 ± 27.2 s) and women (124.5 ± 26.5 s; $t = 1.29$, $p = 0.22$). Also, fatigue-related changes in MVIC torque, doublet torque, twitch torque and voluntary activation show similar trends between men and women (non-significant sex X fatigue interaction ($p > 0.05$)).

DISCUSSION/CONCLUSION: In contrast to other muscle groups, fatigue-related features of the plantar flexor muscles do not appear to be influenced by sex.

Disclosures: **M. Bilodeau:** None. **A. Dugas:** None. **F. Duquette:** None. **C. Giroux:** None. **K. Guertin:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.20/N44

Topic: E.09. Motor Neurons and Muscle

Support: NIH grant 1 R15 AG022908-01A2
NSF grant DBI 0552517

Title: Exercise to the rescue: Effects of aging and long-term exercise on structural plasticity of motor neurons and GDNF expression in spinal cord

Authors: *A. F. CINTRÓN-COLÓN, J. SPITSBERGEN;
Biol. Sci., Western Michigan Univ., Kalamazoo, MI

Abstract: As age progresses the neuromuscular system weakens. A possible reason for this weakening is the loss of connectivity between motor neuron and muscle. Physical exercise has been shown to be beneficial for both nervous and muscle tissue by contributing to neuroprotection and modulation of inflammation. A possible way to achieve neuroprotection is by the production and release of target-derived neurotrophic factors like glial cell line-derived neurotrophic factor (GDNF). GDNF is a potent survival/differentiation factor for somatic motor neurons. Results from previous studies have demonstrated a decline in skeletal muscle GDNF content with increased age and an increase in GDNF content with exercise. The goal of this study was to examine changes in motor neuron size that occur with age and exercise. Our hypothesis is that the size of motor neuron cell bodies will decline with age and that exercise will result in an increase in the size of motor neurons. Spinal tissues were taken from sedentary and exercised Sprague-Dawley rats between 4 weeks and 24 months of age. Sedentary groups consisted of 4-week-old, 14-week-old, 12-month-old, 18-month-old, and 24-month-old rats, while exercised groups consisted of 14-week-old rats that had access to running wheels for 10 weeks; and 12-month-old, 18-month-old, and 24-month-old rats that had access to running wheels for 24 weeks. In sedentary and exercised rats the lumbar region of the spinal cord was removed and processed for immunohistochemical analysis. Antibodies against choline acetyltransferase (ChAT) were used for detection of motor neurons, anti-GDNF was used for GDNF localization, and DAPI was used for nuclear staining. The results show that motor neuron cell body size increased from 4 weeks of age (958.4$\mu m^2 \pm$ 552μm^2) to 14 weeks (1070$\mu m^2 \pm$

505.8μm^2) and 6 months of age (2331.24μm^2±1607.4μm^2) and then decreased at 12 (969.21μm^2 ± 837.5μm^2), 18 (694.15μm^2 ± 542.2μm^2) and 24 months of age (395.5μm^2 ±101μm^2) in sedentary, aging rats. Exercise in age-matched groups caused an increase in motor neuron cell body size at 14 weeks (1180μm^2 ± 638.9μm^2), 12 months (1659μm^2 ± 1295.1μm^2) and 18 months of age (898.9μm^2 ± 697μm^2). Motor neurons in the spinal cord were found to contain GDNF co-localized at the cell body at all ages. These findings suggest that exercise plays a role in the structural plasticity of ChAT-positive cells. Understanding the role that neurotrophic factors play in regulating neural plasticity may help in identifying novel targets for pharmacological development.

Disclosures: A.F. Cintrón-Colón: None. **J. Spitsbergen:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.21/N45

Topic: E.09. Motor Neurons and Muscle

Title: Trans-cranial direct current stimulation changes fore paw dominance in mice

Authors: A. GORIN[1], O. ELWANY[1], B. ABDELRAHMAN[1], A. ELCHARFA[1], M. ARNOS[1], ***Z. AHMED**[2];
[1]Col. of Staten island, Staten Island, NY; [2]Col. of Staten Island, Staten Island, NY

Abstract: Handedness is a strong preference to use either the right or the left hand when performing skilled manual actions. In recent studies, MRI-based methodology has linked this ability to underlying functional and structural motor control. TDCS is a well-known clinical neuromodulation technique which has proved to be of growing interest for applications in neurorehabilitation. The aim of the current study is to examine the effect of applying a subthreshold transcranial direct current (TDCS) on one hemisphere on paw dominance in mice. Animals were placed in a pyrex cylinder and filmed when rearing to explore the environment. The instances in which the mouse uses each paw to touch the cylinder was assessed to determine paw dominance. Baseline testing of paw dominance showed that all animals used in the present study have the right paw dominance. Therefore, we stimulated the left hemisphere (sensorimotor cortex). The results showed that during cathodal-TDCS paw dominance was changed from right forepaw to left forepaw. Moreover, anodal-TDCS diminished paw dominance, the mice used the two forepaws equally. These findings indicate that TDCS could modulate forepaw dominance in mice. Since TDCS is known to modulate neuronal excitability and activity, the present results suggest that laterality in hemispheric excitability is the underlying mechanism of paw dominance and maybe handedness.

Disclosures: **Z. Ahmed:** None. **A. Gorin:** None. **O. Elwany:** None. **B. Abdelrahman:** None. **A. Elcharfa:** None. **M. Arnos:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.22/N46

Topic: E.09. Motor Neurons and Muscle

Support: R01AG055545
R56AG051501
R21NS106313
American Federation for Aging Research Scholarship for Research in the Biology of Aging

Title: Synaptic inputs terminating on alpha motor neurons undergo age-related changes in mice

Authors: *R. W. CASTRO[1], K. VANCE[2], G. VALDEZ[2];
[1]Neurosci., Brown Univ., Providence, RI; [2]Fralin Biomed. Res. Inst., Roanoke, VA

Abstract: The impact of aging on α-motor neurons and their connections in the spinal cord remains largely unexplored despite the central function these cells play in relaying voluntary motor commands. Previous work in our lab revealed that both cholinergic and glutamatergic excitatory synaptic inputs originating from local interneurons and sensory neurons degenerate in the ventral horn of the spinal cord of aged mice and rhesus monkeys. We have now examined the fate of glutamatergic synaptic inputs originating from the cortical and brain stem regions in the ventral horn of aged mice. We also examined the impact of aging on GABAergic and glycinergic inputs. Using light microscopy, we found that aging alters the distribution and number of these additional synaptic inputs and their postsynaptic sites throughout the ventral horn of the spinal cord, and specifically terminating on the soma of alpha-motor neurons. Further, we have determined that microglia become increasingly activated during aging, and may play a role in the age-related loss of α-motor neurons' synaptic connections. These ongoing analyses are necessary to uncover the initial sites in the spinal cord disrupted with advancing age, and that contribute to motor deficits.

Disclosures: **R.W. Castro:** None. **K. Vance:** None. **G. Valdez:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.23/O1

Topic: E.09. Motor Neurons and Muscle

Support: NIH R01 NS072342

Title: A high-density electrode array for mapping corticospinal recruitment of upper-limb muscles after stroke

Authors: *E. H. BEDOY[1], M. URBIN[1], G. F. WITTENBERG[2], G. SHARMA[4], D. J. WEBER[3]; [2]Neurol., [3]Bioengineering, [1]Univ. of Pittsburgh, Pittsburgh, PA; [4]Battelle Mem. Inst., Columbus, OH

Abstract: Nearly 800,000 Americans per year experience a stroke and more than half of survivors are left with disability due to muscle weakness (i.e., hemiparesis) in the arm and hand. Stroke-induced damage to the corticospinal system can result in abnormal muscle synergies, reducing the ability to recruit agonist muscles and increasing co-contraction of agonist and antagonist muscles. The severity of impairments in humans with stroke is also associated with higher thresholds to elicit motor-evoked potentials (MEPs) from transcranial magnetic stimulation (TMS) of primary motor cortex. Previous work has shown that MEPs in paretic muscles are lower in amplitude, delayed in latency and prolonged in duration after stroke, but the spatial distribution of MEPs across different muscles of a limb has not been well characterized. Understanding patterns of corticospinal recruitment may provide unique insights into physiology and function after stroke. Therefore, our group has developed a high-density electromyographic (HD-EMG) array to record MEPs from the entire forearm. The array consists of 150 surface disc electrodes embedded in fabric spanning the length and circumference of the dominant (neurologically-intact) or paretic (stroke) forearm of human subjects. Single-pulse TMS was delivered at multiple increments of resting threshold over the optimal scalp location for eliciting MEPs in the extensor digitorum communis (EDC) muscle. MEPs were recorded in resting forearm muscles, as well as during precision and power grasps at a fixed level of maximum voluntary contraction. Our results show that the spatial extent of corticospinal recruitment is modulated by stimulation intensity and muscle state. Differences in the pattern and timing of recruitment were also noted between intact controls and stroke. Our results show that the HD-EMG array allows high-resolution mapping of corticospinal recruitment across the upper limb. The ability to map recruitment may provide a diagnostic tool capable of evaluating impairments due to stroke and in response to rehabilitation. Our team is also exploring the HD-EMG array as an assistive technology that drives recruitment of weak muscles on an as-needed basis.

Disclosures: **E.H. Bedoy:** None. **M. Urbin:** None. **G.F. Wittenberg:** None. **G. Sharma:** None. **D.J. Weber:** F. Consulting Fees (e.g., advisory boards); Battelle Memorial Institute.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.24/O2

Topic: E.09. Motor Neurons and Muscle

Support: P01NS057228
R56NS099092
DGE-1444932

Title: The potassium-chloride cotransporter KCC2 is regulated by muscle innervation, but not exercise, in spinal motoneurons following peripheral axotomy

Authors: *E. T. AKHTER[1], S. SARIN[1], A. W. ENGLISH[3], F. J. ALVAREZ[2];
[2]Physiol., [1]Emory Univ., Atlanta, GA; [3]Dept Cell Biol., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Following various types of neuronal injury, the potassium-chloride cotransporter (KCC2) becomes dysregulated in multiple cell types. KCC2 is responsible for maintaining the low intracellular chloride levels typical of most adult neurons, and decreases in KCC2 can induce hyperexcitability. After peripheral nerve injuries (PNIs), loss of KCC2 in the dorsal horn contributes to neuropathic pain; after spinal cord injury, KCC2 decreases in motoneurons and induces spasticity. In both of these cases, exercise can attenuate KCC2 loss and ameliorate the symptoms. Additionally, exercise enhances motoneuron regeneration after PNI, and KCC2 is downregulated on these neurons axotomized during nerve injury. However, whether exercise may protect motoneurons from KCC2 loss after PNI is unknown. We tested here whether there is a relationship between exercise and motoneuron KCC2 levels following peripheral axotomy. To investigate this relationship we injured the sciatic nerve by performing complete nerve transections followed by repair in wild-type female mice. We then put the mice through an exercise paradigm that is known to enhance axon regeneration and sacrificed mice prior to any muscle reinnervation (14 days) and as differences in muscle reinnervation between groups (exercised vs non-exercised) were expected to become significant (28 and 35 days). We then compared the degree of KCC2 depletion on injured motoneuron cell bodies between groups and checked for correlations with successful muscle reinnervation by looking for successful neuromuscular junction (NMJ) reinnervation of the muscle as well as maximal muscle response using electromyography. We observed that exercise alone does not upregulate KCC2 in spinal motoneurons after PNI. Instead, KCC2 levels appear to be regulated by peripheral signals; more reinnervation in the periphery is correlated with higher KCC2 levels. Current experiments are blocking signaling at the NMJ using alpha bungarotoxin to determine whether signaling at the

muscle is responsible for maintenance of KCC2 protein in motoneuron somatic membranes. Our results illustrate that KCC2 regulation on axotomized motoneurons occurs via a different mechanism than previously established in other cell types or injury paradigms.

Disclosures: E.T. Akhter: None. **S. Sarin:** None. **A.W. English:** None. **F.J. Alvarez:** None.

Poster

585. Motor Neuron II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 585.25/O3

Topic: E.09. Motor Neurons and Muscle

Support: Graduate School for Biological Sciences Cologne
DFG funded RTG 1960 “Neural circuit analysis on the cellular and subcellular level”

Title: Myoinhibitory peptide is a co-transmitter in common inhibitor motor neurons and decreases slow muscle contraction

Authors: *S. LIESSEM[1], C. GUSCHLBAUER[1], D. KOWATSCHEW[2], S. L. HOOPER[3], S. DIPPEL[4], S. I. KORSCHING[2], A. BLANKE[1], R. PREDEL[1], A. BÜSCHGES[1];
[2]Inst. for Genet., [1]Univ. of Cologne, Cologne, Germany; [3]Ohio Univ., Athens, OH; [4]Dept. of Developmental Biol., Georg-August-University Goettingen, Goettingen, Germany

Abstract: Understanding how nervous systems generate motor behavior requires investigating both neural activity and muscle properties, inasmuch as it is the latter that transform neural activity into movement. Stick insect (*Carausius morosus*) walking is a very well-studied locomotory model system that has provided much information about how the basic walking pattern is produced and controlled, e.g., changes in speed and direction. Stick insect central and peripheral nervous systems are richly endowed with neuropeptides, but relatively little is known about the role these potential neuromodulatory substances play in stick insect behavior and in particular locomotion.
Transcriptomic and neuropeptidomic techniques have been used in prior work to define the neuropeptidome of the stick insect CNS. Here, we report on data obtained from MALDI-TOF single cell profiling of motor neurons to restrict this analysis to putative neuropeptide candidates involved in locomotion. Our analysis revealed the processing of myoinhibitory peptide (MIP) in dorsal unpaired median neurons (DUM) and common inhibitor motor neurons (CI). CIs have been long known to inhibit slow leg muscle fibers via the inhibitory transmitter GABA, and thereby contribute to the generation of fast movements. We then used immunocytochemistry to show that MIP is expressed in DUMs and CIs, and transported to, and released on, *extensor tibiae* muscle fibers. We confirmed the presence of the MIP-receptor in leg muscles by

transcriptomic analysis and are currently defining its localization with *in situ* hybridization. We also investigated the physiological effects of MIP on tibial extensor muscle contractions. MIP application decreased slow muscle fiber isometric force production and isotonic muscle shortening amplitude.
We have thus shown that stick insect common inhibitor neurons contain MIP, that the muscles the CIs innervate contain the MIP receptor, and that these muscles respond to MIP. Given that the CIs also modulate the muscles by GABA release, we conclude that insect CIs affect muscle fibers both via fast synaptic transmission and by neuromodulation. The common effects of GABA and MIP (slow muscle fiber inhibition in both cases) supports the belief that the CIs function to alter muscle temporal response properties, and in particular, to increase the ability of these muscles to produce fast motor patterns.
Supported by the Graduate School for Biological Sciences and the DFG funded RTG 1960 "Neural circuit analysis on the cellular and subcellular level".

Disclosures: **S. Liessem:** None. **C. Guschlbauer:** None. **D. Kowatschew:** None. **S. Dippel:** None. **S.L. Hooper:** None. **S.I. Korsching:** None. **A. Blanke:** None. **R. Predel:** None. **A. Büschges:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.01/O4

Topic: F.02. Behavioral Neuroendocrinology

Support: R01MH107886

Title: Trkb activation is required for 17beta-estradiol induced enhancement of hippocampal memory consolidation

Authors: *K. S. GROSS[1], R. ALF[1], T. R. POLZIN[2], K. M. FRICK[1];
[1]Psychology, Univ. of Wisconsin Milwaukee, Milwaukee, WI; [2]Psychology, Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: The potent estrogen 17β-estradiol (E_2) is known to enhance memory consolidation in object placement (OP) and object recognition (OR) tasks, however the molecular mechanisms underlying these effects are not fully understood. Brain derived neurotrophic factor (BDNF) is an important regulator of hippocampal memory and is also known to interact with E_2, however whether BDNF plays a mechanistic role in E_2-induced enhancement of memory consolidation remains unknown. Previously, we demonstrated that infusion of E_2 into the dorsal hippocampus (DH) leads to increases in BDNF and pro-BDNF proteins via epigenetic modification of *Bdnf* gene promoters. Here, we examined the role that BDNF signaling with its receptor TrkB may

play in the effects of E_2 on hippocampal memory consolidation. To determine whether TrkB activity is required for the memory enhancing effects of E_2, female C57BL/6 mice were ovariectomized and cannulated in the DH and dorsal third ventricle. Immediately following object training, mice were infused with vehicle or a non-memory impairing dose of ANA-12, a TrkB antagonist, into the DH and vehicle or E_2 into the dorsal third ventricle. Object placement or object recognition memory was then tested 24 or 48 hours later, respectively. We found that ANA-12 blocked the memory-enhancing effects of E_2, suggesting that BDNF/TrkB signaling is necessary for E_2-induced memory enhancement. Current work is examining the molecular mechanisms that couple E_2 to TrkB activation in the DH and the influence of TrkB on estradiol-mediated dendritic spine plasticity. In sum, this work will provide new insight into how E_2 exerts its effects on hippocampal memory consolidation.

Disclosures: K.S. Gross: None. **R. Alf:** None. **T.R. Polzin:** None. **K.M. Frick:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.02/O5

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH RF1AG041374

Title: Maintenance of hippocampal estrogen receptor α protein levels following continuous and previous estradiol treatment in aging ovariectomized rats

Authors: *N. E. BAUMGARTNER[1,2], S. M. MCQUILLEN[1,2], M. J. MAROTEAUX[3,1], D. D. HUTSON[3,1], J. M. DANIEL[1,2,3];
[1]Tulane Brain Inst., [2]Neurosci. Program, [3]Psychology Dept., Tulane Univ., New Orleans, LA

Abstract: Work from our lab has demonstrated that previous midlife estradiol treatment enhances memory and results in lasting increases in levels of estrogen receptor (ER) α in the hippocampus of aging ovariectomized rats months after hormone exposure has ended. We have recently shown that both ongoing and previous exposure to estradiol in midlife increases protein levels of ERα in the nuclear compartment of hippocampal cells. The goal of the current project is to determine how these protein levels are maintained following continuous or previous estradiol treatment. Previous work from our lab demonstrated that short-term exposure to estradiol in midlife decreases protein interactions between ERα and the ubiquitin ligase C-terminus of Hsc-70 interacting protein (CHIP), suggesting the sustained ERα protein levels are maintained via decreased degradation through the proteasome. However, it is unknown if continuous or previous exposure to estradiol in midlife also impacts transcription of *Esr1*, the gene that encodes for ERα. In the current project, middle-aged rats were ovariectomized and implanted with capsules

containing either estradiol or vehicle. Forty days later, all capsules were replaced. Rats initially receiving vehicle capsules received another vehicle capsule (ovariectomized controls), and rats initially receiving estradiol capsules received either another estradiol capsule (continuous estradiol) or a vehicle capsule (previous estradiol). One month later, hippocampi were dissected and processed for RNA extraction and RT-PCR with primers for *Esr1* and *Gapdh*. Results show no effect of hormone treatment on *Esr1* RNA levels in the hippocampus. These data support the idea that the elevated ERα protein levels in the hippocampus following continuous or previous estradiol exposure in midlife is maintained through decreased degradation of the protein, rather than through increased transcription of *Esr1*. Ongoing work is further investigating the impacts of hormone treatment on degradation of ERα in the hippocampus.

Disclosures: N.E. Baumgartner: None. **S.M. McQuillen:** None. **M.J. Maroteaux:** None. **D.D. Hutson:** None. **J.M. Daniel:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.03/O6

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC

Title: The interplay of the rapid activation of the G-protein coupled estrogen receptor and/or estrogen receptor beta and the oxytocin receptor on social recognition

Authors: *P. PALETTA[1], I. GREWAL[2], A. CLARKE[1], E. CHOLERIS[1];
[1]Psychology, [2]Biol. Sci., Univ. of Guelph, Guelph, ON, Canada

Abstract: Both estrogens and oxytocin (OT) can influence social recognition (SR). Knocking out the genes for the estrogen receptors, OT, or the OT receptor (OTR) impairs SR, whereas the administration of 17β-estradiol (E2) or the agonists for the estrogen receptors either systemically or intracranially can facilitate SR. An interplay between estrogens and OT in the mediation of SR has been suggested. A model for this interplay was developed that proposes that estrogens binding to their receptors in the paraventricular nucleus (PVN) of the hypothalamus, where most of the OT is produced in the brain, leads to the release of OT into the medial amygdala (MeA), an important region for SR as the olfactory information of individuals being encountered is sent to this region. The OT will then bind to the OTR in the MeA to facilitate SR. We have previously tested this model for estrogens' rapid mechanisms of action and found that E2 in the PVN rapidly facilitated SR and that this facilitation was blocked when a subeffective dose of an OTR antagonist (OTRA) was infused into the MeA, supporting estrogens' rapid mechanism interacting with OT to effect SR as the model describes. In the present study we investigated the

specific estrogen receptors mediating the rapid facilitation of SR by E2 in the PVN. We used agonists for the G-protein coupled estrogen receptor (GPER) and estrogen receptor beta (ERβ) since both estrogen receptors are highly expressed in the PVN. We found that the infusion of the GPER agonist G1, at 50, 100, and 200nM, or the ERβ agonist DPN at 100 and 150nM, were able to rapidly facilitate SR. The next step is to determine whether the same subeffective OTRA dose used in the E2 experiment, a dose that by itself does not block SR, infused into the MeA can prevent the SR facilitating effects of the GPER and ERβ agonists in the PVN. A rapid SR paradigm is used that takes advantage of the natural tendency of mice to prefer novelty, where in 2 sample phases 2 stimulus mice are presented to the experimental mouse followed by a test phase where one of the stimulus mice is replaced with a novel mouse. If the novel mouse is investigated more, it suggests that the other mouse if familiar and SR occurred. This paradigm occurs within 40 minutes to test the rapid effects of estrogens. If the OTRA blocks the facilitation of SR by the agonist, it would suggest that that estrogen receptor is mediating the interplay between estrogens and OT on SR.

Disclosures: P. Paletta: None. **I. Grewal:** None. **A. Clarke:** None. **E. Choleris:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.04/O7

Topic: F.02. Behavioral Neuroendocrinology

Support: Canadian Institutes of Health Research
Alzheimer's Association
Brain Canada

Title: Motherhood has short and long term effects on hippocampal neurogenesis, inflammation, and gene expression

Authors: *P. DUARTE-GUTERMAN[1], S. E. LIEBLICH[1], R. S. EID[1], D. A. SKANDALIS[2], M. IBRAHIM[1], L. A. M. GALEA[1];
[1]Djavad Mowafaghian Ctr. for Brain Health, Psychology, Univ. of British Columbia, Vancouver, BC, Canada; [2]Whitney Lab. for Marine Bioscience, Univ. of Florida, St. Augustine, FL

Abstract: Women are more likely to be diagnosed with Alzheimer’s disease (AD) and show greater AD neuropathology and cognitive decline than men. Pregnancy and motherhood (parity) have dramatic effects on physiology, including the endocrine system, and can modulate brain function in women and animal models in the short and in the long term. Increasing parity is associated with a greater risk of dementia, AD neuropathology, and an earlier age of AD onset. Work from our laboratory suggests that parity influences hippocampal neuroplasticity,

circulating immune markers, and cognition into middle-age in rats. The goals of this study were to determine how parity interacts with aging to influence levels of hippocampal inflammation and adult neurogenesis in female rats and to explore unknown mechanisms of parity through transcriptomics. Female rats were bred once (primiparous), twice (biparous), or not at all (nulliparous). Brain and plasma were collected at 30 days (7 months old; adults) and 240 days postpartum (13 months old; middle-aged). We measured adult neurogenesis through the expression of the immature marker doublecortin (DCX), neuroinflammation through a multiplex system of nine cytokines (IFN-γ, IL-1β, IL-4, IL-5, IL-6, IL-10, IL-13, CXCL1, and TNF-α), and global gene expression through RNA sequencing. In young adults, we found that motherhood decreased the number of DCX-expressing cells relative to nulliparous females. Hippocampal neurogenesis decreased with aging, but more so in nulliparous than parous females. We found that in the hippocampus, interleukin-6 (IL-6) increases in biparous females regardless of age, while plasma IL-6 decreases with age in nulliparous but not parous females. Levels of individual cytokines may result from covariation with other cytokines as well as responses to treatments. We used principal components analysis to group cytokines with similar expression patterns and then constructed classification trees based on these groups. Parity predicted levels of cytokines in the hippocampus, whereas age predicted levels of plasma cytokines. Our work suggests that motherhood has consequences on neurogenesis and neuroinflammation that persists into middle age and that peripheral immune changes do not reflect immune changes occurring in the brain of aging female rats. Finally, RNA sequencing results indicate that in young primiparous and biparous females there is a decrease in the expression of genes related to oxygen transport and metabolism. We are currently analysing middle aged brain samples for changes in gene expression. These data will aid in elucidating how reproductive experience influences brain aging.

Disclosures: P. Duarte-Guterman: None. **S.E. Lieblich:** None. **R.S. Eid:** None. **D.A. Skandalis:** None. **M. Ibrahim:** None. **L.A.M. Galea:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.05/O8

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant 2R15GM118304-02
NIH Grant R01MH107886

Title: Effects of hot flash induction and estrogen receptor beta activation on hippocampus-dependent memory consolidation in ovariectomized mice

Authors: *A. W. FLEISCHER, K. M. FRICK;
Dept. of Psychology, Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: The loss of cycling estrogens underlying the menopausal transition is often associated with problematic symptoms, such as hot flashes, mood disorders, and dementia. Additionally, these symptoms have the capacity to exacerbate one another. For example, disruption of sleep due to hot flashes can prevent proper memory consolidation and result in memory loss. Several of these symptoms have been attenuated via estrogen-based hormone therapies (HT). However, these HTs have been linked to health concerns, such as increased rates of several forms of cancer and heart disease, which have been associated with the activation of estrogen receptor isoform alpha (ERα), but not isoform beta (ERβ). Therefore, development of ERβ-selective treatments are crucial avenues to explore for attenuation of menopause-associated symptoms. Mouse models of hot flashes and learning and memory are found readily throughout the literature, though to our knowledge, no studies have been conducted specifically on the effects of hot flash induction on memory consolidation processes. Here, 10-week-old female C57BL/6 mice were bilaterally ovariectomized. After recovery, they were placed in a large white box with two identical objects placed near the corners and required to spend 30 sec exploring the objects. During testing, one of the objects was replaced with a novel object (object recognition, OR) or moved to a new location (object placement, OP). OR and OP testing occurred 24 or 4 hours later, respectively, time points at which we have shown memory to be intact for these tasks in ovariectomized mice following vehicle administration. To test whether an acute hot flash can disrupt memory consolidation, mice were injected immediately after training with vehicle, 17β-estradiol (E_2), or the ERβ agonist diarylpriopionitrile (DPN) intraperitoneally (IP), and then subsequently injected subcutaneously (SC) with vehicle or senktide, a tachykinin receptor type 3 agonist known to induce hot flash symptoms in humans and rodents. Rodents shed heat through tail skin vasodilation, so tail skin temperature changes from baseline were measured via FLIR camera as a proxy for hot flash-like symptoms. Preliminary data demonstrate that post-training IP injection of E_2 and DPN facilitate memory consolidation in these tasks, and that senktide induces hot flash-like tail vasodilation. Ongoing studies are examining the effects of E_2 and DPN on senktide-induced hot flashes, as well as the effects of hot flash induction and attenuation on memory consolidation.

Disclosures: K.M. Frick: None. **A.W. Fleischer:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.06/O9

Topic: F.02. Behavioral Neuroendocrinology

Support: RGPIN-2018-04301

Title: Quantifying rapid effects of 17β-estradiol on cell signaling pathways in the dorsal and ventral hippocampus

Authors: *T. PURI, P. A. S. SHEPPARD, S. E. LIEBLICH, L. A. M. GALEA;
Psychology, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: 17β-Estradiol (E2) can modulate memory consolidation in the hippocampus *in vivo* through the cell signaling cascades that activate in 5-30 minutes following E2 treatment in male and female mice, and rapidly enhances cell proliferation and long-term potentiation (LTP) in the dentate gyrus of female rats. E2 can have neuroprotective effects that are mediated through mitogen-activated protein kinase (MAPK) pathways, and MAPK cascades in the dorsal hippocampus are necessary for long-term spatial memory. However, E2 has dose-dependent effects on hippocampus-dependent learning, with low physiological levels of E2 enhancing and high levels of E2 impairing performance in spatial working memory and contextual fear conditioning in female rats. Repeated administration (3 days) of E2 has been shown to increase Akt signaling cascade activity in the hippocampus, but rapid effects remain unknown.
This experiment aims to determine whether changes in cell signaling cascades occur in a dose-dependent manner following E2 administration in ovariectomized female rats. We treated adult ovariectomized female rats with high E2 (10µg/0.1mL oil), low E2 (0.3µg/0.1mL oil), or vehicle (sesame oil), and dorsal and ventral hippocampi were extracted and flash frozen either 30 min or 24 hours following E2 administration. Dorsal and ventral hippocampal tissue was homogenized and subsequently analyzed for cell signaling markers using multi-array electro-chemiluminescent detection assays. Preliminary data show a significant interaction of dose and time since E2 administration in the levels of cell signaling proteins pAkt and p70S6K in the dorsal, but not ventral, hippocampus. Both pAkt and p70S6K show increased levels at 30 minutes (compared to 24 hours) following a high dose of E2. However, pAkt and p70S6K levels are higher at 24 hours than 30 minutes for low-level E2 and vehicle administration. These data show that Akt cell signaling is activated in a dose-dependent manner both rapidly and over longer timeframes. Given the ability of 17β-estradiol to rapidly improve memory consolidation, cell proliferation, and LTP, it is important to establish which cell signaling proteins may be activated in the short- and long-term after E2 exposure.

Disclosures: T. Puri: None. **P.A.S. Sheppard:** None. **S.E. Lieblich:** None. **L.A.M. Galea:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.07/O10

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant MH107886 to KMF
UWM Research Growth Initiative Award (101X334) to KMF
UWM Distinguished Dissertator Fellowship to JK

Title: Intrahippocampal infusion of a G-protein coupled estrogen receptor (GPER) agonist increases CA1 spine density and enhances memory consolidation in female mice

Authors: *J. C. SCHALK, J. KIM, W. A. KOSS, K. M. FRICK;
Psychology, Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: Little is known about the role of G-protein-coupled estrogen receptor (GPER) in hippocampal synaptic plasticity and memory consolidation. G-1 is a GPER agonist that mimics the memory-enhancing effects of 17β-estradiol (E2), a potent estrogen. However, the mechanisms through which G-1 enhances memory remain unclear. Here, we examined the effects of dorsal hippocampal infusion of G-1 on memory consolidation and CA1 dendritic spine density. In Experiment 1, ovariectomized mice received bilateral dorsal hippocampal infusion of G-1 (4 µg/hemisphere) or vehicle immediately after training in the object recognition and object placement tasks. Compared to vehicle, G-1 significantly increased the time spent with the novel or moved objects, indicating an enhancement of hippocampal-dependent object recognition and spatial memory. In Experiment 2, ovariectomized mice received bilateral dorsal hippocampal infusion of vehicle or G-1, and then brain tissue was collected 40 minutes later for Golgi staining and dendritic spine analysis. Compared to vehicle, G-1 significantly increased apical dendritic spine density on pyramidal neurons in the CA1 region of the hippocampus. Further analysis showed that G-1 specifically increased the number of mushroom spines, but not thin or stubby spines. These findings suggest that G-1 may enhance hippocampal-dependent memory by increasing mature apical dendritic spines in CA1.

Disclosures: J.C. Schalk: None. **J. Kim:** None. **W.A. Koss:** None. **K.M. Frick:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.08/O11

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC Grant #400212
NSERC Grant #401389

Title: 17β-estradiol rapidly induces activity-regulated cytoskeleton-associated protein (arc) expression

Authors: *Y. RIZWAN[1], J. LALONDE[2], E. CHOLERIS[3];
[1]Dept. of Psychology; Dept. of Mol. and Cell. Biol., [2]Dept. of Mol. and Cell. Biol., [3]Psychology, Univ. of Guelph, Guelph, ON, Canada

Abstract: Administration of estrogens to the mouse dorsal hippocampus produces rapid facilitation of learning and memory, as well as the growth of new dendritic spines in pyramidal neurons. Recently, we found that blocking protein synthesis with anisomycin but not gene transcription with actinomycin D can prevent these rapid estrogenic effects on cognition and structural plasticity of neurons. These results therefore suggest a central role for localized protein synthesis events in the rapid facilitation of learning and spinogenesis by estrogens; however, which specific transcripts may be regulated in this manner to act as intermediary effectors remain unknown. Here, we present efforts to answer this question.
Activity-Regulated Cytoskeleton-associated protein (Arc) is an immediate-early gene that has been implicated in many facets of neuroplasticity, including trafficking of AMPA receptors and morphogenesis of dendritic spines. Notably, *Arc* mRNA transcripts can be transported along dendrites where they will accumulate at the base of postsynaptic structures. There, *Arc* transcripts can then be rapidly translated upon synaptic activity to affect neuron biology. Because of these unique features, we hypothesized that Arc may play a central role in rapid estrogenic effects.
First, using mouse primary cortical neurons we present clear evidence for rapid induction of Arc in response to exogenous application of 17β-estradiol. Specifically, our results show Arc being expressed in a dose-dependent manner within 15 to 40 minutes of acute application of 17β-estradiol (50nM and 100nM). Second, we extended this finding by showing that *in-vivo* administration of 17β-estradiol (100nM) directly into the dorsal hippocampus of ovariectomized adult, female CD1 mice also induces Arc expression within 15 to 40 minutes. Finally, to directly investigate Arc's potential downstream role in 17β-estradiol's rapid facilitation of learning and memory, we used a collection of short-hairpin RNA constructs packaged into lentiviruses. Together, our results strongly support the role for Arc in the positive effects of estrogens on cognition and dendritic spine changes.
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Poster

586. Hormone Modulation of Behavior and Physiology III

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Program #/Poster #: 586.09/O12

Topic: F.02. Behavioral Neuroendocrinology

Support: NIA AG057947

NIDA DA038798
NSF IOS 13-18490
NIH P30 AG034464

Title: Impaired BDNF signaling disrupts modulation of cognition and behavior by estrogens in female rats

Authors: *A. V. PRAKAPENKA[1], M. M. CAMPANICO[2], R. ELMAN[3], A. BERLIN[4], N. RAMIREZ-ESTEVEZ[1], C. E. SORTWELL[5], T. J. COLLIER[5], K. STEECE-COLLIER[5], D. L. KOROL[1];
[1]Dept. of Biol., [2]Forensics Sci. and Natl. Security Inst., Syracuse Univ., Syracuse, NY; [3]Fayetteville-Manlius High Sch., Manlius, NY; [4]Rondout Valley High Sch., Accord, NY; [5]Dept. of Translational Sci. and Mol. Med., Michigan State Univ., Grand Rapids, MI

Abstract: 17β-estradiol (E2), the predominant estrogen in reproductive females, improves hippocampus-sensitive learning and memory yet impairs striatum-sensitive learning and memory. E2 also promotes the transcription and release of brain-derived neurotrophic factor (BDNF), known for its role in neural plasticity and cognition. The single nucleotide polymorphism in humans (SNP, rs6265) with a Val66Met substitution in the prodomain region of *BDNF* is thought to impair BDNF release. If BDNF signaling mediates the cognitive effects of E2 as reported, then modulation of learning and memory in female Met carriers will be blunted compared to the wildtype Val/Val variant. We tested the effects of E2 on hippocampal and striatal learning in a CRISPR/cas9 rat model of the human BDNF Val66Met gene variant (Val68Met in rats). Three weeks after ovariectomy, female homozygous Val or Met rats were treated with vehicle or E2-benzoate (EB, s.c.) 48 and 24 hrs prior to training on a hippocampus-sensitive place or a striatum-sensitive response learning task. In general, Met rats were impaired in learning compared to age-matched Val rats. Moreover, EB-treated Val rats exhibited improved place learning and impaired response learning compared to vehicle-treated Val rats as expected from previous work. EB in Met rats, however, failed to enhance or impair learning in either task, supporting a key role for BDNF release in modulation of learning by estrogens. Findings from a separate study using ovary-intact Val and Met rats showed that typical fluctuations in locomotor activity seen across the estrous cycle in Val rats were blunted in Met rats. Together, our findings suggest that dysfunctional BDNF signaling interferes with estrogen modulation of learning, memory, and other behaviors. Because menopause and its accompanying decline in circulating hormones are associated with increased risk for certain neurological disorders and diseases, ongoing work tests the interaction of age and E2 in these CRISPR rats on various behaviors. Elucidating the role of hormones, and ultimately downstream neural targets, on cognition across the adult lifespan using the Val68Met BDNF rat model could lead to the development of novel or individualized strategies to promote healthy aging in women.

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Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.10/O13

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant AG028084
State of Arizona
ADHS and the Arizona Alzheimer's Disease Core
NIH Diversity Supplement 3R01AG028084-09S1

Title: Let's talk about sex (hormones): Cognitive characterization and evaluation of gonadal hormone deprivation in a rat model of Alzheimer's disease

Authors: *H. L. BULEN[1,3], V. L. PEÑA[1,3], S. N. NORTHUP-SMITH[1,3], C. BARKER[1,3], V. E. WONER[1,3], A. V. PRAKAPENKA[4,3], S. ODDO[2,3], H. A. BIMONTE-NELSON[1,3];
[1]Psychology, [2]Sch. of Life Sci., Arizona State Univ., Tempe, AZ; [3]Arizona Alzheimer's Consortium, Tempe, AZ; [4]Biol., Syracuse Univ., Syracuse, NY

Abstract: As of 2019, the Alzheimer's Association estimates that in the United States alone, 5.8 million individuals are living with Alzheimer's disease (AD), with two thirds of those individuals women. As the population continues to age, it is increasingly imperative to make advancements in our understanding of AD progression and treatment, while additionally focusing on why women have an increased risk of developing the disease. Recently, the TgF344-AD transgenic rat model of AD expressing mutant human amyloid precursor protein (APP_{SW}) and presenilin 1 (PS1ΔE9) genes has been developed. This model exhibits amyloid β (Aβ) plaque-like pathology, tau-like pathology leading to neurofibrillary tangles, and neuronal loss. Although it has been less studied, the TgF344-AD rat also exhibits some behavioral impairment. The goal of this experiment was to delineate the role of hormone deprivation in the TgF344-AD model to elucidate whether gonadectomy (Gdx) impacts behavior- and AD- like pathology. Eight treatment groups were included in this study: male wild type (WT) Sham (n=10), female WT Sham (n=10), male WT Gdx (n=10), female WT Gdx (n=10), male transgenic (TG) Sham (n=10), female TG Sham (n=10), male TG Gdx (n=10), and female TG Gdx (n=10). All animals underwent a behavioral battery consisting of the Water Radial Arm Maze (WRAM) to assess spatial working and reference memory, the Morris Water Maze (MWM) to assess spatial reference memory, the Open Field Task (OFT) to assess locomotor activity and anxiolytic behavior, and the Visible Platform Task to evaluate procedural components of solving a water-escape task. For the WRAM, both sexes with the TG genotype were impaired during learning compared to their respective WT counterparts. Additionally, TG Gdx males demonstrated impaired working memory compared to WT rats during the WRAM learning phase. During

memory retention, both sexes showed improvements in handling an increasing working memory load with Gdx. TG rats also showed reference memory detriments on the MWM compared to WT rats. These data indicate that TG animals of both sexes exhibit learning impairments compared to their respective WT counterparts, and that hormone loss can impact behavioral outcomes. Further behavioral analyses and pathology assessments are ongoing in these behaviorally-tested animals to allow further characterization of the relation between pathology and behavioral outcomes. This work will allow a better understanding of the interactions between sex, hormones, and AD-associated behavior and pathology.

Disclosures: H.L. Bulen: None. **V.L. Peña:** None. **S.N. Northup-Smith:** None. **C. Barker:** None. **V.E. Woner:** None. **A.V. Prakapenka:** None. **S. Oddo:** None. **H.A. Bimonte-Nelson:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.11/O14

Topic: F.02. Behavioral Neuroendocrinology

Support: CIHR MOP102568

Title: Sex and subregion differences in the rapid effects of 17β-estradiol on cell signaling cascades in the dentate gyrus of male and female rats

Authors: *P. A. S. SHEPPARD[1], T. PURI[2], L. A. M. GALEA[1];
[1]Djavad Mowafaghian Ctr. for Brain Health, Psychology, [2]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Rapid effects of estrogens within the hippocampus of rodents have been found to be dependent upon cell signaling cascades (Sheppard et al., 2018; Frick et al., 2018). Whether these pathways are rapidly activated within the dentate gyrus by estrogens has yet to be determined. Exogenous 17β-estradiol (E2) or estradiol benzoate increases cell proliferation in the dentate gyrus of ovariectomized (OVX) rats 2 or 4h (Tanapat et al., 1999; Ormerod et al., 2003; Barha et al., 2009; Mazzucco et al., 2006), but not 48h (Ormerod et al., 2003), following systemic administration. Cell proliferation within the dentate gyrus is also increased 30min following systemic E2 administration in ovariectomized (OVX) female rats, suggesting that rapid, likely non-genomic mechanisms may underlie these effects. Whether these E2-mediated increases also occur in males remains to be determined. Importantly, sex differences exist in the rapid activation of hippocampal cell signaling cascades in response to estrogens (Koss et al., 2018). Here, gonadally intact female rats (estrous phase determined *via* lavage) and OVX female rats were given a subcutaneous injection of either 0.3 (low E2) or 10μg (high E2) of E2 (in 0.1mL

oil) or vehicle (oil); whereas gonadally intact male rats were given 0.525 (low E2) or 17.5µg (high E2) of E2 (in 0.175mL oil) or vehicle – 75% more than females due to larger size. Thirty minutes later, rats were euthanized, and their brains were flash frozen for protein analyses. Using a multiplex electrochemiluminescent reader, we measured levels of phosphorylated extracellular signal-regulated protein kinase (ERK), c-Jun N-terminal kinase (JNK), p38, Akt, glycogen synthase kinase 3 beta (GSK-3β), and ribosomal protein S6 kinase (p70S6K) in the dentate gyrus. OVX females have increased ERK and JNK activation in the ventral DG when compared to males. Phospho-p38 is increased in the ventral DG in males given low E2. Males also show a trend towards an increase in pJNK in the dorsal DG, whereas OVX females show a trend towards an increase in pERK in the same region. ERK, JNK, and p38 analyses are ongoing in intact females, as are analyses of Akt, GSK-3β, and p70S6K in all animals. We are also examining rapid effects of these treatments on cell proliferation in the DG of intact males and females, as these have yet to be explored, with the aim to determine the necessity of these cascades to rapid effects of E2 on cell proliferation.

Disclosures: P.A.S. Sheppard: None. **T. Puri:** None. **L.A.M. Galea:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.12/O15

Topic: F.02. Behavioral Neuroendocrinology

Support: CIHR Grant

Title: A sex-specific role of the basolateral amygdala in fear-based cognitive bias in adult rats

Authors: *T. E. HODGES, L. A. M. GALEA;
Djavad Mowafaghian Ctr. from Brain Health, Psychology, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Negative cognitive bias, an increased perception of neutral situations or objects as negative, is a cognitive symptom of depression and has been found to predict the onset of future depressive episodes. However, the underlying neural mechanisms of cognitive bias have seldom been investigated. Here, adult male and female Sprague-Dawley rats underwent a fear-based cognitive bias task and brains were collected after the task for analysis. Rats were trained for 15 days to distinguish between two situations: one foot-shock-paired situation and a situation paired with no foot-shock. Two days after training (day 17), rats were tested on optimistic (low freezing, positive cognitive bias) or pessimistic (high freezing, negative cognitive bias) behaviours in response to an ambiguous situation. Females displayed less freezing in response to the ambiguous situation compared to their behaviour in the foot-shock-paired situation ($p=0.045$)

and compared to males in the ambiguous situation ($p<0.001$). Males treated the ambiguous situation like the foot-shock-paired situation (a negative cognitive bias). In response to the ambiguous situation, females had greater activation of the basolateral amygdala (as measured by high Fos immunoreactive cell counts) than did males ($p=0.009$). Further, time spent freezing in the ambiguous situation and neural activity in the basolateral amygdala were positively correlated in females ($r=0.812$) and negatively correlated in males ($r=-0.692$). Neural activation was also measured in the prefrontal cortex and hippocampus. Moreover, the impact of hippocampal newborn neurons on cognitive bias was examined. Our data suggest a more positive cognitive bias in females than in males in response to a fear-based cognitive bias task, and a sex-specific role of the basolateral amygdala in these responses.

Disclosures: T.E. Hodges: None. **L.A.M. Galea:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.13/O16

Topic: F.03. Neuroendocrine Processes

Support: MIUR Progetto Eccellenza
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Fondos Feder
Instituto de Salud Carlos III, Madrid, Spain

Title: Sex differences in the brain expression of steroidogenic molecules under basal conditions and after gonadectomy

Authors: *R. C. MELCANGI[1], S. DIVICCARO[1], L. M. GARCIA-SEGURA[2], S. GIATTI[1]; [1]Pharmacol. and Biomolecular Sci., Univ. degli Studi di Milano, Milano, Italy; [2]Inst. Cajal-CSIC, Madrid, Spain

Abstract: The brain is a steroidogenic tissue. It expresses key molecules involved in the synthesis and metabolism of neuroactive steroids, such as steroidogenic acute regulatory protein (StAR), translocator protein 18kDa (TSPO), cytochrome P450 cholesterol side-chain cleavage enzyme (P450scc), 3β-hydroxysteroid dehydrogenases (3β-HSD), 5α-reductases (5α-R) and 3α-hydroxysteroid oxidoreductases (3α-HSOR). Previous studies have shown that the levels of brain steroids are different in male and female rats under basal conditions and after gonadectomy (Caruso et al., *J Neuroendocrinol*. 2010, 22: 1137-47; Caruso et al., *Psychoneuroendocrinology* 2013, 38: 2278-90). In the present study we have assessed gene expression of key

neurosteroidogenic molecules in the cerebral cortex and cerebellum of gonadally intact and gonadectomized adult male and female rats. In the cerebellum, the basal mRNA levels of StAR and 3α-HSOR were significantly higher in females (at the proestrus day) than in males. On the contrary the mRNA levels of TSPO and 5α-R were significantly higher in males. In the cerebral cortex, all neurosteroidogenic molecules analyzed showed similar mRNA levels in males and females. Four months of gonadectomy increased the expression of 5α-R in the cerebral cortex of both sexes. In addition, ovariectomy decreased the expression of 3β-HSD and increased that of P450scc and TSPO in the cerebral cortex. Furthermore, ovariectomy increased the expression of StAR and decreased that of 3α-HSOR in the cerebellum but not in the cerebral cortex. Similar regional differences were observed for the effect of castration on the mRNA levels of TSPO and 5α-R in males. These findings indicate that the expression of steroidogenic molecules in the adult rat brain is sexually dimorphic and presents regional specificity, both under basal conditions and after gonadectomy. Thus, local steroidogenesis may contribute to the reported sex and regional differences in the levels of brain neuroactive steroids (Caruso et al., *J Neuroendocrinol*. 2010, 22: 1137-47; Caruso et al., *Psychoneuroendocrinology* 2013, 38: 2278-90) and may be involved in the generation of sex differences in the adult brain function.

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Poster

586. Hormone Modulation of Behavior and Physiology III

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Program #/Poster #: 586.14/O17

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant AG028084
State of Arizona
ADHS and the Arizona Alzheimer's Disease Core
NIH Diversity Supplement 3R01AG028084-09S1

Title: An assessment of the transition to menopause in the rat in the TgF344-AD model of Alzheimer's disease

Authors: *V. L. PEÑA[1,3], S. N. NORTHUP-SMITH[1,3], V. E. WONER[1,3], H. L. BULEN[1,3], C. A. DYER[4], L. P. MAYER[4], S. ODDO[2,3], H. A. BIMONTE-NELSON[1,3];
[1]Psychology, [2]Sch. of Life Sci., Arizona State Univ., Tempe, AZ; [3]Arizona Alzheimer's Consortium, Tempe, AZ; [4]Senestech, Inc., Flagstaff, AZ

Abstract: In the United States, Alzheimer's disease (AD) is the sixth leading cause of death with over 5.8 million Americans currently diagnosed; of those diagnosed, roughly two-thirds are

women. One possible factor is that women undergo a transition to reproductive senescence, known as menopause, which involves the dysregulation of ovarian hormones as ovarian follicle reserves become deplete. Previous preclinical assessments of menopause and AD have been primarily limited to evaluations of surgical menopause, usually via ovariectomy (the surgical removal of the ovaries). The current project utilized 4-vinylcyclohexene diepoxide (VCD) to model follicular depletion and transitional menopause in the ovary-intact TgF344-AD transgenic rat model of AD expressing two human genes: human amyloid precursor protein (APP_{SW}) and presenilin 1 (PS1ΔE9). This model displays Aβ plaque-like and neurofibrillary tangle-like pathology, neuronal loss, as well as some less-characterized behavioral impairments. The overall goal of this experiment was to investigate the relationship between transitional menopause, behavior, and AD-like pathology. Young adult female rats received either Sham or VCD injections, resulting in four experimental groups: wild type (WT) Sham (n=10), WT VCD (n=10), transgenic (TG) Sham (n=10), and TG VCD (n=10). After the completion of injections, rats underwent a behavioral battery that included the Water Radial Arm Maze (WRAM) to assess spatial working and reference memory, the Morris Water Maze (MWM) to assess spatial reference memory, the Open Field Task to assess locomotor activity and anxiety-like behavior, as well as the Visible Platform control task. Results indicated that TG rats were impaired compared to WT rats during learning on the WRAM. Menopause induction had a negative cognitive impact on the WT rats, but not the TG rats, for WRAM performance. TG rats were also impaired compared to WT rats on the MWM. Overall, initial data analyses suggest that the TG animals are impaired while learning a complex working and reference memory task in the TgF344-AD model, and that whether transitional menopause influences these outcomes might depend on TG status. Further analysis of open field data, AD-like pathology, ovarian histology, and hormone levels are underway to better understand the relationships between transitional menopause status, behavioral outcomes, and AD-like pathology.

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Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.15/O18

Topic: F.02. Behavioral Neuroendocrinology

Support: SAGA-17-419092

Title: APOE genotype, sex, and 17beta-estradiol influence memory and the hippocampus in a mouse model of Alzheimer's disease

Authors: *L. R. TAXIER[1], S. M. PHILIPPI[2], J. M. YORK[3], M. LADU[4], K. M. FRICK[1]; [1]Psychology, Univ. of Wisconsin-Milwaukee, Milwaukee, WI; [2]Univ. of Wisconsin Milwaukee, Milwaukee, WI; [3]Dept. of Anat. and Cell Biol., Univ. of Illinois at Chicago Dept. of Anat. and Cell Biol., Chicago, IL; [4]Anat. and Cell Biol., Univ. of Illinois, Chicago, Chicago, IL

Abstract: Loss of circulating estrogens at menopause is correlated with increased risk of Alzheimer's disease (AD) in women relative to men. Women carriers of the *APOE4* genotype, which is the leading genetic risk factor for late-onset AD, are more likely than women of the *APOE2* or *APOE3* genotypes, and men of any *APOE* genotype to develop AD. Moreover, interactions among *APOE* genotype, sex, and 17β-estradiol (E_2) are not well characterized. Gonadally-intact male and female mice expressing 5 familial AD mutations (5xFAD-Tg) and human *APOE3* (E3FAD) or *APOE4* (E4FAD) were trained on object recognition (OR) and object placement (OP) tasks to test object recognition and spatial memory formation. Two weeks after testing, mice were trained with novel objects, and brains were removed and hemisected 5 minutes later. The dorsal hippocampus (DH) was dissected from one hemisphere for Western blot analysis, and the other hemisphere taken for dendritic spine analyses. To determine whether E_2 mediates memory consolidation in EFAD females, ovariectomized E3FADs and E4FADs were trained in the OR and OP tasks, received an immediate post-training infusion of E_2 into the DH, and memory was tested 4 or 24 hours later. Male E3FAD mice exhibited intact OR and OP memory, whereas E3FAD females and E4FADs of either sex did not, suggesting preserved memory function in E3FAD males relative to females, and impaired memory in E4FAD mice of both sexes. E_2 enhanced OR and OP memory in E3FAD, but not E4FAD, females. Data indicate that levels of PSD95 were reduced in E4FADs compared to E3FADs, and levels of synaptophysin were lower in E4FAD females than every other group. ERα levels were lower in E3FADs relative to E4FADs, and in E3FAD males compared to E3FAD females. Levels of astrocytic and microglial proteins were increased in female EFADs compared to male EFADs, with highest levels in E4FAD females. Spine analysis is ongoing. These data suggest that *APOE* genotype and sex influence memory formation and the ability of E_2 to enhance memory consolidation in the EFAD model, and that alterations in synaptic proteins, glial proteins, and ERα may play a role. The results also suggest sex differences among *APOE3* carriers that could provide insights into neurobiological mechanisms underlying sex differences in AD risk.

Disclosures: L.R. Taxier: None. **S.M. Philippi:** None. **J.M. York:** None. **M. LaDu:** None. **K.M. Frick:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.16/O19

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant AG028084
State of Arizona
ADHS and the Arizona Alzheimer's Disease Core
NIH Grant 1F31AG056110-01A1

Title: The cognitive effects of the highly selective progestin segesterone acetate in a rat model of surgical menopause

Authors: *V. E. WONER[1,2], S. V. KOEBELE[1,2], S. N. NORTHUP-SMITH[1,2], M. N. WILLEMAN[1,2,3], C. BARKER[1,2], A. SCHATZKI-LUMPKIN[1,2], M. VALENZUELA SANCHEZ[1,2], H. A. BIMONTE-NELSON[1,2];
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Abstract: Progestogens, including natural progesterone and progestins (synthetic hormones that mimic some effects of endogenous progesterone) are prescribed for a myriad of health reasons to women across their reproductive and menopausal years. Administration of several different progestogens has been shown to be detrimental to cognition. Parent molecules from which progestins are derived are known to yield biological activities and affinities beyond the progesterone receptor (PR), and could modulate cognitive outcomes. These findings, along with research demonstrating the role of some progestogens with strong affinities for the PR in neurogenesis and neuroprotection, suggest that a 'purely-progestational' molecule that maximizes PR affinity and minimizes affinities to other receptors may be cognitively beneficial. We evaluated the cognitive effects of segesterone acetate (registered trade name: Nestorone™; ST-1435), a 19-norprogesterone derivative with a strong PR affinity and no androgenic or estrogenic receptor affinity, in a rat model of surgical menopause. Middle aged female Fischer-344 rats were given Sham surgery or Ovariectomy (Ovx) followed by daily administration of either medroxyprogesterone acetate (MPA; previously shown by our laboratory to induce cognitive deficits), ST-1435, given at a low or high dose, or Vehicle (administered to the Sham group and one Ovx group). Rats were tested on a behavioral battery involving spatial working and reference memory, including the Water-Radial Arm Maze (WRAM), Morris Maze (MM), Visible Platform control task, and the Open Field Test to measure locomotor activity and anxiety-like behaviors. WRAM results indicated that Ovx rats given the low dose of ST-1435 demonstrated impaired spatial working memory compared to Ovx rats given vehicle, and Ovx rats treated with the high dose of ST-1435 exhibited memory retention deficits. We also found memory retention impairments for MPA-treated Ovx rats on the WRAM, replicating our previous findings. Additionally, Ovx rats given MPA or the high dose ST-1435 were impaired relative to Ovx rats given vehicle on the MM. The cognitive effects and underlying neurobiological mechanisms of ST-1435 merit further study, as the memory deficits with long term administration at both low and high doses reported here are in contrast with other literature suggesting neuroprotective effects of ST-1435. Thus, we seek to characterize the relationship between the biological activity of ST-1435 and subsequent behavioral outcomes in future studies in order to identify a progestin that promotes positive health outcomes for women across the lifespan.

Disclosures: **V.E. Woner:** None. **S.V. Koebele:** None. **S.N. Northup-Smith:** None. **M.N. Willeman:** None. **C. Barker:** None. **A. Schatzki-Lumpkin:** None. **M. Valenzuela Sanchez:** None. **H.A. Bimonte-Nelson:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.17/O20

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant AG028084
State of Arizona
ADHS and the Arizona Alzheimer's Disease Core
NIH Grant 1F31AG056110-01A1

Title: Investigating long-term cognitive effects of variations in gynecological surgery during adulthood in a rat model

Authors: *S. V. KOEBELE[1,3], V. E. WONER[1,3], S. N. NORTHUP-SMITH[1,3], M. N. WILLEMAN[1,3,4], I. M. STROUSE[1,3], H. L. BULEN[1,3], A. R. SCHRIER[1,3], D. F. DENARDO[2], L. P. MAYER[5], C. A. DYER[5], H. A. BIMONTE-NELSON[1,3];
[1]Psychology, [2]Sch. of Life Sci., Arizona State Univ., Tempe, AZ; [3]Arizona Alzheimer's Consortium, Phoenix, AZ; [4]The Translational Genomics Res. Inst., Phoenix, AZ; [5]Senestech Inc., Flagstaff, AZ

Abstract: It is currently estimated that by age 60, about a third of US women will have experienced hysterectomy, or the surgical removal of the uterus. This surgery is often performed in adulthood, prior to the final menstrual period. Although some women undergo a complete ovariohysterectomy in adulthood, the ovaries are retained in about half of hysterectomy cases to avoid premature or abrupt surgical menopause. Research has suggested that hysterectomy, with and without ovarian conservation, can increase the relative risk of developing dementia compared to age-matched reproductive-tract-intact women. This association has piqued interest into how the non-pregnant uterus, which is typically considered to be an endocrine target but otherwise a dormant organ, may influence non-reproductive functions including cognitive processes. Our laboratory recently reported that hysterectomy with ovarian conservation resulted in detrimental effects on spatial working memory in adult Fischer-344-CDF rats six weeks after surgery. The current study aimed to extend these findings and investigate the longitudinal cognitive effects of hysterectomy in adulthood in order to elucidate whether the cognitive effects observed six weeks post-surgery were transient and reversed with time or the observed cognitive changes were the beginning of a long-term, more global cognitive impairment. Adult female rats received either sham, ovariectomy, hysterectomy, or ovariectomy-hysterectomy surgeries. Rats

were then tested on a battery of cognitive tasks evaluating spatial working and reference memory either six weeks, seven months, or twelve months after surgery. Preliminary results indicate that the working memory impairment observed in hysterectomy rats six weeks after surgery persisted in both the middle-aged and aged time points. These behavioral findings will be discussed in the context of serum hormone levels and ovarian follicle profiles for each time point. Understanding the cognitive effects of variations in gynecological surgery is a critical avenue of research to explore with the goal of enhancing quality of life and women's health throughout aging.

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Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.18/O21

Topic: F.03. Neuroendocrine Processes

Support: MIUR Progetto Eccellenza
Post-Finasteride Foundation

Title: Altered methylation pattern of the SRD5A2 gene in cerebrospinal fluid of post-finasteride patients

Authors: ***S. DIVICCARO**[1], L. CASARINI[2], M. MARINO[2], D. SANTI[2], S. SPERDUTI[2], S. GIATTI[1], M. GRIMOLDI[3], D. CARUSO[1], G. CAVALETTI[4], M. SIMONI[2], R. C. MELCANGI[1];
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Abstract: Finasteride is an inhibitor of 5alpha-reductase type 1 and 2 enzymes, encoded by the *SRD5A1* and *SRD5A2* gene, respectively. This enzyme converts neuroactive steroids, such as testosterone and progesterone into dihydrotestosterone and dihydroprogesterone respectively (Melcangi R.C. et al., *Cellular and Molecular Life Sciences* 2008, 65:777-797). Post-finasteride syndrome (PFS) occurs in patients with androgenic alopecia after suspension of the treatment with finasteride, leading to a large variety of persistent side effects, including impairment of sexual behavior, depression, reduction in self-confidence, decreased initiative and difficulty in concentration, forgetfulness or loss of short-term memory, irritability, suicidal thoughts, anxiety, panic attack, sleep problems, muscular stiffness and cramps, tremors, chronic fatigue, joint pain

and muscular ache (Traish AM et al., *Reviews in Endocrine and Metabolic Disorders* 2015, 16:177-198; Giatti S. et al., *Endocrine* 2018, 61: 180-193). Despite the severity of the clinical picture, the mechanism underlying the PFS symptoms onset and persistence is still unclear. We have here studied whether epigenetic modifications may occur in PFS patients. In particular, the methylation pattern of *SRD5A1* and *SRD5A2* promoters was analysed in blood and cerebrospinal fluid (CSF) of 16 PFS patients recruited through the Italian network of finasteride side effects and in 20 blood and 13 CSF samples of age-matched healthy men. Data obtained indicate that the *SRD5A2* promoter was more frequently methylated in CSF of PFS patients compared to controls (56.3 *versus* 7.7%). No promoter methylation was detected in blood samples in both groups. No methylation occurred in the *SRD5A1* promoter of both groups. In conclusion, we demonstrated, for the first time, a tissue-specific methylation pattern of *SRD5A2* promoter in PFS patients. Animal models might be useful to elucidate the link between the use of finasteride, epigenetic changes, neuroactive steroid levels and behavioural disturbances described previously in PFS patients.

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Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.19/O22

Topic: F.03. Neuroendocrine Processes

Support: Miur progetto di Eccellenza
Intramural Grant Line-B from University of Milan

Title: Sex dimorphism of pregnenolone synthesis in the rat spinal cord of a multiple sclerosis experimental model

Authors: *S. GIATTI[1], R. RIGOLIO[2], S. DIVICCARO[1], D. CARUSO[1], G. CAVALETTI[2], R. C. MELCANGI[1];
[1]Dept. of Pharmacol. and Biomolecular Sci., Univ. degli Studi di Milano, Milano, Italy; [2]Surgery and Translational Med., Univ. of Milano-Bicocca, Monza, Italy

Abstract: The incidence of multiple sclerosis (MS) is higher in females than in males (ratio of 2:1). The course of the disease is more benign in women than in men, that develop a more severe pathology (Darlington C., Curr Opin Investig Drugs, 2002, 3:911-14). Neuroactive steroids (NA) are important physiological regulators of the nervous functions and their levels were altered in MS patients as well as in experimental models (Caruso D. et al., J of Neurochem 2014, 130:591-

97; Giatti S. et al., J Neuroimmune Pharmacol 2013 8:238-50). However, whether the synthesis of NA in the nervous system (i.e., neurosteroidogenesis) is affected by the pathology and differently in the two sexes has been poorly investigated. To this aim, using a common MS paradigm, the experimental autoimmune encephalomyelitis (EAE) Dark Agouti rat model, the levels of the first NA produced from cholesterol (i.e., pregnenolone, PREG) were evaluated at acute (i.e., 14 days post EAE induction, DPI), and chronic phase (i.e., 40 DPI), in the spinal cord of male and female (i.e., at diestrous day) animals. We reported that male EAE vs control animals, showed a decrease of PREG levels at acute and chronic phase, while in female EAE animals the levels were decreased only at chronic phase. In agreement, the gene expression of CYP11A1 (i.e., the gene coding the enzyme P450 side chain cleavage responsible for the synthesis of PREG from cholesterol) was decreased at 14 and 40 DPI in males, and only at 40 DPI in females. Decreased PREG levels in males, at least at 40DPI, were also associated with decreased levels of its precursor (i.e., the free cholesterol) in the spinal cord. The effect on the free cholesterol levels was a consequence of a reduction in cholesterol synthesis, since the gene expression of the rate liming step in cholesterol production (i.e., HMG CoA-R) was significantly decreased, as well as to an increase in its metabolism. Indeed, the levels of a cholesterol metabolite, such as the 25OH-cholesterol, were significantly increased at 40DPI. In conclusion, PREG levels present in spinal cord decreased in male at both phases while in female only at the chronic phase. In both sexes, this decrease was associated with an impairment of CYP11A1. Interestingly, altered levels of free cholesterol, possibly due to a decrease in its synthesis and an increase its metabolism, were observed in the male spinal cord at chronic phase.

Disclosures: S. Giatti: None. **R. Rigolio:** None. **S. Diviccaro:** None. **D. Caruso:** None. **G. Cavaletti:** None. **R.C. Melcangi:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.20/O23

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC Grant BGPIN 2016-06653

Title: The effects of ovarian hormones on the nuclear progesterone receptor in the female rat hippocampus

Authors: *C. GAGNE, S. PATEL, A. GHEZZO, W. G. BRAKE;
Concordia Univ., Montreal, QC, Canada

Abstract: Estrogens and progesterone are implicated in a wide array of cognition and behaviors, including learning and memory. Classically thought to act exclusively on nuclear receptors, it is

now evident that both hormones act on membrane-bound receptors in the brain as well. While the distribution of estrogen receptors (ERs) across brain areas is relatively well characterized, less is known about the distribution of both nuclear and membrane-bound progesterone receptors (PRs). Furthermore, it is not known whether fluctuating levels of these ovarian hormones influence the density of PRs. This research investigated the effect of 17β-estradiol (E2) and progesterone (P) on the percent volume of nuclear PRs via epifluorescent microscopy. Here, 18 OVX Sprague-Dawley female rats were assigned to one of three hormonal conditions: low E2, high E2, and high E2 + P. While nuclear PR immunoreactivity was found throughout the hippocampus, there appears to be no effect of hormonal manipulation. Western blot analysis indicates that the antibody used may be detecting a novel isoform of the rat nuclear PR migrating at a similar molecular weight to those observed in humans.

Disclosures: C. Gagne: None. **S. Patel:** None. **A. Ghezzo:** None. **W.G. Brake:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.21/O24

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC Grant BGPIN 2016-06653

Title: The effects of ovarian hormones on the membrane-bound progesterone receptor β in the female rat hippocampus

Authors: *S. PATEL, C. GAGNE, A. LESTAGE, W. G. BRAKE;
Psychology, Concordia Univ., Montreal, QC, Canada

Abstract: Ovarian hormones play a widespread role in female brain and cognition beyond reproductive functions. For example, estrogens play a role in memory system bias in female rodents and women. However, less is known about progesterone (P) which also has been implicated in the bias to use either place or response memory. Two subclasses of progesterone receptors (PR) have been identified: membrane-bound PR (mPR) and nuclear PR (nPR). The recent discovery of mPRs in the female mouse brain provides a potential rapid, nongenomic mechanism in which progesterone may influence nerve cell function. The localization of these novel mPR subtypes in the female rat brain remains unexplored. Thus, the purpose of this study was to determine if mPRβ, the most abundant of these receptors, is localized to the hippocampus, and if its expression is regulated by ovarian hormones. Eighteen ovariectomized, female rats received either high 17β-estradiol (E2) + P, high E2 alone, or low E2 alone. The mPRβ immunoreactivity volume was calculated based on the proportion of receptor volume from epifluorencent images to total volume of a 3D images. High E2 increased the density mPRβ

immunoreactivity relative to low E2 alone. On the other hand, it appears that P down regulates these receptors as the high E2+ P group had low mPRβ immunoreactivity relative to the high E2 alone. These findings provide a potential mechanism for the rapid effects of P on memory bias.

Disclosures: S. Patel: None. **C. Gagne:** None. **A. Lestage:** None. **W.G. Brake:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.22/O25

Topic: F.02. Behavioral Neuroendocrinology

Support: Grants-in-Aid for Scientific Research 17H06096 from MEXT, Japan
Grants-in-Aid for Scientific Research 24657082 from MEXT, Japan

Title: Training-induced neurosteroids enhance remote spatial memory in mice

Authors: *K. SHIMIZU[1], K. MAEHATA[1], T. IKENO[1], Q. WANG[2], T. TAKAO[2], Y. FUKADA[1];
[1]Dept. Biol. Sciences, The Univ. of Tokyo, Tokyo, Japan; [2]Inst. for Protein Research, Osaka Univ., Osaka, Japan

Abstract: Neurosteroids are neuroactive steroids that are synthesized in the brain and they regulate a variety of biological functions including cognition and behavior. These neurosteroids are synthesized from cholesterol by a series of cytochrome P450 enzymes, among which a new member of P450 hydroxylase, cytochrome P450-7b1 (CYP7B1), has been shown to catalyze formation of 7-hydroxylated neurosteroids, 7α-hydroxypregnenolone (7α-OH-Preg) and 7α-hydroxydehydroepiandrosterone (7α-OH-DHEA). Here we found that the mRNAs encoding the enzymes required for the synthesis of 7α-OH-Preg and 7α-OH-DHEA from cholesterol were detected in all the brain regions we examined. Higher level of *Cyp7b1* mRNA expression were determined in the mouse hippocampus among various brain regions. We identified 7α-OH-Preg and 7α-OH-DHEA in the mouse hippocampal extract by using liquid chromatography coupled with *electrospray* ionization tandem mass spectrometry. In the Morris's water maze test, we found a dawn-dusk change in remote spatial memory in WT mice, the memory performance at ZT1 (dawn) was significantly higher than that at ZT11.5 (dusk). The remote memory performance at ZT1 was impaired by *Cyp7b1* deficiency. In *Cyp7b1*-deficient mice, chronic intracerebroventricular administration of 7α-OH-Preg and 7α-OH-DHEA improved remote spatial memory performance. Furthermore, the administration of mixture of these neurosteroids was more effective than the single administrations. We conclude that 7α-OH-Preg and 7α-OH-DHEA play a cooperative role for the long-term maintenance of remote spatial memory in mice.

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Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.23/O26

Topic: F.02. Behavioral Neuroendocrinology

Support: Start-up funds to JW

Title: Effects of developmental and acute exposure to environmental estrogenic compounds on anxiety and memory in male and female rats

Authors: M. VOGT[1], J. ASBERRY[1], ***J. WILLING**[2];
[2]Psychology, [1]Bowling Green State Univ., Bowling Green, OH

Abstract: There are a variety of different ways to humanely house laboratory rodents in animal research facilities. As such, animal facilities at universities and other organizations utilize a vast number of different environmental/housing protocols, which are often unreported in scientific literature. However, recent research shows that many elements of these environments, including bedding, diet, water bottles, and cage material, inadvertently expose laboratory rodents to natural and synthetic substances that can affect the development of the body, brain and behavior. Notably, these environmental variations can expose rodents to increased levels of estrogen and endocrine-disrupting compounds. Exogenous estrogens have been shown to induce developmental and acute changes in neural functioning that can have long-term effects on anxiety and learning/memory. Here, we compare male and female rats raised from birth in an environment high in estrogen (standard rodent chow, plastic cages, plastic water bottles, corn cob bedding) to rats raised in a relatively low-estrogen environment (phytoestrogen-free chow, polyethylene cages, glass water bottles and wood-chip bedding) on several behavioral, developmental and reproductive endpoints. Additionally, we examine the acute effects of these housing conditions in littermates whose environmental condition was switched in adulthood. Specifically, we report the effects of environment on anxiety-like behavior in the elevated plus maze and long-term memory in the object recognition task. These results provide further evidence for the role of environmental endocrine compounds in development and behavior, and may provide insight into issues of reproducibility in animal sciences stemming from environmental context-dependent results.

Disclosures: **M. Vogt:** None. **J. Willing:** None. **J. Asberry:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.24/O27

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant DA029613

Title: Anabolic-androgenic steroids impair biconditional task performance in male rats

Authors: *R. I. WOOD[1], R. O. SERPA[2];
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Abstract: Our goal is to understand the consequences of anabolic-androgenic steroid (AAS) abuse on cognitive function, using rats as a model. Although AAS abuse is now widespread, there has been relatively little research on how steroid abuse impacts cognition. In the present study, rats were tested for their ability to use contextual information to guide decision-making in biconditional discrimination. The Stroop task is a classic human test for contextual decision-making. Subjects are asked to read a color word (e.g. "green", "orange") and name the ink color in which the word is printed (green or orange). Subjects respond faster when the word and ink are congruent ("green" printed in green ink), than when they are incongruent ("green" printed in orange ink). In rodents, biconditional discrimination challenges subjects to use contextual cues in the operant chamber to resolve the correct lever response when auditory and visual cues are incongruent. The hypothesis is that chronic high-dose testosterone impairs biconditional discrimination. Rats were trained in 24 trials/day over 14 days, in alternating sessions with each environment On a flat floor with the houselight illuminated, auditory cues (clicker vs tone) signified the active lever. On a barred floor with no light, rats used visual cues from 2 stimulus lights (constant vs blinking) to identify the active lever. Rats treated chronically with testosterone (7.5 mg/kg) were unimpaired in initial task acquisition, and all rats learned to select the correct lever in response to auditory or visual cues. During extinction, vehicle controls made significantly more correct than incorrect responses in congruent trials ($p<0.05$ by paired t-test), but testosterone-treated rats failed to show a similar preference. This was reflected by a significant effect of testosterone ($F_{1,76}=5.875$, $p<0.05$), as well as a significant interaction of drug, cue agreement, and response accuracy ($F_{1,76}=8.076$, $p<0.05$). These results suggest that testosterone impairs cognitive flexibility, and demonstrates the potential for AAS abuse to impair cognitive function in humans.

Disclosures: R.I. Wood: None. **R.O. Serpa:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.25/O28

Topic: F.02. Behavioral Neuroendocrinology

Title: Hippocampal estrogen and androgen modulate dendritic spines and LTP in non-genomic manner

Authors: *S. KAWATO[1,2], M. SOMA[2], M. OGIUE-IKEDA[2], Y. KOMATSUZAKI[3];
[1]Univ. of Tokyo, Tokyo, Japan; [2]Teikyo Univ., Tokyo, Japan; [3]Nihon Univ., Tokyo, Japan

Abstract: We demonstrated (1) hippocampal synthesis of estrogen and androgen, and (2) non-genomic synaptic modulation by these sex-steroids. [Synthesis] We showed expression as well as neuronal/synaptic localization of essential enzymes (mRNA and protein) in the adult male rat hippocampus. Mass-spectrometric analysis demonstrated that exact levels of estradiol (E2), testosterone (T), dihydrotestosterone (DHT) were 8 nM, 18 nM and 7 nM, respectively, which are much higher than their levels in plasma. Castration significantly decreased T and DHT in the hippocampus, indicating that plasma-derived T is efficiently converted to DHT within the hippocampus. Even after castration to deplete circulating T, the male hippocampal E2 level was not decreased, indicating that E2 is mainly synthesized from hippocampal T. Female hippocampal levels of E2 (0.5-4 nM), and T (1 nM) were less than those of male, but much higher than those in female plasma. [Synaptic Modulation] E2-induced rapid non-genomic modulation (1- 2 h) was demonstrated by analysis of spinogenesis and LTP of adult male rat hippocampal ‘acute’ slices (steroid-depleted slices). Spine analysis was performed for pyramidal neurons in hippocampal slices. The density of spines and their head diameters were obtained by mathematical and automated software Spiso-3D which identifies spines by calculating geometrical parameters. E2 at 1 nM rapidly increased the density of small-head spines, in CA1 pyramidal neurons. T and DHT at 10 nM increased the density of small-head spines and large-head spines, respectively. Signaling pathways are: synaptic ERalpha or AR→LIMK, MAPK, Src, PKA, PKC →cofilin or cortactin → actin polymerization→ new spines. LTP analysis showed that 1 nM E2 induced full-LTP (E2-LTP) upon weak sub-threshold stimulation, although without E2 the weak sub-threshold stimulation did not induce full-LTP. Kinase inhibitors against MAPK, PKA, PKC blocked E2-LTP. Only 20 min application of letrozole (aromatase inhibitor) suppressed full-LTP upon full teta-burst stimulation, indicating that rapid E2 synthesis is necessary for LTP in hippocampal slices. References: Kawato et al., 2002 Methods in Enzymol, Hojo et al., 2004 PNAS, Mukai et al., 2007 J. Neurochem, Hojo et al., 2009 Endocrinology, Mukai et al. 2011 Cerebral Cortex, Ooishi et al. 2011 Cerebral Cortex, Komatsuzaki et al., 2012 PLoS-ONE, Okamoto et al., 2012, PNAS, Kato et al., 2013, Frontier Neurosci. Hasegawa et al.,

2015 Brain Res., Hatanaka et al., 2015 Brain Res., Murakami et al., 2015 Brain Res., Soma et al., 2018 Frontier Neurosci., Hojo and Kawato 2018 Frontier Neurosci.

Disclosures: S. Kawato: None. **M. Soma:** None. **M. Ogiue-Ikeda:** None. **Y. Komatsuzaki:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.26/O29

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH R01 MH109471
CHHE P30ES025128

Title: The impact of the estrous cycle and novelty on female rat behavior in the open field test

Authors: *C. K. MILLER, H. B. PATISAUL, J. MEITZEN;
North Carolina State Univ., Raleigh, NC

Abstract: Many natural factors impact animal behavior. In females, one important consideration is hormone status due to cyclic hormone changes such as in the menstrual cycle in humans and the estrous cycle in rats. These behaviors include those related to anxiety, locomotion, depression, and motivation, which are often assessed in rodents using the open field test. In female rats, exploratory behaviors such as locomotion and propensity to enter areas perceived as dangerous fluctuate naturally across the estrous cycle. However, it is not well-explored as to how behavioral differences induced by hormone cycles interact with other factors such as exploration in a novel environment. Thus, hormone-induced behavioral differences may be masked by novelty-induced behavioral changes. Here, we aim to disassociate differences in exploratory behaviors in the context of the estrous cycle from differences resulting from a novelty effect. We hypothesized that behaviors in the open field such as total distance traveled and time spent in the center would be increased both during initial exposure to the open field as well as in the estrus stage compared to diestrus stage, when hormone effects are limited. We found that both the estrous cycle stage and day of exposure to the open field influenced exploratory behavior. This is important to note in the context of the open field test, as hormone-induced behavioral differences may not be detected as robustly due to the presence of the novelty effect. This approach to open field testing should be considered when exploring hormone-induced behavioral changes across the natural cycle.

Disclosures: C.K. Miller: None. **H.B. Patisaul:** None. **J. Meitzen:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.27/O30

Topic: F.02. Behavioral Neuroendocrinology

Title: Hibiscus is a source of phytoestrogens that modulates spatial memory and hippocampal BDNF expression: A behavioral and molecular study

Authors: *G. LORENZANA[1], A. SANTERRE[1], I. ANDRADE-GONZALEZ[2], J. BAÑUELOS-PINEDA[1];
[1]Univ. of Guadalajara, Zapopan, Mexico; [2]Inst. Tecnológico de Tlajomulco, Tlajomulco, Mexico

Abstract: INTRODUCTION Ovaric hipofunction (OH) is characterized by decay in brain derived neurotrophic factor (BDNF), a neurotrophin critical for neuron survival and function, associated with cognitive and memory decline. Hormone replacement therapy (HRT) is the most common treatment against OH, however this therapy may increase odds of endometrial cancer, blood clots, stroke and breast cancer. Phytoestrogens may offer a safer natural alternative to the synthetic estrogen used in HRT. *Hibiscus sabdariffa* L. (Malvaceae) is known to present health benefits related with its high content of anthocyanins which present structures similar to other compounds, known for their phytoestrogenic activity. In the present study an ovarectomarized rat model was used to assess the phytoestrogenic effect of an anthocyanin extract of *H. sabdariffa*, through BDNF expression and spatial memory evaluation. **MATERIALS** Preparation of the *H. sabdariffa* anthocyanin extract (HSAE) was according to Gonzalez-Palomares et al., 2009. Adult female Wistar rats (90 days old) were randomly separated in six groups. Rats from four groups were ovariectomized (OVX) and injected physiological dose of estradiol (E2), or given HSAE in drinking water at 50 or 100 mg/kg of body weight (bw), for six weeks. Two control groups were included (intact and sham). At day 52 of treatment the Barnes maze tasks were performed to assess short and long term memory (STM, LTM); then hippocampal BDNF expression was evaluated by RT-qPCR and western blot (day 62). **STATISTICAL ANALYSIS** Data for multiple variable comparisons were analyzed by one-way analysis of variance (ANOVA). For the comparison of significance between groups, Tukey's post hoc test was used; $p<0.05$ was considered significant. **RESULTS AND DISCUSSION** The analysis of Barnes´ tests data showed that the administration of HSAE reversed the negative effect of ovariectomy on STM and LTM parameters. A stronger effect was observed in animals administered the lower dose of the anthocyanin extracts (50 mg/kg bw) compared to the higher dose (100 mg/kg bw), probably due to the better acceptation of the extract. The administration of HSAE restored BDNF protein expression. In particular, BDNF protein expression was higher in hippocampus of rats that received 50 mg/kg bw compared to all other study groups. Moreover, the animals that received HSAE presented a significant increase in BDNF transcriptional expression (mRNA) compared to

the rest of the groups. In conclusion HSAE acted as a phytoestrogen, improving hippocampal BDNF expression and spatial memory performances. Further work is now needed to determine if this effect involves ERα, ERβ, as well as GPR30 estrogen receptors.

Disclosures: G. Lorenzana: None. **A. Santerre:** None. **I. Andrade-Gonzalez:** None. **J. Bañuelos-Pineda:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.28/O31

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH grant: 1R21HD091788-01A1

Title: Postnatal progesterone receptor activity influences adult episodic-like memory in the rat

Authors: *A. J. N. NEWELL, C. K. WAGNER;
Univ. at Albany, Albany, NY

Abstract: The transcription factor progesterone receptor (PR) is expressed in Cajal-Retzius (CR) cells of the hippocampal dentate gyrus during the postnatal period. CR cells are critical for dentate gyrus morphogenesis and establishing hippocampal connectivity with the entorhinal cortex via the perforant path. Therefore, postnatal PR activity in CR cells may influence the development of these connections and in turn, affect the behaviors dependent on this pathway, such as episodic memory. To test this hypothesis, Sprague-Dawley rats were treated for the first postnatal week with the PR antagonist, RU486 (20 mg/kg s.c. daily injections) or the vehicle alone. In adulthood, animals were assessed on the Episodic-Like Memory (ELM) task, a test of entorhinal and hippocampal connectivity. In the ELM task, animals are required to integrate functional components of episodic memory, ‘what’, ‘when’, and ‘where’, into a conjoined representation. Results indicate that vehicle treated rats were able to distinguish a stationary object from one which had been displaced when the objects were encountered at a distant time point rather than more recently, but showed no difference in exploration time for recent objects regardless of their position. This suggests integrated memory for the ‘what’, ‘where’ and ‘when’ components of ELM. In contrast, rats treated with the PR antagonist, RU486, spent equal time with objects, regardless of when or where the objects were experienced. This suggests a disruption in the ability of RU486 treated rats to recall episodic specifics and a disruption of an integrated memory for the ‘what’, ‘where’ and ‘when’ components of ELM. However, when the ‘what’ and ‘when’ components were tested separately in a different task, both oil treated and RU486 treated rats were able to distinguish objects and their relative order of presentation, indicating that both groups can recall these components individually in a task that does not

require the integration of the what, when, and where components of ELM. Taken together, these observations suggest that PR activity in CR cells during the postnatal period is critical for fully integrated episodic-like memory in adulthood and generates the hypothesis that PR is involved in the development of the lateral perforant path.

Disclosures: A.J.N. Newell: None. **C.K. Wagner:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.29/O32

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH RO1 AG0546564-01

Title: Luteinizing hormone fluctuations across the estrous cycle impacts synaptic markers in the cingulate and hippocampus

Authors: *M. E. MEY[1], G. CASADESUS SMITH[2], S. BHATTA[1], N. MULLINS[3], K. SRACIC[3];
[1]Biomed. Sci., [2]Biol. Sci., [3]Kent State Univ., Kent, OH

Abstract: The hypothalamic-pituitary-gonadal (HPG) axis has long been associated with changes in behavior and neuronal morphology. Over the course of the estrous cycle, the HPG axis steroid hormones fluctuate and these fluctuations have been associated with estrous-cycle related variations in learning and memory and underlying neuronal plasticity. Recently, luteinizing hormone (LH) has also emerged as another potential regulator of cognition. However, whether LH fluctuation over the course of the estrous cycle is a player in the regulation of synaptic markers is unknown. To address this, cingulate and hippocampal levels of synaptic plasticity markers (synaptophysin, spinophilin, PSD95, BDNF) were measured from animals at different stages of the estrous cycle. Our results thus far indicate a differential and inverse relationship between levels of peripheral LH and the plasticity markers mentioned above. Together, these findings support emerging data demonstrating a CNS role for LH signaling, particularly in neuronal communication and synaptic plasticity.

Disclosures: M.E. Mey: None. **G. Casadesus Smith:** None. **S. Bhatta:** None. **N. Mullins:** None. **K. Sracic:** None.

Poster

586. Hormone Modulation of Behavior and Physiology III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 586.30/O33

Topic: F.02. Behavioral Neuroendocrinology

Support: KSU Foundation Grant
KSU University Research Council

Title: Long term ovariectomy in a nonhuman primate model of menopause reduces hippocampal volume and shifts microglial morphology toward an inflammatory profile; conjugated equine estrogens are not protective

Authors: A. MAFI[1], E. BLAGINYKH[2], S. MISTRY[1], P. MIRJALILI[1], A. BESSKEN[1], E. HOPKINS[1], G. HOWE[1], ***G. P. TINKLER**[1];
[1]Biol. Sci., [2]Col. of Publ. Hlth., Kent State Univ., Kent, OH

Abstract: Loss of circulating ovarian hormones that accompanies menopause may increase the risk of dementia with aging. Inflammation is a key component to many diseases of brain aging, and administering ovarian hormones (estrogen therapy, ET) can quell inflammatory responses. Nonhuman primates are an excellent animal model with which to study menopause, given their similarities to humans. We hypothesized that ovarian hormone loss (ovariectomy, OVX) would increase inflammation in the hippocampus, an area relevant for cognitive processes such as learning and memory, as measured by microglial proliferation and morphology. We further hypothesized that conjugated equine estrogens (CEE) would prevent inflammation in this area. Our study employed the brains from 25 perimenopausal monkeys (age approximately 20 years). These animals were previously ovariectomized and treated for either six or 24 months with placebo (OVX) or estrogens (OVX+CEE). A separate group of animals were available as intact, cycling controls (INT). Using stereological methods, we assessed brain inflammation by quantifying the numbers of microglia in the hippocampus. Compared to INT, the hippocampus of both 24 month OVX and OVX+CEE animals was reduced in volume, while microglia densities were increased in both groups. Interestingly, animals that were OVX or OVX+CEE for only 6 months were not statistically different from INT control animals. Morphological analysis of hippocampal microglia indicated that in the 24 month OVX condition, there was a shift away from the ramified (resting) phenotype toward the amoeboid (activated) morphology. CEE was not effective at preventing this shift. Our results suggest that there may be long term neurobiological consequences to OVX which do not manifest in shorter time frames, and that CEE may not be effective at mitigating chronic inflammatory events that accompany OVX.

Disclosures: G.P. Tinkler: None. **A. Mafi:** None. **E. Blaginykh:** None. **S. Mistry:** None. **P. Mirjalili:** None. **A. Bessken:** None. **E. Hopkins:** None. **G. Howe:** None.

Poster

587. Stress and Adolescence

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 587.01/O34

Topic: F.04. Stress and the Brain

Support: NSF Grant 1460949

Title: Social instability in adolescence alters dendritic morphology in medial prefrontal cortex and its response to stress in adult rats

Authors: *M. R. BREACH, K. M. MOENCH, C. L. WELLMAN;
Psychological and Brain Sci., Indiana Univ., Bloomington, IN

Abstract: Women are more susceptible to many stress-linked psychological disorders, including depression and posttraumatic stress disorder. Dysfunction of prefrontal cortex is implicated in many stress-linked disorders. Thus, understanding how stress may differentially influence prefrontal cortex in males and females may shed light on the neurobiological underpinnings of these sex-biased stress-linked disorders. Chronic restraint stress (CRS) induces sex-specific changes in pyramidal neurons in rodent medial prefrontal cortex (mPFC). For example, apical dendrites of adult male rats retract after 10 days of CRS, which is followed by outgrowth after 7 days of rest. Conversely, apical dendrites of stressed female rats exhibit minimal changes throughout the post-stress period. As adolescence is an important period for HPA axis development and synapse maturation, stress during this time could produce long-lasting changes in stress-sensitive brain regions and alter later stress-induced changes in the adult brain. However, little is known about how stress in adolescence affects these sex-dependent stress-induced changes in adulthood. We investigated the effects of adolescent social instability stress (SIS) on adult dendritic morphology in mPFC of male and female rats. We then examined dendritic reorganization following chronic restraint stress with and without a rest period in adolescently-stressed rats. Golgi-Cox stained pyramidal neurons in mPFC were reconstructed. Dendritic length and spine density analyses revealed that adolescent SIS confers long-term alterations in PL of males and females, whereby females show reduced apical length and basilar thin spine density and males show reduced basilar length. In addition, CRS does not induce dendritic or spine changes immediately after the cessation of CRS. However, CRS reduces apical dendritic length and increases mushroom spine density in adolescently-stressed male rats given a rest period. Conversely, CRS produces outgrowth and decreases mushroom spine density in adolescently-stressed females given a rest period. Both sexes experienced an increase in thin spine density following a rest period after chronic stress. These results corroborate previous evidence of sex-dependent stress-induced changes in mPFC and suggest that stress during

adolescence alters development of the prefrontal cortex and may modulate stress-induced dendritic changes in adulthood.

Disclosures: **M.R. Breach:** None. **K.M. Moench:** None. **C.L. Wellman:** None.

Poster

587. Stress and Adolescence

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 587.02/O35

Topic: F.04. Stress and the Brain

Title: Stress during puberty decreases sexual motivation and affects the correlation testosterone-electroencephalographic activity in adult male rats

Authors: *E. HERNANDEZ-ARTEAGA[1], M. L. RAMÍREZ-RENTERÍA[2], M. HERNÁNDEZ-GONZÁLEZ[2], M. A. GUEVARA[3], H. BONILLA-JAIME[4], A. AGMO[5]; [1]Inst. De Neurociencias, Guadalajara, Mexico; [2]Inst. de Neurociencias, Guadalajara, Mexico; [3]Univ. de Guadalajara, Guadalajara, Jalisco, Mexico; [4]Univ. Autónoma Metropolitana, Mexico city, Mexico; [5]Univ. of Tromsø, Tromsø, Norway

Abstract: Puberty is a critical period of development during which occur neurophysiological changes that allow the manifestation of sexual behavior in the adulthood. This behavior requires adequate levels of testosterone, which affects the functionality of the brain structures such as the medial prefrontal cortex (mPFC) and basolateral amygdala (BLA). A prevalence of electroencephalographic (EEG) theta band (4-13 Hz) has been reported during sexually motivated states. Several studies have reported the deleterious effects that stress exerts on sexual behavior. Considering the above, the aim of this study was to evaluate the effect of stress by social isolation during puberty on sexual motivation and on the association between testosterone levels and the theta band in the mPFC and BLA of male rats. 60 male rats were classified into two groups (n=30), as follows: a stressed group (SG, each male was maintained in social isolation from day 25 to 50 postnatal), and a control group (CG, 4 males housed per cage). At 90 days of age, all rats were subjected to three copulatory tests to select the sexually-experienced individuals, which were implanted bilaterally in the mPFC and BLA to record the EEG activity during the awake-quiet state in a subgroup without sexual motivation (n=15, stimulated with a non-receptive female) and in a subgroup with sexual motivation (n=15 stimulated with a receptive-female). Immediately afterward, blood samples were obtained for quantifying testosterone levels. Pearson correlations (r) were then calculated between the absolute power values of the theta band and the testosterone levels for each of the 4 sub-groups, obtaining one correlation for each brain structure. Subsequently, these r values were compared between groups. All the males of the stressed subgroups spent less time in the incentive zone of the receptive female than those of the control subgroups. The control males without sexual motivation showed

a positive r while those with sexual motivation showed a negative r. In the stressed subgroups, no correlation between testosterone levels and absolute power was observed. These data show that stress during puberty affects the association between testosterone levels and brain function and so has an impact on sexual motivation in male rats.

Disclosures: E. Hernandez-Arteaga: None. **M.L. Ramírez-Rentería:** None. **M. Hernández-González:** None. **M.A. Guevara:** None. **H. Bonilla-Jaime:** None. **A. Agmo:** None.

Poster

587. Stress and Adolescence

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 587.03/O36

Topic: F.04. Stress and the Brain

Support: COLCIENCIAS/Predoctoral fellowship 646.

Title: Effects of social stress exposure during adolescence on impulsivity

Authors: *L. F. GONZALEZ MARTINEZ, K. MORAN, G. GRAY, C. MALONE, Y. DELVILLE;
Psychology, The Univ. of Texas at Austin, Austin, TX

Abstract: Adolescent male hamsters exposed to chronic social stress become themselves aggressive adults, characterized by increased attack frequency and shorter latencies to engage opponents. Perhaps, this enhanced aggression is associated with a lack of impulse control, particularly the ability to inhibit responses (i.e. action inhibition) and waiting to respond (i.e. waiting impulsivity). Male golden hamsters were exposed daily to aggressive adults from postnatal day 28 to 42. Later, the animals were trained in conditioning chambers and tested in a Go-NoGo task to evaluate action inhibition. Overall, previously stressed hamsters were less likely to inhibit a conditioned lever pressing response during NoGo trials, showing a decreased ability to withhold responses, consistent with higher attack frequencies. To test waiting impulsivity, animals learned to respond to a main house-light by nose-poking in any of two, adjacent illuminated ports in a modified version of a 5-choice-serial-reaction-time task. During testing, random and varying delays were introduced between the main house-light presentation and illumination of the ports, and premature nose-poking responses were considered an indicator of waiting impulsivity. As delays grew longer, animals performed more premature responses. However, previously stressed animals were 25% less likely to perform such actions by the longest delay. These studies show that early stress exposure enhanced the capacity to wait to perform a response, which is unrelated to aggression. Aspects of perseverance also were tested in additional studies. Previously stressed animals were intolerant to delays in reward in specific conditions. In summary, exposure to chronic social stress in early adolescence causes a variety of

behavioral changes including enhanced aggression, decreased action inhibition and improved waiting impulsivity. This ambiguous relation between aggressive and impulsive behaviors shows that there are multiple types of impulsive-aggressive profiles likely related to different brain mechanisms. We propose that the concept of aggression should be reconsidered as a multidimensional construct mediating multiple aspects of personality.

Disclosures: L.F. Gonzalez Martinez: None. **K. Moran:** None. **G. Gray:** None. **C. Malone:** None. **Y. Delville:** None.

Poster

587. Stress and Adolescence

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 587.04/O37

Topic: F.04. Stress and the Brain

Title: Effects of prolonged social isolation in adolescence: Sex differences in anxiety and sociability behavior in rats

Authors: *E. MRACKOVA, J. ROSENKRANZ;
Dept. of Cell. and Mol. Pharmacol., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: Early life stress such as prolonged social isolation is regarded as a risk factor for the development of depression and anxiety in adulthood. Extensive research has found that sex differences in anxiety-like behaviors emerge during adolescence, with females more at risk than males. Despite the rising social isolation and loneliness across the world, the causes and effects of social isolation in adolescence remain still poorly understood. The purpose of this study was to determine whether the housing condition of rats (social isolation vs group housing), social isolation duration (1-week vs 4-week continuous isolation), or sex (male vs. female) would affect sociability behavior as well as the development of anxiety-like behaviors. Four behavior tests (open field, conditioned place preference, social interaction, and appetitive operant conditioning) were administered at postnatal days 53-69 to determine the effects of social isolation on hyperactivity, thigmotaxic behavior, social behavior, and reward seeking. Overall, we found that 4 wk social isolation in both males and females increased thigmotaxic behavior and in female rats decreased social interaction. Furthermore, 1 wk social isolation in male rats resulted in an increased social place preference compared to a novel object. Lastly, while 4 wk social isolation did not significantly impact conditioned appetitive sucrose seeking behaviors, it increased sensitivity of conditioned seeking to a bright light anxiogenic stimulus. Overall, this research adds new insight into the understanding of sex differences associated with prolonged social isolation and subsequent anxiety-like behaviors. Future research will focus on immunohistochemistry staining of brain areas implicated in anxiety.

Disclosures: E. Mrackova: None. **J. Rosenkranz:** None.

Poster

587. Stress and Adolescence

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 587.05/O38

Topic: F.04. Stress and the Brain

Title: Maternal separation produces immune activation in the brain leading to neuropsychiatric disorders in the adolescence

Authors: *S. BACHILLER[1], A. PAULUS[1], I. GARCIA-DOMINGUEZ[2], Q. DENIS[1], S. VAZQUEZ-REYES[1], A. BOZA-SERRANO[1], T. DEIERBORG[1];
[1]Exptl. Med. Sci., Lund Univ., Lund, Sweden; [2]Biochem. and Mol. Biol., Fac. of Pharm., University of Sevilla, Spain

Abstract: Epidemiological and clinical studies have shown that early life experiences could be involved in the development of emotional and affective disorders, such as depression and anxiety in adulthood (1,2). There is also a general consensus, emerging from epidemiological studies, that the activation of the immune system in response to inflammatory agents, plays an important role in the pathophysiology of stress and depressive states (2).We are trying to link early inflammatory events with depressive-like behavior *in vivo* and we have established a model of maternal separation (MS, postnatal day 2 to 14, 3 h per day). Our preliminary results show robust microglial activation in the brain just after the MS at P15 (24 h after the last MS session) as well as significant alteration peripheral and hippocampal inflammatory response. Furthermore, at 6 weeks old (considered the adolescence period in mice (3)), the exposure to MS leads to several changes in the brain, including down-regulation of synaptic plasticity genes and growth factors as well as cognitive impairment and anxiety- and depressive-like behavior, in a sex-dependent manner.Our results will try to answer how priming events of microglial reaction can participate in the manifestation of depressive and anxiety-like behavior in the adolescence, in a sex-specific manner.References:(1) Nugent et al., 2011.(2) Reus et al., 2017.(3) Brust et al., 2015.

Disclosures: S. Bachiller: None. **A. Paulus:** None. **I. Garcia-Dominguez:** None. **Q. Denis:** None. **S. Vazquez-Reyes:** None. **A. Boza-Serrano:** None. **T. Deierborg:** None.

Poster

587. Stress and Adolescence

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 587.06/O39

Topic: F.04. Stress and the Brain

Support: Hope for Depression Research Foundation
Ludmer Centre for Neuroinformatics and Mental Health
Sackler Program for Epigenetics and Psychobiology at McGill University

Title: Chronic social crowding and instability stress with Enviro-dri: A novel mouse model of anxiety and depression-like behavior

Authors: *C. PARENT[1,2], K. CRAIG[1,2], E.-M. CHARBONNEAU[1], A.-M. AREL-DUBEAU[1,2], A. MARTEL[1,2], M. J. MEANEY[1,2,3], T. ZHANG[1,2];
[1]Douglas Mental Hlth. Univ. Inst., Montreal, QC, Canada; [2]Dept. of Psychiatry, Sackler Program for Epigenetics and Psychobiology at McGill University, Ludmer Ctr. for Neuroinformatics and Mental Hlth., Montreal, QC, Canada; [3]Singapore Inst. for Clin. Sci., Singapore, Singapore

Abstract: Chronic stress increases the risk for stress-related disorders including anxiety and depression. A major form of chronic stress in humans is social in nature. Sex based differences exist in the resilience and susceptibility to develop stress-related disorders. Most basic research using models of chronic stress focus on using males only. Our main objective was to develop a model of chronic social stress that could be applied in both male and female mice. We examined a 7-week model of chronic social crowding and instability (CSCI) stress in mice. We also tested a 30-day model of CSCI stress in the presence and absence of paper nesting material, Enviro-dri and nestlets. Eight same sex mice were placed in a standard sized mouse cage with or without Enviro-dri and nestlets. Every 2-5 days the group composition of the cages was changed in an unpredictable manner using a randomized schedule. The control mice were housed in same sex pairs in a standard sized mouse cage with or without nesting material and handled when the CSCI stress mice were rotated cages. A battery of behavioral tests to measure depression and anxiety-like behavior were given at the end of the CSCI stress protocol. We found that 7-week CSCI stress without Enviro-dri significantly increased the latency to feed in a novelty suppressed feeding test in males but not females, compared to the control groups. Thirty days of CSCI stress without Enviro-dri did not have an effect on any behavioral tests measuring anxiety and depression-like behavior. However, thirty days of CSCI stress with Enviro-dri (10g) significantly increased the latency to feed in a novelty suppressed feeding test in both males and females. CSCI stress also increased immobility time in a forced swimming test in males but not females, and increased plasma corticosterone levels in females. The results suggest that CSCI stress with

Enviro-dri is a novel and practical animal model to measure anxiety/depression-like behavior that can be applied in both sexes.

Disclosures: C. Parent: None. **K. Craig:** None. **E. Charbonneau:** None. **A. Arel-Dubeau:** None. **A. Martel:** None. **M.J. Meaney:** None. **T. Zhang:** None.

Poster

587. Stress and Adolescence

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 587.07/O40

Topic: F.04. Stress and the Brain

Title: The effect of maternal deprivation on behavior in a mouse model

Authors: *M. D. THOMPSON, S. L. P. LIPPI, C. M. KREITLER;
Psychology and Sociology, Angelo State Univ., San Angelo, TX

Abstract: Foster care is a growing concern in Texas and in the United States. According to the U.S. Department of Health and Human Services (2016), the number of children in the foster care system has been increasing by approximately 10,000 children every year since 2012. The emotional deprivation experienced by a foster child leads to a form of brain trauma that has lasting effects through adulthood. There is a dearth of research investigating the long-term effects of maternal deprivation. The current research sought to investigate behavioral outcomes in a mouse model of maternal deprivation and highlight those behavioral changes through adulthood. In this study, we sought to explore the short-term and long-term behavioral effects. The study used four timed-pregnant C57BL/6J mice, two of which were randomly assigned to the maternal deprivation condition and were separated from their pups for 24 hours on postnatal day 4. The pups did not have access to food or water during these 24 hours (Kentrop, 2018). Pups were then returned to their home cages, until weaning at 3 weeks. At 4 weeks the pups began behavioral testing including the open field test, elevated zero maze, Morris water maze, and activities of daily living. Behavioral testing was repeated at 10 weeks of age; this was done to assess longer changes. Repeated measures ANOVAs were conducted for each behavioral test. Significant differences of age were found in the open field, elevated zero maze, and burrowing. There was a significant difference in the open field at 4 weeks between the two groups. Brain tissue will be assessed for markers related to learning and inflammation. The purpose of this project was to examine early life stress experiences in a mouse model on behavior both in short and long-term timeframes. Results showcase the impact of maternal deprivation as was found by the open field at 4 weeks of age, with maternally deprived mice spending significantly more time in the surround ($F(1,17) = 11.435$, $p < .01$). Indeed, we hope to raise awareness of foster care needs in the country and highlight the far-reaching impact on children's cognition and behavior.

Disclosures: **M.D. Thompson:** None. **S.L.P. Lippi:** None. **C.M. Kreitler:** None.

Poster

587. Stress and Adolescence

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 587.08/O41

Topic: F.04. Stress and the Brain

Title: Chronic mild unpredictable stress and high-fat diet given during adolescence impact both cognitive and noncognitive behaviors in young adult mice

Authors: ***S. L. P. LIPPI**, M. D. THOMPSON, L. C. VOTH, A. M. FLORES;
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Abstract: Stress and diet are intricately linked and often interact in a negative fashion. Increases in stress can lead to poor food choices; adolescence is a period that is often accompanied by increased levels of stress. Adolescents are noted to engage in emotional eating behaviors, which often involve poor food choices. The period of adolescence has shown a high prevalence of obesity (Bibiloni et al., 2013) and adolescent mice given diets high in fat have shown impairments in memory. Given that both stress and poor dietary choices can affect learning and memory, it is important to understand their combined effects when encountered during crucial developmental periods. Few studies have examined both chronic stress and intake of high-fat diet on behavior; in those that have, often only one sex has been used and diet administration starts at varying time points (Yang et al., 2016). The current experiment explored how chronic mild unpredictable stress (CMUS) and high-fat diet (HFD) affect animal memory and behavior when given during the period of adolescence (starting at PND 28). C57BL/6J mice received *ad libitum* access to either a control diet (D12450J – 10 kcal% fat) or a high-fat diet (D12492 – 60 kcal% fat) starting at four weeks of age and experienced either no stress or four weeks of CMUS (4 – 8 weeks). Behavioral tests run included: open field, elevated-zero maze (EZM), and Morris Water Maze (MWM). Non-cognitive tests were also run; these included burrowing and nesting assays. Both male and female mice were used in this study. Mice experiencing CMUS exhibited behavioral disinhibition; spending significantly more time in the open arms of the EZM, $p < .05$ and significantly less time in the center of the open field, $p = .01$. In MWM, there were significant effects of training day for latency to find the hidden platform and thigmotaxicity ($p < .001$). Mice that underwent CMUS made significantly fewer crosses on the final 24-hour probe trial compared to those with no stress, $p < .05$. Additionally, a significant diet x stress interaction was noted in time spent in the target quadrant on the final 24-hour probe trial, $p < .05$. Mice given a HFD with no stress spent significantly longer in the target quadrant than the HFD mice with CMUS, $p < .01$. CMUS mice burrowed significantly more peagravel after 2 hours in the burrowing assay, $p < .05$ and had higher rated nest scores than non-stressed mice, $p < .05$. High-

fat diet mice built significantly poorer nests compared to those on a control diet, $p < .05$. These results show that CMUS and HFD administration given during adolescence have the ability to affect both cognitive and non-cognitive behaviors in early adulthood.

Disclosures: S.L.P. Lippi: None. **M.D. Thompson:** None. **L.C. Voth:** None. **A.M. Flores:** None.

Poster

587. Stress and Adolescence

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 587.09/O42

Topic: F.04. Stress and the Brain

Support: NIH RO1 AG033605
NIH T32 AA013527
NIH RO1 AA021517

Title: Alternative splicing of glucocorticoid receptor (GR) increases in the brain following acute and chronic stress

Authors: *J. CHANG, A. ASIMES, T. PAK;
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Abstract: Alternative splicing increases the diversity of proteins that arise from a single pre-mRNA transcript. The brain has a high incidence of alternative splicing, which can be modulated under a variety of pathological conditions. For instance, alcohol abuse causes dramatic changes in gene alternative splicing, leading to neuroadaptive changes in the brain. In addition, our lab and others have shown that adolescent “binge pattern” alcohol abuse caused dysregulation of the physiological stress response mediated by the hypothalamo-pituitary-adrenal (HPA) axis. The hypothalamic glucocorticoid receptor (GR) mediates the negative feedback effects of cortisol on the HPA axis and dysregulation of this negative feedback pattern causes increased anxiety-like behaviors, which leads to the development of mood disorders. Previously, our lab showed that binge pattern alcohol (ETOH) exposure in adolescent rats caused disruptions in GR negative feedback in the hypothalamus. Therefore, we hypothesized that the observed dysregulation could be due to increased alternative splicing of GR to the dominant negative isoform, GRβ, which does not have ligand-binding ability. To test this hypothesis, we used a binge model of ETOH exposure in rat hypothalamic-derived cell lines. Briefly, cells were treated with 50 or 100 mM ethanol for two hours once/day for 3 consecutive days. The cells were collected every 24 hours and we measured GRβ expression using RT-qPCR. Our results showed an initial increase of GRβ expression, which decreased following subsequent ETOH exposures. Next, we tested whether the increased expression of GRβ was specific to ETOH or generalized stressors by

subjecting the cells to heterotypic stressors. Consistent with ETOH exposure, GRβ expression was also increased following heterotypic stress exposure. We then assessed GRβ expression in a rat model of adolescent "binge" ETOH exposure and in a chronic stress model. Similar to our *in vitro* data, GRβ was increased in both of these *in vivo* paradigms. Together, these results demonstrate prolonged changes in GR splicing following a stressor, which can impact HPA axis regulation leading to the development of mood disorders in later life.

Disclosures: J. Chang: None. **A. Asimes:** None. **T. Pak:** None.

Poster

587. Stress and Adolescence

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 587.10/O43

Topic: F.04. Stress and the Brain

Support: NIH Grant MH101729
NIH Grant T32DK059803-13
NIH Grant MH049698
VA Grant I01BX003858

Title: Mechanisms of resilience after adolescent chronic stress: Implications for PTSD

Authors: *E. M. COTELLA[1], R. D. MOLONEY[1], P. MAHBOD[1], J. NIBLACK[1], M. FITZGERALD[1], J. B. CHAMBERS[2], J. P. HERMAN[1];
[1]Pharmacol. and Systems Physiol., [2]Univ. of Cincinnati, Cincinnati, OH

Abstract: Posttraumatic stress disorder (PTSD) is a psychiatric condition that can develop after exposure to traumatic experience. Not everybody that experiences trauma develops the disorder, suggesting that mechanisms exist to confer resilience to some individuals but not others. Chronic stress during development is generally associated with later emergence of psychopathology, particularly under conditions of severe stress. However, mild to moderate stress during this period can also promote an adaptive response to stressful situations later in life, contributing to stress resilience. We recently demonstrated that chronic variable stress (CVS) during adolescence attenuates the impact of single prolonged stress (SPS), a potent rodent model of PTSD, on extinction and reinstatement of fear conditioning. These results suggest that stress during adolescence can evoke a resilient phenotype. In the present study, we analyzed the neuronal recruitment in the cortico-amygdalar circuitry after SPS and reinstatement in animals exposed to CVS in late adolescence. To identify possible molecular candidates mediating resilience to SPS, we then assayed expression of stress-related mRNAs using low-density PCR arrays, immediately and after 5 weeks of adolescent CVS. Our results suggest that the infralimbic division (IL) of the prefrontal cortex is involved in SPS resilience. We observed a

reduction of IL neuronal activation in SPS animals after reinstatement of fear ($p<0.05$) and this was prevented by CVS in adolescence (adol CVS). This was not accompanied by changes altered Fos activation basolateral (BLA) and central nuclei (CeA) of the amygdala, although we cannot discard differences regarding activation of principal neurons versus interneurons. Notably, at the level of the amygdala, adol CVS reduced the expression of the pituitary adenylate cyclase-activating polypeptide (PACAP) ($p<0.05$). PACAP is a neuromodulator associated with enhancement of fear conditioning. Therefore, based on our results, we propose a prefrontal cortex-amygdala circuit mechanism whereby previous adolescent stress buffers the effects of SPS during adulthood through 1) maintenance of top-down control onto the amygdala by the infralimbic cortex and 2) reducing intrinsic excitability of the amygdala mediated by PACAP.

Disclosures: E.M. Cotella: None. **R.D. Moloney:** None. **P. Mahbod:** None. **J. Niblack:** None. **M. Fitzgerald:** None. **J.P. Herman:** None.

Poster

587. Stress and Adolescence

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 587.11/O44

Topic: F.04. Stress and the Brain

Support: NIH R01 MH108342
NIH 2T32NS061788

Title: Previous studies have shown that though the outward symptoms of these disorders are similar between adults and adolescents, some physiological and psychological differences between the two groups are apparent. It is likely that the underlying mechanisms by which anxiety disorders develop differ between the two age groups

Authors: M. A. CORTES[1], K. M. CORDER[2], *L. E. DOBRUNZ[1];
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Abstract: Anxiety disorders are the most common family of neuropsychiatric disorders diagnosed in adolescence and adulthood. Previous studies have shown that though the outward symptoms of these disorders are similar between adults and adolescents, some physiological and psychological differences between the two groups are apparent. It is likely that the underlying mechanisms by which anxiety disorders develop differ between the two age groups. To investigate the underlying mechanisms of stress-induced anxiety, a variety of rodent stress models have been used that vary in exposure times, nature of the stressor, and predictability of the onset of the stressor. Most studies have looked at the consequence of stress in adult rodents, whereas much less work has been done studying anxiety behaviors in adolescents. Footshock is a physical stressor that has been shown to cause anxiety and fear responses in adult rodents,

although the effects in adolescents are unclear. Here we used a 30-minute footshock protocol to investigate the differences in anxiety between adolescent (6 weeks old) and adult (3 months old) male C57Bl6/J mice. This protocol consists of a 2-minute habituation period, followed by 15 footshocks over the course of 26 minutes (1 mA, 2 s duration, randomized time intervals between shocks), and ending with a 2-minute recovery period. Anxiety phenotypes were assessed on the elevated plus maze and open field after stress exposure. One week after footshock exposure, the adults showed reduced open arm time and entries on the elevated plus maze, indicative of typical anxiety-like behavior. In contrast, the adolescents displayed no change in open arm time or entries, both one week and one day after footshock, suggesting no increase in anxiety-like behavior. Both age groups displayed reduced activity levels in the elevated plus maze and open field at one week after the stressor. The hypolocomotion did not relate to motor deficits, as there were no differences between footshock and control groups using rotarod. It is possible that the reduced activity levels in adolescents are due to generalized fear (increased freezing), as has been documented in the literature for adults. To investigate this, we will measure elevations of corticosterone in blood plasma and fecal pellets, c-fos staining in the amygdala, and levels of the anti-anxiety molecule Neuropeptide Y in regions associated with anxiety behaviors. In summary, we find that the behavioral consequence of a 30-minute session of randomized footshocks is different between adolescent and adult mice, indicating that there are differences in fear expression and anxiety-like behaviors to a physical stressor.

Disclosures: M.A. Cortes: None. **K.M. Corder:** None. **L.E. Dobrunz:** None.

Poster

587. Stress and Adolescence

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 587.12/P1

Topic: F.04. Stress and the Brain

Support: NIMH Grant R01 MH115020-01
NARSAD Independent Investigator Award

Title: Acute traumatic stress during adolescence alters myelination in the rodent prefrontal cortex

Authors: *J. BRETON, M. BARRAZA, A. VADHRI, N. GALOUSTIAN, D. KAUFER; Univ. of California Berkeley, Berkeley, CA

Abstract: Myelination is altered in patients suffering from post-traumatic stress disorder (PTSD), depression, and other psychiatric illnesses. For example, PTSD patients have increased myelin content in the hippocampus compared to trauma-exposed individuals, and this altered hippocampal myelin is correlated with PTSD symptom severity. Previous work from our lab

established that a single acute traumatic stress similarly increases myelin in the hippocampus of rats. However, it is unknown whether these stress-induced changes in myelination generalize to other regions of the brain. In particular, dysfunction of the prefrontal cortex (PFC) is implicated in these same disorders; yet the effect of traumatic stress on PFC myelination remains unknown. Furthermore, an important remaining question is whether there are critical time periods during development when stress is especially harmful. During adolescence, myelination of the PFC is still ongoing. Therefore, adolescence may be a time period when the developing brain is particularly vulnerable to the effects of stressors. In the current study, we used a rodent model to test how exposure to an acute, traumatic stressor during adolescence affects myelination in the PFC. Male and female adolescent Sprague Dawley rats (p26) were exposed to three hours of severe stress (restraint stress with exposure to a predator odor). Subsequent fear and anxiety-like behavior was assayed either one-week later, or in adulthood (p90), to test for short or long term effects respectively. Brains were then analyzed for oligodendrocyte and myelin markers using immunohistochemistry and fluorescent microscopy. We found that acute traumatic stress increased myelination in PFC regions one week later ($F(1,116) = 11.31$, $p=0.0010$). Interestingly, the long term effects of traumatic stress interacted with sex; female animals showed reduced myelination in PFC regions, while male animals had no change ($F(1,100) = 10.70$, $p=0.0015$). In both short and long term conditions, the number of oligodendrocytes remained unchanged. Our findings suggest that the PFC is vulnerable to a single traumatic stressor, and that there are both immediate and long-term effects on myelination. Stress during adolescence may provoke early maturation of the PFC, and also lead to sex-specific long-term changes. Overall, our data indicate that stress-induced changes in myelination may be a novel and underappreciated mechanism by which psychopathologies such as PTSD and anxiety emerge. Findings in rodents will inform our knowledge of how traumatic stressors may impact human prefrontal cortex development and mental health.

Disclosures: **J. Breton:** None. **M. Barraza:** None. **A. Vadhri:** None. **N. Galoustian:** None. **D. Kaufer:** None.

Poster

587. Stress and Adolescence

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 587.13/P2

Topic: F.04. Stress and the Brain

Support: NIH-NIAAA F30AA-024948 to EJK
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NIH-NIAAA P50AA-022538 to SCP

VA Senior Research Career Scientist Award to SCP

Title: miR-137 drives anxiety-like behavior and epigenetic remodeling in the adult amygdala after adolescent alcohol exposure

Authors: *E. J. KYZAR, J. P. BOHNSACK, H. ZHANG, S. C. PANDEY;
Psychiatry, Univ. of Illinois at Chicago, Chicago, IL

Abstract: Adolescent binge drinking is a major risk factor for alcohol use disorder (AUD) and comorbid psychiatric disorders including anxiety in adulthood, and epigenetic mechanisms likely play a role in the lasting deleterious effects of early life alcohol exposure. We thus investigated miR-137, which is a crucial microRNA for normal neurodevelopment, in the amygdala in adolescent intermittent ethanol (AIE) exposure-induced epigenetic reprogramming, anxiety, and alcohol intake in adulthood. Sprague-Dawley rats were exposed to 2g/kg ethanol (AIE) or intermittent n-saline (AIS) on a 2 days on-2 days off schedule via intraperitoneal injection (i.p.) during postnatal days (PND) 28-41 and allowed to grow to adulthood for analysis of behavior, miRNA expression, and epigenetic measures in the amygdala. miR-137 was increased and the miR-137 target genes lysine-specific demethylase 1 (*Lsd1*) and *Lsd1+8a*, which are histone demethylases known to be involved in epigenetic regulation and alcohol exposure, were decreased in the AIE adult amygdala. LSD1 occupancy was decreased on the chromatin at the *Bdnf* exon *IV* promoter region in the amygdala of AIE adult rats, correlating with decreased *Bdnf IV* mRNA expression in AIE-exposed adult rats. Interestingly, miR-137 was increased in the postmortem amygdala of human subjects with AUD, indicating that these results translate across species. Infusion of a locked nucleic acid antagonist to miR-137 (miR-137 antagomir) directly into the central nucleus of the amygdala (CeA) rescues AIE-induced alcohol drinking and anxiety-like behaviors, and also normalizes the decreased *Lsd1* expression, decreased LSD1 chromatin occupancy, and decreased *Bdnf IV* expression due to increased repressive H3K9 dimethylation (H3K9me2) occupancy in AIE adult rats. Further, concomitant *Lsd1* siRNA infusion into the CeA prevents the miR-137-mediated reversal of AIE-induced adult anxiety, gene expression changes, and chromatin remodeling at the *Bdnf IV* promoter. These results indicate that AIE causes an enduring increase in amygdala miR-137 leading to *Lsd1* downregulation and epigenetic reprogramming, anxiety, and higher alcohol intake in adulthood. Our results highlight miR-137 and the targeting of LSD1 as a potential therapeutic avenue for treatment of anxiety and AUD susceptibility after adolescent alcohol exposure.

Disclosures: **E.J. Kyzar:** None. **J.P. Bohnsack:** None. **H. Zhang:** None. **S.C. Pandey:** None.

Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.01/P3

Topic: F.04. Stress and the Brain

Support: NIDA 1R15 DA044500-01A1

Title: Effect of fatty-acids amylase inhibitor (FAAH) on TRPV1 and CB1 receptors regulating anxiety and depression behaviors within the mesolimbic system

Authors: *W. NORZÉ, L. RODRÍGUEZ SANTOS, P. MUÑOZ RODRÍGUEZ, A. RAMOS ROLÓN, V. ENCARNACIÓN CORTES, E. OLMEDO LÓPEZ, F. GONZÁLEZ HERNÁNDEZ, C. MALDONADO VLAAR;
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Abstract: Fatty acid amide hydrolase (FAAH) is an integral membrane enzyme that hydrolyzes the endocannabinoid anandamide and related amidated signaling lipids. Converging evidence suggests that the endocannabinoid system is an important constituent of neuronal substrates involved in brain reward processes and emotional responses to stress. We investigated the effects of fatty-acids amylase inhibitor (URB597) in (a) eliciting anxiolytic responses (b) enhancing depression behavior (c) changes in TRPV1 and CB1 receptors expression within the mesocorticolimbic structures. To evaluate anxiety and locomotor behavior, male Sprague Dawley rats were exposed to the locomotor activity chambers after receiving systemic intraperitoneal injections of (saline 0.9%) 0.3mg/kg/ip or 1mg/kg/ip during five consecutive days. On the testing session (D7), separate groups of male rats received: 0, 0.3, 1 mg/kg/ip of URB597 prior being exposed to the associated environment followed by the Elevate Plus Maze (EPM). In addition, separate groups of animals were exposed to the Forced Swim Test (FST) in order to examine the effects of URB597 on depression-like behaviors. One group of animals received a single dose of 0.1mg/kg URB597 and another group were treated for 4 days with either vehicle or URB597 dose before testing in the FST. Our results suggest that fatty acid amide hydrolase inhibitor significantly decreased locomotor behaviors and tend to decrease anxiety at dose 0.3mg/kg/ip. In addition, URB597 tended to decrease floating and increase mobility behaviors in the FST. Ongoing biochemical analysis of the changes in expression of TRPV1 and CB1 receptors following treatment with URB597 will support mechanistic explanations for the present behavioral results. These findings suggest that URB597 might be an innovative therapeutic approach for treating anxiety and depression via the endocannabinoid system.

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Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.02/P4

Topic: F.04. Stress and the Brain

Support: NWO Grant 864.10.003
Veni Grant 863.15.008

Title: The memory engram for trauma and its implications for vulnerability to PTSD

Authors: *B. C. J. DIRVEN[1,2], J. R. HOMBERG[2], T. L. KOZICZ[3,1], M. J. A. G. HENCKENS[2];
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Abstract: A great deal of experimental investment is directed towards understanding the mechanisms of memory storage and the neuronal ensembles and circuits that hold specific memories. This search has become increasingly urgent, as we now understand that some memories can become the nucleus of later psychopathology, like anxiety disorders or post-traumatic stress disorder (PTSD). While previous studies have mainly addressed the *capacity* for memory storage, recent advances in technology have allowed us to identify and study the engrams for specific *individual* experiences. Memory engram technology, which is based on the experimental coupling of immediate early gene expression (e.g. *c-fos* and *arc*) to fluorescent molecular labels, enables the labeling of neurons that are active during a given learning experience.
By employing this new technology in an established mouse model of PTSD - where we phenotypically subdivide animals in vulnerable and resilient subgroups, based on their scores on a battery of PTSD-related behavioral tasks after trauma exposure - we study the neuronal populations involved in creating the memory engram for a traumatic experience. Immunohistochemical data from our lab show that the basolateral amygdala is more active both during the encoding and recollection of traumatic memory in PTSD-vulnerable vs. PTSD-resilient animals. The CA1 area of the ventral hippocampus in these animals, on the other hand, shows reduced activation during trauma recollection, but not encoding. This reduced hippocampal activity is accompanied by an increase in parvalbumin-positive neuronal density, suggesting that structural differences might also be involved. Collectively, these data suggest that vulnerability to PTSD psychopathology might be underlain by subtle changes in activity of specific neuronal populations during exposure to and recovery from trauma.
By employing a novel technique to clear, immunolabel and 3D image whole brain tissue,

iDISCO+, we are now investigating neuronal activation during trauma exposure at the neural network level, going beyond the subareas of the hippocampus and amygdala. These experiments are essential towards a finer understanding of the distinct processing of traumatic memory that distinguishes the PTSD-resilient from the PTSD-vulnerable brain.

Disclosures: B.C.J. Dirven: None. **J.R. Homberg:** None. **T.L. Kozicz:** None. **M.J.A.G. Henckens:** None.

Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.03/P5

Topic: F.04. Stress and the Brain

Support: MOST 102-2420-H-009-003-MY3
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Taipei Veterans General Hospital-National Yang-Ming University Excellent Physician Scientists Cultivation Program, No. 108-V-B-008

Title: EEG activity increased in the vestibular cortex after noisy galvanic vestibular stimulation in bilateral vestibular hypofunction patients

Authors: *C.-L. KAO[1], L.-W. KO[2], R. CHIKARA[2], P.-Y. CHEN[3], Y.-C. JHENG[3];
[1]Physical Med. & Rehabil., Natl. Yang-Ming University, Vet Gen Hosp, Taipei, Taipei, Taiwan; [2]Dept. of Biol. Sci. and Technology, Natl. Chiao Tung University, Hsinchu, Taiwan, Hsinchu, Taiwan; [3]Dept. of Physical Therapy and Assistive Technology, Natl. Yang-Ming Univ., Taipei, Taiwan

Abstract: Damage of vestibular function bilaterally produces difficulty in maintaining balance, especially when walking at night, and a reduction in the patient's capability to see clearly during head movements. Because of these difficulties, patients with HBV may limit their activities and socially isolate themselves. The neural mechanisms involved in the maintenance of postural stability are not yet well understood. However, non-invasive treatment options for bilateral vestibular hypofunction (BVH) patients are very limited. Therefore, in this study, we use noisy galvanic vestibular stimulation (nGVS) method that non-invasively excites the brain of BVH patients. The aim of this study is to investigate the EEG brain dynamics before nGVS and after

nGVS in the vestibular cortex of BVH patients. We utilized higher temporal resolution electroencephalography (EEG) method with 32 channels to acquire the EEG signals from ten healthy subjects and seven BVH patients in walking and standing conditions. The terms of behavioral results we observed that the center of pressure (COP) sway decreased after nGVS during standing in both groups of subjects. In walking, both groups revealed the improvement in 2Hz head yaw movements after nGVS. However, in EEG results we investigated that the EEG activity in theta, alpha, beta and gamma bands increased in the vestibular cortex after nGVS during walking and standing in both groups. These results displayed a novel non-invasive therapeutic method to improve postural stability in BVH patients through nGVS.

Disclosures: C. Kao: None. **L. Ko:** None. **R. Chikara:** None. **P. Chen:** None. **Y. Jheng:** None.

Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.04/P6

Topic: F.04. Stress and the Brain

Support: NRSAID Young Investigator Award (Brain & Behavior Research Foundation)

Title: Prefrontal cortical Rap1 expression regulates synaptic morphogenesis, *in vivo* neuronal engagement, and cognition

Authors: *B. A. KERMATH, A. M. VANDERPLOW, A. M. NOVAK, M. E. CAHILL; The Univ. of Wisconsin-Madison, Madison, WI

Abstract: The complex mechanisms underlying cognitive deficits in neuropsychiatric disorders remain unclear. Protein expression of the Rap1 small GTPase is decreased in the prefrontal cortex of subjects with schizophrenia and major depressive disorder. Surprisingly, we found that in a model of acute stress, a risk factor for the etiology of neuropsychiatric disorders, Rap1 levels are increased in synaptic fractions of the mouse prefrontal cortex (PFC). As this stress protocol also results in impaired cognitive function in mice, we were interested in determining how PFC-specific manipulation of Rap1 impact cognitive endophenotypes. To this end, we used viral-mediated gene transfer to augment Rap1 levels in the PFC, and assessed neuronal structure, cognitive behavior, and neuronal engagement during cognitive processing. We found that Rap1 overexpression impaired performance in a spontaneous alternation test of spatial working memory and resulted in deficits in object location associative memory. Preliminary studies further indicate that impairments in object location memory upon Rap1 overexpression in the PFC are likely due to a reduced engagement of PFC neurons, as measured by immediate early gene expression profiles, during object exploratory behavior. Current studies are aimed at

assessing dendritic spine density and morphology in PFC pyramidal neurons following *in vivo* manipulation of Rap1 levels. Overall, these data support the hypothesis that changes in Rap1b expression in the prefrontal cortex are sufficient to alter cognitive function and may underlie some of the cognitive deficits seen in stress-based disorders.

Disclosures: B.A. Kermath: None. **A.M. Vanderplow:** None. **A.M. Novak:** None. **M.E. Cahill:** None.

Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.05/P7

Topic: F.04. Stress and the Brain

Support: NIH MH049698
NIH NS007453

Title: Inhibition of GABA-ergic parvalbumin interneurons during chronic stress prevents stress mediated behavioral and physiological phenotypes

Authors: *N. NAWREEN[1], R. MORANO[2], P. MAHBOD[1], E. M. COTELLA[1], K. DALAL[1], M. FITZGERALD[1], S. MARTELLE[1], B. PACKARD[1], R. D. MOLONEY[3], J. P. HERMAN[4]; [2]Psychiatry, [3]Psychiatry and Behavioral Neurosci., [4]Dept Pharmacol. and Systems Physiol., [1]Univ. of Cincinnati, Cincinnati, OH

Abstract: Hypofunction of the prefrontal cortex (PFC) is thought to underlie neuropsychiatric illnesses such as post-traumatic stress disorder (PTSD) and depression. However, little is known about the mechanisms leading to reduced PFC functional activity in the context of stress-related mood disorders. Several lines of evidence suggest that enhanced activity of parvalbumin (PV) expressing GABA-ergic interneurons (IN) in the PFC might play a crucial role in chronic stress related pathologies. These studies test the ability of PV IN inhibition during chronic variable stress (CVS) to rescue chronic stress associated phenotypes in male mice. PV-cre C57/Bl6 mice were bilaterally injected with Cre-inducible AAV2 (hM4Di) designer receptors exclusively activated by designer drugs (DREADDs) or control virus into the infralimbic (IL) PFC. The first stressor in the CVS paradigm was a tail suspension test (TST) to determine effects of acute PV IN inhibition on stress coping. Animals then underwent 2 weeks of CVS, during which PV INs were inhibited prior to each stressor exposure. Acute PV IN inhibition reduced struggling behavior and increased in immobility in the TST. Following CVS, coping strategy was measured in the forced swim test (FST), followed by collection of brain for assessment of Fos expression in the IL and IL targets. Our results indicate that chronic inhibition of PV IN during stress increases active and reduces passive coping behaviors in FST. Furthermore, PV IN inhibition

during CVS prevents stress mediated adrenal hypertrophy and Fos activation in key limbic regions after FST (prelimbic cortex, basolateral amygdala and ventrolateral periaqueductal gray). Our results indicate that inhibition of PV activity in the mPFC can prevent some of the chronic stress mediated phenotypes suggesting an important role of PV neurons in driving stress pathologies. Our results also show differential actions of PV INs in acute vs chronic stress conditions. Together, our results highlight modulation of PV IN activity in the IL PFC as a possible therapeutic target in preventing chronic stress related neuropsychiatric illnesses.

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Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.06/P8

Topic: F.04. Stress and the Brain

Support: 071611

Title: Acute stress transiently regulates DUSP6 in murine hippocampal neurons

Authors: *E. CRAIG[1], K. NICHOLSON[1], W. NG[1], N. J. MACLUSKY[2];
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Abstract: Physiological stress modulates neuronal growth, differentiation and survival in the hippocampus. Stress released glucocorticoids (GCs) induce shrinkage of dendrites in the hippocampus, and rapidly inhibit the ability of estradiol (E_2) to induce increases in spine density. The mechanism underlying GC potency remains unknown. One possible explanation is that GCs interfere with extracellular signal-regulated kinases 1 and 2 (ERK 1/2), potentially through modulation of the ERK 1/2 specific regulator dual-specificity phosphatase 6 (DUSP6). Long term stress and the development of depression is associated with DUSP6 downregulation in a sex-specific manner (Labonte et al Nat Med, 23 (2017) 1102-1111). Given the fine tuning involved in ERK 1/2 phosphorylation and signaling, we sought to determine the effects of acute GC exposure on DUSP6. Immortalized hippocampal neurons derived from a female murine embryo (mHippoE-14; Gingerich et al Neuroscience, 170 (2010) 54-66) were allowed to grow to 60-80% confluency and subsequently transferred to medium containing 1% charcoal stripped fetal bovine serum for 18 hours. Cells were treated with 10 nM of the synthetic glucocorticoid dexamethasone or vehicle control and collected 1, 10, or 24 hours afterwards. DUSP6 protein levels were assessed through western blotting. Significant change was detected between treatment groups [n=4, two-way ANOVA; $F(3,24)=3.375$, $p=0.0349$], without significant differences between DUSP6 isoforms [$F(1,24)=1.081$, $p=0.3089$] or a significant interaction

effect between the treatment and isoform factors [F(3,24)=0.05406, p=0.9830]. Cells exposed to dexamethasone for 1 hour had elevated DUSP6 levels compared to the vehicle control, suggesting rapid activation of DUSP6 in response to acute stress. DUSP6 levels also appear to be sensitive to medium and confluency conditions in this model. Our findings, combined with those previous reported by Labonte et al. (2017), suggest biphasic regulation of DUSP6 levels in response to dexamethasone. Understanding the effects of stress hormones on DUSP6 regulation may enhance our understanding of how stress contributes to neurological disease.
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Poster

588. Stress-Modulated Pathways

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Program #/Poster #: 588.07/P9

Topic: F.04. Stress and the Brain

Support: NIH R01MH106568

Title: Chemogenetic inhibition of the infralimbic division of the medial prefrontal cortex blocks acquisition of social familiarity-induced anxiolysis (SoFiA)

Authors: *A. R. BURKE[1], S. MAJUMDAR[2], A. R. ABREU[2], E. A. LUNGWITZ[2], A. DIETRICH[1], K. D. ANDREWS[2], W. A. TRUITT[1];
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Abstract: Familiar social support attenuates anxiety and facilitates the success of exposure-based therapy for anxiety disorders. The neural circuitry underlying this effect, termed social familiarity-induced anxiolysis (SoFiA), remains elusive. SoFiA is modeled in rats by employing the social interaction habituation (SI-hab) protocol. Using SI-hab protocol it has been determined that SoFiA represents social safety learning, which requires both anxiogenic stimulus and social familiarity during training sessions (5-6 daily social interaction sessions), and SoFiA expression is dependent on infralimbic cortex (IL). Here, the neural mechanisms underlying acquisition of SoFiA are investigated. Inactivation of the IL with bilateral infusions of muscimol (90 pmol) 10 min prior to the SI test blocked the acquisition of SoFIA. Next, we targeted glutamatergic neurons in the IL using chemogenetics. The designer receptors exclusively activated by designer drugs (DREADDs) virus, pAAV5-CAMKIIa-hM4D(Gi)-mCherry, was infused into the IL 6 weeks prior to SI testing. Clozapine-n-oxide (CNO) or vehicle was injected (0.5 mg/kg, ip.) to stimulate the hM4D inhibitory receptor 30 mins prior to each SI test. While vehicle treated rats acquired SoFiA, defined as a sustained significant increase in SI compared to the first SI-hab session (when the SI partner rat was novel), CNO treated rats continued to show low SI times

indicative of an anxiogenic response. These CNO treated rats, continued with the SI-hab protocol for 5 more days except they were given vehicle injections in place of CNO. These rats gradually acquired SoFiA. Social interaction times of fifth vehicle SI session were significantly greater than the first vehicle SI session. Thus, inhibition of IL neurons not only blocks SoFiA expression, but also blocks safety learning such that when the inhibition is lifted, rats acquire SoFiA at the same rate as naïve rats. Experiments to determine the input to the IL that are pivotal for SoFiA acquisition are on going. Overall, learning to associate the familiar partner with a signal of safety requires activity of glutamatergic neurons in the IL, implicating the IL in the acquisition of SoFiA.

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Poster

588. Stress-Modulated Pathways

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Program #/Poster #: 588.08/P10

Topic: F.04. Stress and the Brain

Support: Z01 ES100221

Title: Role of mineralocorticoid receptors in the development of hippocampal area CA2 and in CA2- dependent behavior

Authors: *K. E. MCCANN, D. J. LUSTBERG, E. K. SHAUGHNESSY, K. E. CARSTENS, S. FARRIS, G. M. ALEXANDER, S. M. DUDEK;
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Abstract: In the brain, glucocorticoid (GR) and mineralocorticoid (MR) receptors mediate behavioral and physiological responses to stress. In the adult hippocampus, the distribution of GRs and MRs is subregion-specific, with the highest MR:GR mRNA ratio found in area CA2 in mice ($F(3,8)=40.51$, $p<0.0001$) and in humans ($F(3,20)=21.39$, $p<0.0001$). In mice, CA2 pyramidal neurons have a distinct molecular makeup resulting in a plasticity-resistant phenotype that distinguishes them from cells in CA1 and CA3. Thus, we asked whether MRs regulate CA2 neuron properties and related behaviors. Using three conditional knockout methods at different stages of development, we found a striking decrease in all tested CA2 markers. This effect was mimicked by chronic antagonism of MRs. Furthermore, embryonic deletion of MRs also enabled synaptic potentiation of the normally LTP-resistant synaptic currents in CA2 and disrupted inputs into the hippocampus from the supramammillary nucleus (SuM). Specifically, we found that staining for VGLUT2, an axon terminal marker that labels SuM inputs, was significantly reduced in CA2 of cre-positive mice, and that a neuronal tracer injected into the SuM did not

travel to CA2 to the same degree as seen in cre-negative mice. We also found that CA2-targeted MR knockout was sufficient to similarly disrupt behaviors as observed with whole brain MR deletion. MR knockout mice exhibited normal social investigation behavior; however, these mice failed to discriminate between a familiar and a novel conspecific. In addition, MR knockout mice showed hyper-reactivity in response to novel objects. Finally, we tested the mice for anxiety-like behavior in an elevated plus maze and found that mice with a CA2-targeted deletion of MRs spent more time in the open arms of the maze, suggesting an anxiolytic-like behavioral phenotype. Together, these results demonstrate a novel role for MRs in regulating CA2's molecular profile and provide insight into their role in regulating CA2-related behavior.

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Poster

588. Stress-Modulated Pathways

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Program #/Poster #: 588.09/P11

Topic: F.04. Stress and the Brain

Support: NIH Grant R00 HL122454

Title: Activation of infralimbic cortical glutamate neurons reduces cardiovascular and endocrine stress reactivity

Authors: *B. MYERS, D. SCHAEUBLE, T. WALLACE, S. A. PACE, A. J. CHICCO; Biomed. Sci., Colorado State Univ., Fort Collins, CO

Abstract: Stress, a real or perceived threat to homeostasis or well-being, has a considerable role in the pathogenesis of mood and anxiety disorders. Moreover, prolonged stress and mood disorders are significant risk factors for numerous cardiometabolic conditions that further burden health-related quality of life. The neurobiological mechanisms of stress-related health detriments remain elusive; however, we have identified a specific population of glutamate neurons in the infralimbic cortex (IL) that regulate multiple aspects of stress responding. To test the hypothesis that IL glutamate neurons reduce stress reactivity and prevent the cardiovascular consequences of chronic stress, we used optogenetics to stimulate these cells while investigating physiological stress responses. Additionally, we investigated whether increased IL neuronal activity mitigates chronic stress-induced changes in cardiac function. These hypotheses were addressed in two experiments in which male rats received intra-IL injections of adeno-associated virus containing a construct coding for the light-sensitive cation channel, channelrhodopsin-2, or a control construct expressing yellow fluorescent protein. Both constructs were expressed under the calcium/calmodulin-dependent protein kinase IIα promoter, permitting the activation of IL

glutamate neurons. In the first experiment, animals were exposed to restraint stress to measure stress-evoked plasma glucose and corticosteroid levels. For the second experiment, after rats were instrumented for optogenetics, electrocardiography-enabled radiotelemeters were implanted to examine cardiovascular stress reactivity and cardiac autonomic balance during novel environment exposure. Additionally, these animals underwent echocardiographic assessment of cardiac function during IL optic stimulation, both before and after chronic variable stress. Our results indicated that activation of IL glutamate neurons reduced endocrine stress reactivity. IL activation also decreased novel environment stress-induced effects on heart rate, arterial pressure, and sympathovagal balance. Moreover, chronic variable stress increased left ventricular fractional shortening, consistent with a chronic elevation of sympathetic tone driving cardiac contractility and load; however, this effect was prevented by IL optical stimulation. Collectively, these studies highlight IL cortical neurons as a critical component of the neural network(s) integrating physiological responses to stress. These findings also provide a neurobiological mechanism for the relationship between stress and cardiovascular health outcomes.

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Poster

588. Stress-Modulated Pathways

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Topic: F.04. Stress and the Brain

Support: EMBO ALTF 89-2016
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FCT - POCI - 01-0145-FEDER-007038

Title: Cell type specific impact of chronic stress in striatum neurons

Authors: *D. RODRIGUES, N. SOUSA, P. MONTEIRO;
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Abstract: In today's society, people are constantly challenged to a high level of performance, competition and perfection. As consequence of modernization, this increasing pressure in modern society leads to an insidious increase in chronic stress, which can trigger mental illnesses, such as anxiety spectrum disorders, depression and post-traumatic stress disorder, for which current therapeutic approaches are insufficient. Given the impact of chronic stress on

mental well-being, the brain alterations associated with chronic stress are being intensively studied. However, the specific neuronal circuits affected by chronic stress continue to unravel. Evidence shows that chronic stress induces atrophy of dorsomedial striatum (DMS), a brain region essential for cognitive performance and decision making. Besides the morphological alterations, nothing is known about the functional impact and the specific neuronal cell types that are affected by chronic stress within this brain region. Using bacterial artificial chromosome (BAC) transgenic mice expressing the modified DsRed fluorescence protein, tdTomato, under the control of parvalbumin (PV) promotor or D1 dopamine receptor promoter, and the fluorescence reporter protein EGFP under the control of D2 dopamine receptor promotor, we investigated the functional impact of chronic stress at cell-type specific level. Mice were subjected to a well-established protocol of chronic unpredictable stress which consists in exposing the animals once a day to one of three stressors: forced swimming, restraint and social defeat. After 21 days, whole-cell patch clamp recordings were performed from D1-MSNs, D2-MSNs and PV interneurons located in DMS. Looking at these cell populations in chronic stressed mice, we have now found that stress leads to cell type specific changes. Our electrophysiology data, together with optomanipulations, demonstrate for the first time the functional impact of chronic stress in specific neuronal populations.

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Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

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Topic: F.04. Stress and the Brain

Support: Department of Navy, Office of Naval Research Multidisciplinary University Research Initiative (MURI) Award, Award number N00014-15-1-2809.

Title: Prebiotics, commensal probiotics and modulation of stress responsive neurocircuitry

Authors: R. S. THOMPSON[1,3], S. HOPKINS[2], M. GAFFNEY[2], T. KELLEY[2], T. R. JOUARD[2], F. VARGAS[4], A. GONZALEZ[4], M. VITATERNA[6], F. TUREK[6], C. A. LOWRY[2,3], P. C. DORRESTEIN[4,7], R. KNIGHT[4,5], K. P. WRIGHT, Jr.[2], ***M. FLESHNER**[2,3];
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Abstract: Commensal gut bacteria and their metabolites can impact host physiology and complex brain function. There is growing interest in discovering ways to optimize health-promoting microbial ecology and metabolic signatures. **Prebiotics are substrates that are selectively utilized by host microorganisms conferring health benefits.** Galactooligosaccharide (GOS) and polydextrose (PDX) are FDA-approved prebiotics that produce favorable changes in the gut microbiome/metabolome and promote a stress robust phenotype. Organisms that are stress robust can endure more intense and prolonged stressors before suffering negative health consequences. We have previously reported that GOS/PDX prevents the effect of uncontrollable tail shock on learned helplessness behavior (LH) and dorsal raphe-prefrontal cortex circuitry responsible for LH. It remains unknown, however, if stress robustness produced by GOS+PDX will also modulate impacts of social defeat (SD) on brain and behavior. Juvenile male rats (10/group) ate GOS+PDX enriched diet or nutrient/calorically matched control diet, and were implanted with biotelemetry devices to record *in vivo*, undisturbed EEG and core body temperature (CBT). Fecal samples were collected for microbiome (16SrRNA, metagenomics shotgun, qPCR, selective culture) and metabolite analyses (liquid chromatography, mass spectrometry). After 6 weeks, rats were either exposed to no stress or SD using the colony-intruder model. Using *in situ* hybridization, changes in serotonin receptors ($5HT1_A$, $5HT2_C$) and c-fos gene expression were assessed in stress-responsive regions of the brain. Rats ingesting GOS+PDX, compared to control diet, have divergent fecal microbiome/metabolome beta diversity and increased abundance of a consortium of probiotic microbes. GOS+PDX prevented SD-induced decreases in dorsal raphe (DRN) $5HT1_A$ receptors, decreased SD-induced increases in DRN c-fos, increased SD-induced c-fos in PFC and had no effect on 5HT2C. SD had little impact on EEG and/or CBT. Unexpectedly, however, CBT and sleep EEG diurnal rhythmicity were disrupted every day of rat handling, regardless of SD or GOS+PDX. Based on these findings and recent evidence that ingestion of GOS+PDX activates nucleus tractus solitarius (vagal afferent termination site) and prefrontal cortex (stress modulatory site), we hypothesize that metabolites released from gut microbes fueled by GOS+PDX, signal the brain via vagal afferents and modulate neural circuitry responsive to IS and SD in ways relevant to changes in behavior.

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Poster

588. Stress-Modulated Pathways

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

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Topic: F.04. Stress and the Brain

Support: NIH Grant R00 HL122454

Title: Infralimbic cortex glutamate output is necessary for the neural and behavioral consequences of chronic stress

Authors: *S. A. PACE[1], C. CHRISTENSEN[1], M. SCHACKMUTH[1], T. WALLACE[1], J. M. MCKLVEEN[2], W. BEISCHEL[3], R. MORANO[4], J. SCHEIMANN[4], S. WILSON[5], J. P. HERMAN[4], B. MYERS[1];
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Abstract: Exposure to prolonged stress is a major risk-factor for psychiatric disorders such as anxiety and major depressive disorder (MDD). Human imaging studies have identified structural and functional abnormalities in the prefrontal cortex of MDD patients, particularly Brodmann's area 25 (BA25). Further, deep brain stimulation of BA25 successfully reduces symptoms of treatment-resistant depression. The rat homolog of BA25 is the infralimbic cortex (IL) which is critical for cognitive appraisal, stress reactivity, and mood. Previous studies indicate that the IL undergoes stress-induced changes of excitatory/inhibitory balance culminating in reduced activity of glutamate output neurons. However, the regulatory role of IL glutamate output in mood-related behaviors after chronic variable stress (CVS) is unknown. Here, we utilized a lentiviral-packaged small-interfering RNA to reduce translation of vesicular glutamate transporter 1 (vGluT1-siRNA), thereby constraining IL glutamate output. After confirming the efficacy of our viral approach, we examined the interaction of CVS and reduced IL glutamate output using behavioral assays examining coping, anxiety-like behavior, associative learning, and nociception in adult male rats. IL glutamate knockdown decreased immobility during the forced swim test compared to GFP controls, both in rats exposed to CVS as well as rats without previous stress exposure. Further, vGlut1-siRNA prevented CVS-induced reductions in exploratory behavior with no significant changes in associative learning or nociception. Next, we performed a quantitative anatomical analysis of cells expressing the stable immediate-early gene product ΔFosB, which accumulates in response to repeated neural activation. Through assessment of ΔFosB-expressing neurons across the frontal lobe, we mapped regions altered by chronic stress and determined the coordinating role of the IL in frontal cortical plasticity. Specifically, CVS-exposed rats had increased density of ΔFosB-expressing cells in the IL and decreased density in the anterior insula. The later effect was dependent on IL glutamate output. Further analysis identified ΔFosB-expressing cells as exclusively co-expressing the pyramidal cell marker calcium-calmodulin dependent protein kinase IIα. Ultimately, this study identifies the necessity of IL glutamatergic output for regulating frontal cortical neural activity and behavior following chronic stress. These findings also highlight how disruption of excitatory/inhibitory balance within specific frontal cortical cell populations may impact neurobehavioral adaptation and lead to stress-related disorders.

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Poster

588. Stress-Modulated Pathways

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Topic: F.04. Stress and the Brain

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Title: The role of hemispheric lateralization on the mPFC-VTA pathway on stress resilience

Authors: *R. KAMALETDINOVA[1], M. SHANLEY[2], A. ONOICHENCO[1], R. KARIM[1], A. K. FRIEDMAN[1];
[1]Hunter College, City Univ. of New York, New York, NY; [2]The Grad. Center, City Univ. of New York, New York, NY

Abstract: Social stress is a powerful environmental factor that induces changes in brain circuitry. Individuals exhibit varying degrees of susceptibility to environmental stressors, a phenomenon which is also found in genetically identical mouse model (C57-BL/6J). Previous work has demonstrated that following stress, susceptible mice exhibit a decreased firing in ventral tegmental area (VTA) dopamine neurons that project to the medial prefrontal cortex (mPFC) as compared to stress resilient mice. However, the role of the mPFC neuronal feedback to the VTA in this context is unclear. Dynamics of mPFC neurons is highly heterogeneous and may depend on their long-range projection targets. We hypothesize that the mPFC pyramidal neurons projecting to the VTA have may have distinct cortical hemispheric roles in mediating the behavioral stress response, and that these interactions change as the result of stress exposure. Previous studies have shown that repetitive transcranial magnetic stimulation (rTMS) had a positive effect on people's mood when administered on the right prefrontal cortex, but not the left prefrontal cortex. Similarly, lateralization of optogenetic stimulation of the mPFC in mice has been shown to have opposing effects on susceptibility and resilience to social stress. To determine lateralization of the mPFC-VTA specific projection, we utilized a dual intracranial infusion strategy of two different color retrograde bead tracers into the contralateral and ipsilateral VTA. This retrograde tracer is taken up into the axons of the mPFC neurons that project to the VTA and transported into the cell bodies of the mPFC. Utilizing confocal microscopy, we have visualized the two different color retrograde tracers and have confirmed our injection site in the VTA. We found that mPFC neurons project to both ipsilateral and contralateral VTA, with the confocal visualization of both color beads in both two cortical hemispheres. We then quantified mPFC-VTA neurons to determine if there is a quantitative difference between the two hemispheres. Further, projection specific electrophysiological characterization of the lateralization of these mPFC neurons will inform our understanding of the

mechanisms of stress response, with the predication that increased plasticity of this pathway may confer resilience.

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Poster

588. Stress-Modulated Pathways

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Topic: F.04. Stress and the Brain

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Title: Digging deeper into the molecular effects of acute stress on mouse hippocampus

Authors: *A. FLORIOU-SERVOU[1], L. VON ZIEGLER[1], R. R. DAS GUPTA[2], O. STURMAN[1], H.-Y. LIN[1], H. U. ZEILHOFER[2], J. BOHACEK[1];
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Abstract: The hippocampus is a brain region implicated in memory, spatial navigation and emotion regulation, and it is particularly sensitive to the impact of stress. However, dorsal (dHC) and ventral hippocampus (vHC) vary dramatically in terms of molecular composition, connectivity and function. We previously showed that both regions respond very differently to acute stress on a transcriptomic and proteomic level. Here, we extend these analyses in three ways: 1) Since transcriptional changes are down-stream of fast acting phosphorylation cascades we investigate whether changes in protein phosphorylation can be observed immediately after acute stress. 2) Since the molecular consequences of stress unfold over time, we chase the transcriptomic stress response in dorsal and ventral hippocampus across time using RNA-sequencing. 3) To gain cell-type specificity, we employ BAC-TRAP technology to capture actively translated mRNA from inhibitory interneurons in dorsal and ventral hippocampus after stress.

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Poster

588. Stress-Modulated Pathways

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Topic: F.04. Stress and the Brain

Support: CONACyT 238313
CONACyT 221092

Title: Chronic exposure to environmental noise differentially affects the newborn phenotypes in male rat brain

Authors: *F. CRUZ MENDOZA[1], D. FERNÁNDEZ-QUEZADA[2], S. LUQUIN[2], F. PAJARITO[2], Y. RUVALCABA-DELGADILLO[2], F. JAUREGUI[2];
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Abstract: Environmental noise has been described as an environmental stressor that can activate HPA axis and affect the central nervous system. Regulation of neurogenesis and differentiation has been reported to be linked to stress response. Then, environmental stressors may affect the cell fate of newborn cells, which might differentiate to neurons or glial cells. The newborn cells in adult mammals has been shown to remain mainly in two zones, the sub-ventricular zone (SVZ) and the dentate gyrus of hippocampus (DG), but there is also reports showing cytogenesis in other regions of the brain. Then, we hypothesized that environmental noise is capable to affect neurogenesis and gliogenesis in the central nervous system (SNC). We used a model of environmental noise adapted to the rat's audiogram that included traffic, airplane and machine noise. We exposed adult male wistar rats for 21 days to this model and then realized immunohistochemistry to identify proliferation (BrdU+ cells); and differentiation of these newborn cells (BrdU+/NeuN+ BrdU+/GFAP+). We found differential effects that were dependent on the examined region (DG vs SVZ) and the examined phenotype (neurons vs glia). We concluded that environmental noise, besides the well-known effects on auditory organs, might affect central nervous processes indispensable for brain regeneration and plasticity.

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Poster

588. Stress-Modulated Pathways

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Topic: F.04. Stress and the Brain

Support: CONACyT 238313
CONACyT 221092

Title: Chronic exposure to environmental noise promote changes in dendritic arborization of male rat cortex and limbic system

Authors: *D. FERNÁNDEZ-QUEZADA, S. LUQUIN, A. GARCÍA-ZAMUDIO, Y. RUVALCABA-DELGADILLO, F. JAUREGUI-HUERTA;
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Abstract: Noise is an inarticulate auditive stimulus that threats health in different ways. Environmental Noise (EN) is one of the most important pollutant factors affecting cognition and mood. It is also an environmental stressor that consistently activates the HPA axis. Stress-like effects could in turn promote structural and/or functional changes in neurons. Dendritic arborization has been shown to be a hallmark of neuron plasticity. Then, measuring spine changes could evidence regional changes associated to environmental noise exposure. Here, we exposed a group of rats to environmental noise and assessed the effects of these exposure on the dendritic morphology of neurons belonging to cortical and limbic regions. We employed a rats' audiogram-fitted adaptation to mimic noisy environments and presented the noisy stimuli during 21 days. We examined neuronal dendritic morphology following the protocol of FD Rapid Golgi-Stain kit (FD NeuroTechnologies; PK401). Rats were decapitated and brains were cut with a thickness of 200 μm. Images from the distal dendrites in the hippocampus, amygdala, habenula, thalamus, hypothalamus, and auditory areas were captured with a Leica DMi8 microscope. Dendritic analysis was made using Image J, Neuronstudio, and Bonfire program. Data obtained evidenced that exposed rats diminished the length, number and branching pattern of dendrites compared with the control group. Changes were differentially evident in neurons from limbic and cortical structures. Then, our data suggest that environmental noise may elicit potent stress-like effects that change the pattern of organization of neuron dendrites belonging to regions crucial for individual adaptation.

Disclosures: D. Fernández-Quezada: None. **S. Luquin:** None. **A. García-Zamudio:** None. **Y. Ruvalcaba-Delgadillo:** None. **F. Jauregui-Huerta:** None.

Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.17/P19

Topic: F.04. Stress and the Brain

Support: National Science Foundation Graduate Research Fellowship Program (DGE-1311230)
The College, Liberal Arts and Sciences

Title: The effect of chronic stress and a post-stress rest period on the hippocampal GABAergic neurons

Authors: J. B. ORTIZ[1,2], J. M. NEWBERN[3], ***C. D. CONRAD**[2];
[1]Child Hlth., Univ. of Arizona Col. Med., Phoenix, AZ; [2]Psychology, [3]Sch. Life Sci., Arizona State Univ., Tempe, AZ

Abstract: Chronic stress leads to deficits in hippocampal mediated cognition and a retraction of hippocampal CA3 dendrites, which improve when chronic stress ends and a post-stress rest period is given. Past work found that chronic stress altered the expression of genes associated with subtypes of hippocampal inhibitory neurons, such as somatostatin (SOM) and calretinin (CR). But, whether a post-stress rest period impacts these inhibitory neuron subtypes is unknown. Moreover, some studies report that chronic stress decreases hippocampal inhibitory neuron number, while other reports fail to find effects. We utilized a transgenic mouse model that contained an indelible marker for GABAergic neurons throughout the brain to determine whether chronic stress and a post-stress rest period altered the total number of GABAergic neurons and/or the expression of different neurochemical markers for various GABAergic cell types. Mice carrying a vesicular GABA transporter (VGAT) promoter-driven Cre recombinase (VGAT:Cre$^{+/-}$) were crossed with a Cre-dependent tdTomato reporter mouse line (Ai9$^{+/+}$). *VGAT:Cre Ai9* offspring exhibit expression of the red fluorescent protein, tdTomato in all GABAergic neurons. At 3 months of age, mice were chronically stressed in wire mesh restrainers for 6h/d/21d (Str) or not (Con), and then allowed a 21d post-stress rest period (Str-Rest) or not (Str-Imm). Following the last day of the stress paradigm, mice were perfused and brains were collected and prepared for immunohistochemistry. Epifluorescent microscope images of the hippocampus were collected and the total number of tdTomato expressing GABAergic neurons and the number of SOM and CR positive neurons were quantified. Chronic stress or a post-stress rest period had no statistically significant effect on the total number of hippocampal GABAergic cells, nor did they alter the number of SOM+ neurons. Chronic stress and a post-stress rest period significantly altered CR+ interneurons. Chronic stress reduced the number of CR+ neurons in the CA3 region of the hippocampus, with marginal effects in the CA1

and DG region. This stress-induced decrease returned to levels of non-stressed controls following a rest period. These results demonstrate that the total GABAergic number does not change in response to chronic stress or the weeks following the end of chronic stress and point to CR+ as being a potential new lead to understand mechanisms facilitating the previous reported spatial memory improvements that occur in the weeks following the end of chronic stress.

Disclosures: **J.B. Ortiz:** None. **J.M. Newbern:** None. **C.D. Conrad:** None.

Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.18/P20

Topic: F.04. Stress and the Brain

Support: Military Operational Medicine Research Program

Title: Comparative effects of diverse acute stressors on dendritic spines in the male rat amygdala, hippocampus, and prefrontal cortex

Authors: ***J. A. ABETTAN**[1], R. SHANSKY[2], N. L. MOORE[3], K. CRAVEDI[4], M. MAY[5], I. JEONG[6];
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Abstract: PTSD is a highly prevalent and complex psychiatric disorder that develops after exposure to a traumatic event. Rodent stress models have been extremely helpful in studying both the pathophysiology and circuitry implicated in this debilitating disease. In particular, lasting structural changes in the hippocampus, amygdala, and prefrontal cortex can occur after traumatic stress, but whether these changes are dependent on the type of stress itself is not known. Here, we examined the effects of two separate rodent stress models: underwater trauma (UWT) and acute predator exposure (APE) on dendritic morphology in three stress-sensitive regions. We performed iontophoretic microinjections of fluorescent dye into neurons in the basolateral amygdala (BLA), medial prefrontal cortex (mPFC) and ventral hippocampus (vHPC) in both stress and control animals. Raw Z-stack images of dendritic segments were acquired via confocal microscopy, and deconvolved prior to analysis for spine number and shape (thin or mushroom). This study will provide insight into the structural plasticity of these relevant regions with regards to traumatic stress, including whether different forms of trauma induce discrete patterns of plasticity.

Disclosures: **J.A. Abettan:** None. **R. Shansky:** None. **N.L. Moore:** None. **K. Cravedi:** None. **M. May:** None. **I. Jeong:** None.

Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.19/P21

Topic: F.04. Stress and the Brain

Support: NIH Grant HD091376
NIH Grant ES028202
NIH Grant HD097093
NIH Grant MH104184
NIH Grant MH108286

Title: Pubertal stress reprograms inhibitory tone in the PVN at genetic and electrophysiological levels

Authors: *K. E. MORRISON[1], A. B. COLE[2], P. J. KANE[1], S. M. THOMPSON[3], T. L. BALE[4];
[2]BRB-5-017, [1]Univ. of Maryland Sch. of Med., Baltimore, MD; [4]Pharmacol., [3]Univ. of Maryland Baltimore, Baltimore, MD

Abstract: Adverse childhood experiences, specifically during the pubertal transition, are one of the greatest predictors for affective disorder presentation for women. 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 depends on hormonal status. Our previous work has shown that pubertal stress enacts lasting reprogramming in the transcriptome of the paraventricular nucleus of the hypothalamus (PVN), where corticotropin-releasing factor (CRF) neurons are a critical node in the stress response pathway. To determine whether the transcriptional reprogramming is driven by changes in chromatin accessibility, we utilized ATAC-Seq to interrogate which genes are available for transcription. Female mice exposed to chronic stress from postnatal day 21-34 were sacrificed in adulthood, either as virgins or in late pregnancy. We found that pubertal stress resulted in significant differences in open peaks in the PVN of pregnant females. Genes aligned to the significantly different open peaks clustered into biological pathways related to how cells respond to input at the synapse. These findings suggest both that there is an enduring programmatic event in the chromatin underlying the transcriptomic findings and that there should be a functional consequence of the altered transcriptome. We have previous evidence that the rise in allopregnanolone in pregnancy interacts with the GABA system to unmask the

dysregulated stress response. Using whole-cell voltage-clamp, we recorded spontaneous inhibitory postsynaptic currents (sIPSCs) from CRF neurons in the PVN of pubertally stressed or control virgin and pregnant mice. Consistent with the sequencing results, we found that only in pregnant, pubertally stressed females did CRF neurons have an elevated sIPSC frequency. These studies support the conclusion that pubertal stress results in lasting changes to the chromatin that are associated with functional changes in CRF cells in the PVN. As the PVN sequencing was performed on all cell types, these cell-specific electrophysiological findings suggest that reprogramming of the peri-PVN GABA may be responsible for the phenotype. The underlying causes of peripartum affective dysfunction are complex, and these studies provide evidence that pubertal adversity is an important factor in determining how women will respond to pregnancy and to hormone-based therapies aimed at treating affective symptoms.

Disclosures: K.E. Morrison: None. **A.B. Cole:** None. **P.J. Kane:** None. **S.M. Thompson:** None. **T.L. Bale:** None.

Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.20/P22

Topic: F.04. Stress and the Brain

Support: 1R01DA039533

Title: Kappa opioid regulation of lateral habenula neurons and response to early life stress

Authors: *S. C. SIMMONS, R. D. SHEPHERD, S. GOUTY, R. HAMMACK, L. LANGLOIS, B. M. COX, F. S. NUGENT;
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Abstract: The lateral habenula (LHb) is an epithalamic brain region associated with value-based decision making and stress evasion through its modulation of dopamine-mediated reward circuitry. Specifically, increased activity of the LHb is associated with drug addiction, schizophrenia and stress-related disorders such as depression, anxiety and PTSD. Previously, we have shown that maternal deprivation (MD), a severe early life stress, increases LHb intrinsic excitability while blunting LHb neuronal response to central corticotropin releasing factor (CRF) signaling suggesting an MD-induced dysregulation of the LHb. Kappa opioid receptor (KOR) signaling is an additional mediator of stress response in reward circuitry and also mediates part of central CRF stress response. Surprisingly, there has been little study of direct KOR regulation of the LHb despite its distinct role in stress, reward and aversion processing. Here, we show that maternal deprivation significantly increases immunolabeled dynorphin(DYN) fibers (endogenous KOR agonist) in LHb. Consistent with a possible MD-induced hypertrophy of

DYN signaling, we also found a significant decrease in mRNA levels of KORs in LHb tissues from MD rats compared to those from control animals. To elucidate the functional role of a DYN-KOR signaling in the LHb, we utilized ex-vivo electrophysiology combined with pharmacological tools in rat LHb slices. We found that even under non-stress control conditions, tonic KOR stimulation may contribute to basal LHb neuronal excitability which can be uncovered using KOR antagonist, norBNI. Additionally, we show that KOR agonists (U50,488, and dynorphin) have distinct effects on LHb neuronal excitability through changes in passive and active membrane properties based on the presence of an Ih current in neurons. Specifically, KOR stimulation increases neuronal excitability in LHb neurons with large Ih currents (Ih+) while decreases neuronal excitability in Ih negative (Ih-) neurons. Additionally, KOR activation alters both glutamatergic and GABAergic synaptic transmission onto LHb neurons assessed through mEPSC and mIPSC recordings. To our knowledge this is the first demonstration of existence of the DYN-KOR signaling in the LHb that can be modulated in response to severe early life stressors such as MD.

Disclosures: S.C. Simmons: None. **R.D. Shepherd:** None. **S. Gouty:** None. **R. Hammack:** None. **L. Langlois:** None. **B.M. Cox:** None. **F.S. Nugent:** None.

Poster

588. Stress-Modulated Pathways

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.21/P23

Topic: F.04. Stress and the Brain

Support: NIH grant R00 HL122454
College of Veterinary Medicine and Biomedical Sciences Research Council

Title: Prefrontal cortical modulation and encoding of motivation, social behavior, and stress responding

Authors: *T. WALLACE, D. SCHAEUBLE, S. A. PACE, B. MYERS;
Biomed. Sci., Colorado State Univ., Fort Collins, CO

Abstract: Brodmann's Area 25 (BA25) of the medial prefrontal cortex has a pivotal role in depression. Specifically, patients experiencing depression display altered metabolic activity in BA25; further, electrical stimulation of BA25 ameliorates symptoms in patients with treatment-resistant depression. The rat BA25 homologous region, infralimbic cortex (IL), is responsive to stress in models of depression and has been implicated in aspects of social behavior. The IL is thought to regulate behavior through glutamatergic projections to a variety of limbic and forebrain structures. However, the precise neural mechanisms through which the IL may integrate motivational, social, and hedonic behaviors remain to be determined. In the current

study, we hypothesized that IL glutamatergic neural output regulates depression-relevant behaviors and that chronic stress exposure may disrupt the activity of IL projection neurons, potentially accounting for reduced motivation and sociability. To address this hypothesis, we first sought to determine how increasing IL activity may modulate affective valence and sociability. In brief, adult male rats received bilateral injections of an adeno-associated virus (AAV) in the IL to express the light-sensitive cation channel, channelrhodopsin-2 (ChR2), specifically in glutamatergic projection neurons. Following an incubation period for ChR2 expression, a fiber optic cannula was implanted into the IL to permit light delivery. In the real-time place preference assay, rats displayed a preference for optic stimulation, demonstrating IL activity has a positive motivational valence. In a 3-chambered social behavior assay, IL stimulation increased social motivation compared to YFP controls, indicating IL glutamate neurons promote sociability. In a second study, we utilized fiber photometry to monitor IL neural activity during depression-relevant behaviors. For these experiments, an AAV was injected in the IL to express the genetically-encoded calcium-indicator GCaMP6s in glutamatergic neurons, followed by fiber optic cannula implantation. Rats were then exposed to social stimuli, restraint stress, and chocolate. Analysis of GCaMP fluorescence indicated that IL glutamate neurons encode social interaction, stress responding, and hedonic food reward. Ongoing studies aim to determine how chronic variable stress exposure may alter IL activity to disrupt appropriate encoding of social, stressful, and hedonic stimuli. Taken together, our data indicate that the IL is a critical node for modulating social behavior and mood, as well as encoding depression-relevant stimuli.

Disclosures: **T. Wallace:** None. **D. Schaeuble:** None. **S.A. Pace:** None. **B. Myers:** None.

Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.22/P24

Topic: F.04. Stress and the Brain

Support: NIH Grant R01MH111751
CHOP Postdoctoral Fellowship for Academic Diversity

Title: Corticotropin-releasing factor administration into locus coeruleus affects theta activity in medial prefrontal and orbitofrontal cortex differentially in female and male rats

Authors: *S. BATES[1], J. ARNER[1], A. L. CURTIS[2], S. BHATNAGAR[3];
[1]Children's Hosp. of Philadelphia, Philadelphia, PA; [2]Dept Anesthesiol., Children's Hosp. Philadelphia, Philadelphia, PA; [3]Dept Anesthesiol., Univ. Pennsylvania, Children's Hosp Philadelphia, Philadelphia, PA

Abstract: The locus coeruleus (LC) is part of a stress responsive system that is involved in arousal and cognitive function. This is accomplished through extensive projections to many regions, including the prefrontal cortex (PFC). The PFC is comprised of regions with distinct functions. Among these regions are the medial PFC (mPFC) and the orbitofrontal cortex (OFC). The reciprocal connection between the LC and the PFC has been shown to underlie the role of arousal in cognition. Additionally, this circuit is disrupted following chronic stress, and is thought to underlie impairment in executive function that arises during stress. Previous work in the lab has shown that the LC is activated by corticotropin-releasing factor (CRF) that is released during stress. This study examined the effects of CRF administered into the LC of adult male and female rats on mPFC and OFC network activity, measured as local field potentials (LFPs). Network activity was recorded in awake animals in the mPFC and OFC for 30 minutes before and after intra-LC infusion of aCSF, 2ng of CRF, or 20ng of CRF in adult male and female Sprague-Dawley rats. Our data show that 20ng of CRF increases high theta (7-9 Hz) activity in the mPFC in female, but not male animals. This dose did not induce any significant effects in the OFC. Conversely, 20ng of CRF decreased low theta (4-6 Hz) activity in the mPFC and OFC selectively in males. The 2ng dose of CRF did not produce any significant effects in either brain region in males or females. Theta activity in the PFC has been associated with improved working memory and attention to environmental cues. Therefore, these data suggest that a high dose of CRF may increase attention to the environment in females. These data are consistent with sex differences in the ability of CRF to alter LC activity, and provide new evidence that this alteration may affect downstream cortical regions. In ongoing studies, we are analyzing coherence between mPFC and OFC in animals that received intra-LC CRF. Additionally, we are examining if activating LC with CRF has behavioral and cognitive ramifications.

Disclosures: **S. Bates:** None. **J. Arner:** None. **A.L. Curtis:** None. **S. Bhatnagar:** None.

Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.23/P25

Topic: F.04. Stress and the Brain

Title: Differential effects of ten-days of stress on BDNF-TrkB signaling in the hippocampus and prefrontal cortex

Authors: *A. MOGUL[1], E. TAYLOR-YEREMEEVA[2], A. KHAN[3], S. ROBINSON[2], H.-Y. WANG[3];
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Abstract: Brain-derived neurotrophic factor (BDNF) signaling through its cognate receptor, tropomyosin receptor kinase B (TrkB), is critical for optimal neuronal function and is altered in neurodegenerative conditions and depression. TrkB is expressed in the nervous system and immune cells, influencing cell development, maturation and survival. In the hippocampus (HC) and prefrontal cortex (PFC), TrkB signaling regulates long term potentiation (LTP) and learning in part through interaction and activation of *N*-methyl-d-aspartate receptors (NMDARs). NMDAR activity through TrkB signaling increases mRNA expression and protein levels of the immediate early gene, activity regulated cytoskeletal protein (Arc). Arc is a regulator of synaptic plasticity, heavily influencing learning and cognition.Reduced TrkB signaling contributes to defective synaptic plasticity and cognition observed in depression and dementia associated with Parkinson's and Alzheimer's diseases. Correspondingly, treatments, such as exercise and transcranial stimulation, that reduce disease symptoms also restore TrkB signaling. These disorders involve an amalgamation of different causes, making it difficult to identify a specific process or experience that may be responsible for TrkB signaling abnormalities. Because stress is a risk factor for neurodegenerative disorders, anxiety and depression, stress may be one of the causal factors that shape TrkB signaling. Data showing that Arc mRNA is disrupted by stress or cortisol treatment supports the view that reduced BDNF-TrkB and TrkB-NMDAR interactions may be involved. BDNF-TrkB signaling and TrkB-NMDAR coupling, however, have not been studied in the context of stress. To test whether stress effects these signaling pathways, we subjected rats to two different stress induction paradigms: five stressors in one day or two stressors every day for ten days. We then assessed basal and BDNF-stimulated TrkB signaling cascades, TrkB-NMDAR coupling and BDNF-induced Arc expression in the HC and PFC.Our results show that in both the HC and PFC, ten-day stress elevated basal Arc but decreased BDNF-induced Arc protein expression relative to non-stressed controls. In the HC, both stress groups had diminished BDNF-TrkB signaling and TrkB-NMDAR coupling. Like the HC, in the PFC, one day of stress reduced BDNF-TrkB and TrkB-NMDAR signaling, however ten days of stress reduced BDNF-TrkB signaling but *strengthened* TrkB-NMDAR coupling. These data indicate differential regulation of stress on TrkB signaling between the HC and PFC. The data may suggest a previously unknown early signaling alteration that could lead to sustained brain function changes.

Disclosures: A. Mogul: None. **E. Taylor-Yeremeeva:** None. **A. Khan:** None. **S. Robinson:** None. **H. Wang:** None.

Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.24/P26

Topic: F.04. Stress and the Brain

Support: NIH Grant K08 MH109735
Hope for Depression Research Foundation

Title: Acute restraint stress reorganizes VTA-NAc communication and affects reward processing

Authors: *D. C. LOWES[1], E. S. HOLT[1], L. YUSUFOVA[1], Z. H. BRETTON[1], A. FIRDOUS[1], J. A. GORDON[2], A. Z. HARRIS[1];
[1]Columbia Univ., New York, NY; [2]Office of the Director, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Acute stress has been shown to inhibit reward-seeking and VTA reward activity. However, the mechanism through which acute stress impacts the VTA-NAc circuit is unclear. To determine the effect of acute stress on the VTA-NAc circuit, we simultaneously recorded single unit and local field potential (LFP) activity in the VTA and LFP activity in the NAc of mice during restraint. We found that restraint induces a low-frequency oscillation in the NAc. Lag analysis of VTA multi-unit activity revealed that VTA activity precedes this oscillation, and pharmacological inhibition of the VTA with muscimol prevents this oscillation. We used optogenetic inhibition to dissect which neuronal subtypes within the VTA contribute to this stress-induced oscillation. Conversely, we were able to use optogenetic stimulation of the VTA to recapitulate this long-range oscillation in the NAc. Moreover, stimulating at this frequency produced reward processing deficits similar to those observed after restraint stress. These data suggest that altered VTA-NAc communication may be the mechanism through which acute stress impairs reward processing.

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Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.25/P27

Topic: F.04. Stress and the Brain

Support: EY13079
F31 MH112372
NYU Research Challenge Fund
NYU Dean’s Dissertation Fellowship

Title: Medial prefrontal cortex-mediated control of food restriction-evoked hyperactivity differs for the pathway projecting to dorsal striatum versus dorsal raphe versus an all-inclusive corticofugal pathway

Authors: *A. N. SANTIAGO, S. GEORGE, I. HANDA, C. AOKI;
New York Univ., New York, NY

Abstract: Anorexia Nervosa (AN), defined by compulsive food restriction (FR) and excessive exercise, has the highest mortality rate of all neuropsychiatric illnesses. A mouse model, termed activity-based anorexia (ABA), restricts food availability to the first 2hrs of the dark phase (2FA) of adolescent mice with wheel access. This evokes voluntary FR during 2FA and a paradoxical FR-evoked hyperactivity (FREH), measured as wheel running, especially during the light-phase hrs preceding 2FA, termed food anticipatory activity (FAA). These behaviors precipitate rapid and potentially lethal weight loss as compared to FR without wheel access. As in AN, the extent of mouse FREH correlates with anxiety-like behavior. AN patients and ABA rodents both exhibit reduced cognitive flexibility, which requires the prefrontal cortex (PFC). FAA requires D1 receptor activity in dorsal striatum (DS). PFC-to-dorsal raphe (DR) activity is associated both with increased escape behavior and reduced food consumption. We therefore hypothesized that medial (m)PFC circuits drive maladaptive wheel running, with mPFC-DS activity controlling FAA and mPFC-DR activity controlling 2FA activity.
We tested this hypothesis with two DREADDs (Designer Receptors Exclusively Activated by Designer Drugs): hM3D(Gq), which activates cell firing upon binding to C21, and KORD, which suppresses cell firing upon binding to Salvinorin B (SalB). We used a CAMKII promotor to express both DREADDs in mPFC pyramidal cells (Part 1). We then used cre-conditional DREADD virus to test how activation vs suppression specifically of the mPFC-DS pathway (part 2) and mPFC-DR pathway (part 3) alter FREH.
Upon target of the mPFC-DS pathway, we observed an increase in FREH upon C21 activation and a decrease upon SalB suppression, specifically during the FAA hrs with no effect during the 2FA period. These effects were not recapitulated during the same hrs once mice recovered from ABA, or by general mPFC pyramidal cell activation or suppression. We will also present correlations with measures of cFos activity and results from the mPFC-DR pathway activation and suppression.
These findings reveal that mPFC provides flexible modulation of FR stress-induced escape behavior through differential recruitment of mPFC pathways, during 2FA, which demands making the decision to eat vs run and during FAA, which demands making the decision to forage vs conserve energy.

Disclosures: A.N. Santiago: None. **S. George:** None. **I. Handa:** None. **C. Aoki:** None.

Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.26/P28

Topic: F.04. Stress and the Brain

Support: NIH R01MH111751 to S. Bhatnagar

Title: Social stress alters locus coeruleus and medial prefrontal cortex network activity and coherence in adult and adolescent female rats

Authors: *J. ARNER[1], A. L. CURTIS[1], M. BATES[1], H. GUAJARDO[1], R. J. VALENTINO[2], S. BHATNAGAR[1,3];
[1]Children's Hosp. of Philadelphia, Philadelphia, PA; [2]Natl. Inst. on Drug Abuse, Washington, DC; [3]Univ. of Pennsylvania Perelman Sch. of Med., Philadelphia, PA

Abstract: Incidences of stress-related psychiatric disorders tend to be higher in women as compared to men. This may be related to sexual dimorphism in network activity of brain regions that are related to stress. The locus coeruleus (LC) is a component of a stress-responsive system that is involved in arousal and cognitive function. This is accomplished through extensive projections to many regions, including the medial prefrontal cortex (mPFC). Previously, we identified age-specific responses in stress-induced LC activity in socially-defeated male rats (Zitnik et al., 2016). The present study was conducted in adolescent and adult female rats and examined the effects of social stress using the resident-intruder model (30 minutes per day) on LC and mPFC activity in awake animals. Single-unit and local field network activity were recorded in LC and mPFC before and during the 1st and 5th exposure to resident-intruder stress. Although basal LC single-unit activity was higher in adolescent than adult females prior to the 1st defeat, we found that neither group exhibited a significant change in single-unit activity as a result of the initial stressor. By the 5th defeat, LC single-unit activity during stress was increased in both adolescent and adult females. With regards to network activity, social stress decreased the power of low theta (4-6 Hz) LC activity in both ages on days 1 and 5. In the mPFC, there were no effects of the 1st exposure to social defeat. However, there was increased network activity in the mPFC within low theta during the 5th defeat in adults, but not in adolescents. In LC-mPFC coherence, stress produced similar changes in coherence in both ages on days 1 and 5 with reductions in coherence within the low theta range. In addition, on day 5, adolescents showed increased coherence in the beta (12-20 Hz) and gamma (20-40 Hz) frequency ranges, whereas the adults showed no change. In conclusion, we observed both LC single-unit and network activity as well as LC-mPFC coherence that was largely similar between adolescent and adult female rats as a result of stress. The similarity across age suggests that adolescent females are exhibiting adult-like activity in this circuit. These findings help to improve our understanding of the basis of sex differences relevant to stress-related psychiatric disorders.

Disclosures: J. Arner: None. **A.L. Curtis:** None. **M. Bates:** None. **H. Guajardo:** None. **R.J. Valentino:** None. **S. Bhatnagar:** None.

Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.27/P29

Topic: F.04. Stress and the Brain

Title: Association between chemotherapy induced brain structural alterations and cognitive performance in breast cancer patients revealed by GQI

Authors: *W. CHUANG[1], J.-C. WENG[1,3], V.-H. CHEN[3,2], Y.-H. TSAI[4];
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Abstract: Breast cancer (BC) is the most common cancer and the second leading cause of cancer-related mortality in women worldwide. Approximately 11 to 35% of BC patient had cognitive impairment before treatment that may result from post-traumatic stress disorder (PTSD). In addition, chemotherapy is a widely-used treatment in BC, however, chemotherapy can induce cognitive impairment and emotional disturbance, and the change of brain is termed chemo brain. In this study, we tried to use generalized q-sampling imaging (GQI) to investigate the alteration of white matter structure, and aimed to detect the association between the GQI indices and neuropsychological scales, including Patient Health Questionnaire-9 (PHQ9) and anxiety of Hospital Anxiety and Depression Scale (HADS).
The study included 45 women with a history of BC but did not receive any treatment and 62 women who had completed their chemotherapy less than 12 months. All subjects were acquired by 3T MRI (Verio, Siemens). We used FSL (FMRIB Software) for eddy current correction, and normalized all diffusion images of participants with SPM (statistical parameter mapping). The GQI indices, including generalized fractional anisotropy (GFA) and normalized quantitative anisotropy (NQA), were calculated using DSI Studio. The multiple regression analysis was performed to obtain the relationship between the GQI indices and neuropsychological scales. Age and education year were used as covariates.
The result of multiple regression analysis with p-value less than 0.01 showed that the GQI indices of BC patient before treatment were significant negative correlated with the neuropsychological scales (i.e., PHQ9 and HADS-anxiety) in the regions of left posterior thalamic radiation, left superior longitudinal fasciculus, left anterior cingulate gyrus, left precuneus, and left temporal gyrus. The GQI indices of BC patient after chemotherapy were highly negatively correlated with the neuropsychological scales in the region of left precentral gyrus, left superior temporal gyrus, left inferior parietal gyrus, right postcentral gyrus, and right middle frontal gyrus. It indicated that people with higher depression and anxiety score had higher demyelination, which is probably due to PTSD or chemotherapy. In conclusion, our GQI study

discovered that breast cancer patients have an association between brain structure alterations and cognitive performance due to PTSD or chemotherapy.

Disclosures: **W. Chuang:** None. **J. Weng:** None. **V. Chen:** None. **Y. Tsai:** None.

Poster

588. Stress-Modulated Pathways

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 588.28/P30

Topic: F.04. Stress and the Brain

Title: The effect of aging and ancestral stress on T2 relaxation values in the hippocampus

Authors: ***L. S. TRUICA**[1], M. AMBESKOVIC[2], J. K. MCCREARY[3], G. A. METZ[4]; [1]Canadian Ctr. For Behavioral Neurosci., Lethbridge, AB, Canada; [2]Canadian Ctr. for Behavioural Neurosci., Univ. of Lethbridge, Lethbrigde, AB, Canada; [3]Neurosci., Univ. of Lethbridge, Lethbridge, AB, Canada; [4]Univ. Lethbridge, Lethbridge, AB, Canada

Abstract: Introduction: Adverse environments early in life reprogram brain development and behaviour with lifelong consequences. Specifically stress during pregnancy may lead to permanent morphological alterations in the offspring brain and subsequent generations. However, little is known about the effects of generational stress on the aging brain. Here, for the first time we investigate brain tissue age-related changes in the ancestral stress animal model and its implications using MRI structural and T_2 -relaxometry model. Methods: F4 generation Long-Evans male offspring were derived from a rat lineage in which their parental mothers (F0-F3) were stressed during pregnancy. A non-stress lineage served as control. To generate mutigenerationally stressed (MPS) group three consecutive generations were stressed, and only great-great grandmothers were stressed to generate transgenerationally (TPS) stress group. Adult (6 month), middle aged (12 months) and aged (18 months) offspring were imaged longitudinally using a 4.7 T Oxford magnet (Oxford, UK). Structural and T_2 relaxometry measurements was used for quantification. A region of interest (ROI) based analysis was performed for all groups and mean values were extracted from the T_2 maps with Image J (NIH, USA). Central slice HPC was used for the analysis, where ROIs corresponding to both HPC hemispheres were drawn and their average was obtained. T_2 values were calculated using Marquardt-Levenberg fitting routines from software written in our lab in IDL (ITT, USA). All images were co-registered. Quantitative Mean Grey Value (MGV) analysis was also performed on structural images corresponding to a same size ROI. Results: Aging exhibited a decrease in both MGV and T_2 value in all groups across the lifespan. Ancestral stress exacerbated aging associated decrease in MGV and T2 values with most profound reduction from young to middle age. The reduction in T_2 relaxation may arise from an increase in neuropil, such as larger dendritic complexity to compensate for the neuronal loss. These findings indicate that ancestral stress may compromise

neuronal integrity which could lead to neurodegeneration and accelerated aging. Discussion: Our study showed that ancestral stress affects the biological aging processes of the brain and our results suggest that this neuronal remodeling and possible compensation may be occurring not only in the hippocampus, but also in other brain areas as stress accumulates across generations and with aging. Taken as a whole, T2 relaxometry offers a valuable insight into the neuro-morphological changes induced by aging and stress.

Disclosures: L.S. Truica: None. **M. Ambeskovic:** None. **J.K. McCreary:** None. **G.A. Metz:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.01/DP09/P31

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: Natural Sciences and Engineering Council of Canada
Canadian Foundation for Innovation
Desjardins Foundation - Doctoral Scholarship

Title: Evaluating blood brain barrier contribution to cortical extracellular glucose and lactate fluctuations during motor behaviour

Authors: *A. BELAND, C. MESSIER;
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Abstract: The relative contribution of glucose and lactate to neuroenergetics is a controversial topic. Despite this controversy, there is much evidence demonstrating the brains ability to take up and use a variety of blood-borne metabolites to meet its energetic needs. Therefore, we aimed to examine the role of metabolite availability as well as the role of BBB metabolite transport in sustaining extracellular cortical levels of glucose and lactate. The mice were subjected to glucose transporter 1 (GLUT1; WZB117) and monocarboxylate transporter 1 (MCT1; AZD3965) inhibition. Following this inhibition of the two most common transporters found on the BBB barrier, the mice received an injection of either glucose, lactate, fructose or beta-hydroxybutyrate. The mice were subjected to motor behaviors that typically elicit a rise in extracellular lactate and a decrease in extracellular glucose. Inhibition of individual transporters attended the extracellular glucose and lactate decoupling as well as decreased grip strength. Combined inhibition, however, exaggerated the observed decoupling, suggesting a large

upregulation of BBB transporters. These results will be compared to observed changes in cortical endothall levels of GLUT1 and MCT1.

Disclosures: A. Beland: None. **C. Messier:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.02/P32

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NMSS Grant RG150704951
NIH Grant R01AG029523

Title: Baseline brain oxygen metabolism predicts fatigue in multiple sclerosis

Authors: *K. L. WEST[1], D. SIVAKOLUNDU[2], M. D. ZUPPICHINI[1], G. B. MARUTHY[1], H. LU[3], D. T. OKUDA[4], B. RYPMA[1];
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Abstract: Fatigue is one of the most prevalent and debilitating symptoms in Multiple Sclerosis. While fatigue is thought to result from auto-immune pathogenesis, there are currently no objective techniques capable of monitoring fatigue non-invasively. Global cerebral metabolic rate of oxygen ($CMRO_2$), a measure of oxygen metabolism throughout the brain, reflects cellular activity at rest. If fatigue indeed reflects ongoing auto-immune activity, we postulate that $CMRO_2$ should also reflect this, however the relationship between $CMRO_2$ and fatigue remains unknown. Assessing relationships between $CMRO_2$ and fatigue could provide new insights into the pathophysiology of fatigue in MS and indicate a clinically-feasible biomarker.
We performed a cross-sectional study comparing 34 RRMS MSP and 14 age- and sex-matched healthy controls (HC). All MRI scans were conducted on a Philips 3T MRI system with a 32-channel head coil. T_2-Relaxation-Under-Spin-Tagging (TRUST) was acquired to assess venous oxygenation (Y_v). Phase contrast (PC) MRI was acquired to estimate whole-brain cerebral blood flow (CBF). Using Yv and CBF from the superior sagittal sinus, baseline global $CMRO_2$ was calculated. T_2-FLAIR was used to assess RRMS lesion volume. High resolution MPRAGE was acquired for co-registration and atrophy estimates. Participants also underwent neuropsychological evaluation including Modified Faitigue Index Scales (MFIS) and patients were split by MFIS <38 (non-fatigued MSP; n=18) and MFIS>38 (fatigued MSP; n=17). Associations were assessed using Pearson correlations ($p<0.05$).
Global baseline $CMRO_2$ correlated with MFIS score in MSP ($R= 0.43$, $p=0.01$) but not in HC

(R=-0.23, p=0.46). Further, $CMRO_2$ and MFIS correlated strongly in fatigued MSP (R=0.59, p=0.02) but not in non-fatigued MSP (R=0.15, p=0.567). Hierarchical regression was performed to determine if the addition of $CMRO_2$ improved the prediction of fatigue in MSP. The addition of $CMRO_2$ to the prediction of MFIS after age, gender, education, and atrophy led to a significant increase in R^2 of 0.137 (F(1,27)=5.626, p=0.025). This result supports the hypothesis that $CMRO_2$ reflects on-going sub-clinical disease activity leading to fatigue in MSP. These simple, brief (eg, 90sec) resting scans used to measure $CMRO_2$ could provide a clinically meaningful biomarker of fatigue for better monitoring and treatment in MS.

Disclosures: K.L. West: None. **D. Sivakolundu:** None. **M.D. Zuppichini:** None. **G.B. Maruthy:** None. **H. Lu:** None. **D.T. Okuda:** 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.; Biogen. F. Consulting Fees (e.g., advisory boards); Celgene, EMD Serono, Genentech, Genzyme, and Novartis. **B. Rypma:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.03/P33

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Developmental changes in [2,4-$^{13}C_2$] beta-hydroxybutyrate and [1-^{13}C] glucose metabolism in rat brain

Authors: *K. SAKOGAWA, T. KANAMATSU;
Dept. of Envrn. Engin. for Symbiosis, Grad. Sch. of Engin., Soka Univ., Hachioji, Tokyo, Japan

Abstract: Glucose is the primary energy substrate for the adult brain. However, under conditions of starvation, diabetes, and hypoglycemia, lactate and ketone bodies such as beta-hydroxybutyrate (BHB) and acetoacetate support cerebral metabolism in the adult brain. It is also well known that monocarboxylic acid is the cerebral fuel for the immature brain of newborns under normal physiological conditions. The purpose of this study was to investigate the developmental changes in BHB metabolism when compared with that of glucose metabolism in the rat brain. Wistar rat pups, in day 1-, 4-, 8-, 12-, 16-, 20-, 22-, 24-, and 26-days old (the day of birth was day 0), were given an intraperitoneal bolus injection of [2,4-$^{13}C_2$]-BHB or [1-^{13}C]-glucose (0.5 g/kg-body weight, both 99% ^{13}C enriched). After 30 min, the pups were decapitated, and the blood was collected and the forebrain dissected, weighed, and frozen. Frozen tissue was ground with 75% ethanol (10:1 vol/wt) followed by extraction of amino acid fractions using a water saturated chloroform. Supernatants were clarified by centrifugation, lyophilized, and resuspended in 600 µL of a deuterium oxide containing 3-trimethylsilyl propionate (TSP) as the

external standard. Samples were subjected to proton decoupled ^{13}C-NMR spectroscopic measurement. The total amount of ^{13}C spectra intensity calculated by integrating the peaks of Glu, Gln, Asp, and GABA obtained by ^{13}C NMR spectra by measuring relative intensity for TSP. The total ^{13}C-signal intensity in Glu, Gln, Asp and GABA (total signal intensity of ^{13}C) derived from [2,4-$^{13}C_2$]-BHB increased with progressive development (from age, 1-day to 20-days), and then decreased at 26-days old. However, total signal intensity of ^{13}C derived from [1-^{13}C]-glucose weakend from 1-day to 16-days, and then sharply increased when the pups were 26-days old. In terms of the ^{13}C labeling ratio of C3 to C4 in Glu, which means the ratio of the second turn of the TCA cycle to the first turn of the TCA cycle, both BHB and glucose content increased till the pups were 20-days old, thereafter (in 26-days old pups), there was no change. These data may indicate that BHB is the preferred substrate for energy source over glucose in the brain during the early postnatal period and that the metabolic switch between the utilization of BHB and glucose in the rat brain occurs when the pups are exists 20-days old. It may be suggested that this switching is induced by stabilization of the TCA cycle.

Disclosures: K. Sakogawa: None. **T. Kanamatsu:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

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Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH Grant DK1186111
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Madalene & George Shetler Diabetes Research Award from Miami University
Ohio University Institutional Fund

Title: Innervation is required for apolipoprotein A-IV-induced fatty acid uptake by adipose tissues

Authors: *C. C. LO[1], H. SHI[2], Q. ZHU[2], J. WENG[1], M. SHEN[2];
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Abstract: Apolipoprotein A-IV (ApoA-IV) synthesized by the small intestine in the presence of dietary lipids regulates lipid metabolism. ApoA-IV, a well-known satiating protein, acts on vagal afferent nerves to suppress food intake. We hypothesized that ApoA-IV increased fatty acid (FA) uptake by adipose tissues via the nervous system. After 3 weeks feeding of either a low-fat diet (LFD) or a high-fat diet (HFD), mice with unilateral denervation of brown adipose tissue (BAT) received intraperitoneal administration of recombinant Apo A-IV protein and intravenous

infusion of lipid mixture with radioactive triolein. Both denervated and intact BAT were exposed to the same circulating factors, whereas the denervated BAT did not receive neural signals as their contralateral intact BAT. In LFD-fed mice, ApoA-IV administration increased FA uptake by the intact BAT. In contrast, ApoA-IV failed to elevate FA uptake by the contralateral denervated BAT. ApoA-IV had no effect on FA uptake by epididymal or inguinal white adipose tissue (EWAT and IWAT, respectively). In HFD-fed mice, ApoA-IV elevated FA uptake by EWAT, but not BAT or IWAT. The immunoblots showed that ApoA-IV increased expression of lipoprotein lipase (LPL) and tyrosine hydroxylase in both intact BAT and IWAT of the LFD-fed mice. In HFD-fed mice, ApoA-IV only elevated LPL in intact BAT. Thus, the observations suggest that ApoA-IV is dependent on intact neural signal to upregulate LPL in BAT and subsequently increase FA uptake by BAT.

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Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.05/P35

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: CONACyT Grant 257549

Title: Hypothyroidism modifies the expression of insulin, GLUT4, aromatase and estrogen receptors in pancreas of female rabbits

Authors: *J. RODRIGUEZ CASTELAN[1,2], C. ACEVES[1], F. CASTELÁN[4], E. CUEVAS-ROMERO[3];
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Abstract: Hypothyroidism promotes pancreatitis, insulitis, failure of β cells and insulin resistance. For its part, estrogens regulate the β cells differentiation and insulin secretion. Although there is a link between thyroid hormones and estrogens, any study has been done to analyze the impact of hypothyroidism on the estrogen receptors (ER) and local synthesis of estrogens in the pancreas. This study was aimed to analyze the impact of hypothyroidism on insulin, GLUT4, aromatase and ER (α and β), as well as GPR30 expression in islet cells of the pancreas of female rabbits. Twelve Chinchilla-breed virgin female rabbits were divided into control (n=6) and hypothyroid (n=6; methimazole 10 mg/kg for 30 days). Insulin

immunohistochemistry was used for analyzed histological characteristics of islets. Expression of insulin, GLUT4, aromatase and ERs were determined by western blot. Hypothyroidism increased the number of small and extra small islets. It also increased the expression of insulin and GLUT4, but decreased the expression of aromatase. The expression of ERα was increased, while ERβ, and GPR30 were decreased in the hypothyroid group. Interesting, hypothyroidism seems to promote the formation of new islets. These results describe for first time the impact of hypothyroidism on the expression of insulin and GLUT 4, and on the actions of estrogens in the pancreatic islet cells. Our results may be important to understand the link reported between hypothyroidism and diabetes, particularly in women.

Disclosures: J. Rodriguez castelan: None. **C. Aceves:** None. **F. Castelán:** None. **E. Cuevas-Romero:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.06/P36

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: ANR-17-CE14-0007 (BABrain)
E.G.I.D., ANR-10-LABX-46
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Title: The bile acid receptor FXR: A new actor of the brain control of energy homeostasis

Authors: *K. BANTUBUNGI[1], B. DECKMYN[2], D. DOMENGER[2], S. DUCASTEL[2], E. NICOLAS[2], E. DORCHIES[2], E. CARON[3], J. CHARTON[4], E. VALLEZ[2], B. DEPREZ[4], J.-S. ANNICOTTE[5], S. LESTAVEL[2], A. TAILLEUX[2], C. MAGNAN[6], B. STAELS[2];
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Abstract: The Farnesoid X receptor (FXR) is a bile acid receptor belonging to the nuclear receptor superfamily of ligand-regulated transcription factors. FXR has been described to be highly expressed in the liver and intestine, where it regulates the expression of target genes to control bile acid, glucose and lipid metabolisms. While FXR has been reported to be expressed in brain, its central function remains unknown. Here, we specifically found that FXR is expressed in neurons of the arcuate nucleus of the hypothalamus, suggesting a role in the brain control of energy homeostasis. In line, sub-chronic intracerebroventricular (ICV) administration of the synthetic FXR agonist GW4064, performed in C57Bl6/J chow-fed lean mice, induced a significant decrease of energy expenditure and enhanced food efficiency along with an increased

body weight gain, suggesting a positive energy balance. Interestingly, these changes elicited by the ICV injection of the FXR agonist were associated with a decrease of Uncoupling Protein 1 (*Ucp1*) and an enlargement of adipocytes in brown adipose tissue as well as to the inability of the latter to respond to the peripheral administration of the β3 agonist CL316243. These effects were linked to a decreased TH expression in afferent BAT adrenergic neurons and a reduced activity of the sympathetic nervous system upon ICV treatment with GW4064. Effects of ICV FXR agonist were found to arise from changes in PKA-CREB signaling and TH expression in the hypothalamus and to be FXR-dependent since effects of GW4064 were found to be lost in FXR-KO animals. These findings identify a new function of brain FXR and shed new light on the complex control of energy homeostasis by bile acids through this nuclear receptor.

Disclosures: K. Bantubungi: None. **B. Deckmyn:** None. **D. Domenger:** None. **S. Ducastel:** None. **E. Nicolas:** None. **E. Dorchies:** None. **E. Caron:** None. **J. Charton:** None. **E. Vallez:** None. **B. Deprez:** None. **J. Annicotte:** None. **S. Lestavel:** None. **A. Tailleux:** None. **C. Magnan:** None. **B. Staels:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.07/P37

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: AHA SDG
Loyola University Chicago

Title: C2 domain protein involved in MC4R trafficking and hypothalamic control of energy balance

Authors: *C. K. GAVINI, T. COOK, D. RADEMACHER, V. MANSUY-AUBERT;
Cell and Mol. Physiol., Loyola Univ. Chicago, Maywood, IL

Abstract: Rates of overweight and obesity epidemic have risen significantly in the past few decades, and 34% of adults and 15-20% of children and adolescents in the United States are now obese. Melanocortin receptor 4 (MC4R), contributes to appetite control in hypothalamic neurons and is a promising target for anti-obesity treatments or drug development. While the presence of functional MC4R is crucial for normal neural control of homeostasis and is altered in obesity and in presence of lipids, the mechanisms underlying altered MC4R trafficking are unknown. Our studies identified a novel C2-domain protein, C2CD5 that appears to contribute to the regulation of MC4R trafficking. We found that 1) the expression of C2CD5 is decreased in diet-induced obesity models compared to controls, 2) C2CD5 knock-out mice exhibit pronounced obesity partially due to an increase in food intake compared to control mice when fed a high-fat diet, 3)

C2CD5 colocalize and interacts with MC4R complex, 4) loss of functional C2CD5 alters MC4R endocytosis, and, 5) C2CD5 knock-out mice exhibit decreased acute responses to Melanotan-II injection into the paraventricular hypothalamus. Based on these, we hypothesize that hypothalamic C2CD5 is a MC4R trafficking protein that responds to metabolic cues and is involved in neural control of energy balance. These studies provide evidence for a novel pathway and targets, to develop therapeutic drugs potentially to rescue energy balance defects that contribute to the development and maintenance of obesity.

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Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

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Program #/Poster #: 589.08/P38

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH Grant HL084207
NIH Grant HL127673

Title: The role of lateral hypothalamic area leptin receptor circuitry in behavior and metabolism

Authors: *B. A. TOTH[1], U. SINGH[1], K. C. DAVIS[1], K. SAITO[1], D. A. MORGAN[1], K. RAHMOUNI[1,2,3,4], H. CUI[1,2,3,4];
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Abstract: While it has been known that heterogeneous groups of neurons in the lateral hypothalamic area (LHA) play a vital role in maintaining metabolic homeostasis, the mechanisms by which these neurons sense peripheral metabolic cues and carry out homeostatic behaviors affecting metabolic functions are incompletely understood. In the current study, we first characterize projections from lateral hypothalamic leptin receptor (LepR)-expressing neurons - a subset of LHA GABAergic neurons distinct from well-known orexin and MCH neurons. Using anterograde viral-mediated tract tracing we confirmed a broad innervation of these LepR-positive GABAergic neurons to the brain regions known to regulate feeding, locomotor activity, and autonomic function, including but not limited to paraventricular nucleus, arcuate nucleus of hypothalamus, ventral tegmental area, ventrolateral preoptic area, locus coeruleus, and ventrolateral medulla. To delineate the behavioral effects of these projections, using a viral-mediated Cre-LoxP system, we deleted LepR specifically from the LHA and observed that loss of LepR signaling in the LHA results in the reduction of both body weight and locomotor activity. Furthermore, we find that deletion of LepR signaling in LHA decreases

orexin expression levels, indicating that active LepR signaling in the LHA is crucial in maintaining orexin expression. These finding identify the LHA as a key site where adipocyte-derived metabolic hormone, leptin, acts to control homeostatic behaviors, likely through the modulation of orexin signaling.

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Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.09/P39

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Differential regulation of glucose metabolism in the cerebrospinal fluid and peripheral circulation in wild-type mice

Authors: *T. NAKAJIMA[1], S. TAKEDA[2], A. OYAMA[1], Y. ITO[2], Y. TAKAMI[1], Y. TAKEYA[1], K. SUGIMOTO[1], K. YAMAMOTO[1], H. RAKUGI[1], R. MORISHITA[2]; [1]Dept. of Geriatric and Gen. Med., [2]Dept. of Clin. Gene Therapy, Grad. Sch. of Medicine, Osaka Univ., Suita-city, Japan

Abstract: Recent investigations have demonstrated that diabetes can be a risk factor for Alzheimer's disease. Abnormalities of cerebral glucose metabolism are indicated in the mechanism of pathologic interaction between Alzheimer’s disease and diabetes mellitus. We previously reported that decreased insulin concentration and insulin sensitivity in the brain underly the exacerbated cognitive impairment in the mouse model of diabetic Alzheimer’s disease (PNAS 2010). However, little is known about the dynamic interaction between peripheral and central glucose metabolisms. Here we assessed temporal changes in glucose levels of cerebrospinal fluid and blood using a unique method to collect cerebrospinal fluid in free-behaving mice. We also analyzed the relationship between steady-state glucose levels in blood and cerebrospinal fluid in patients with cognitive impairment. An intraperitoneal glucose tolerance test (2 g/kg) was performed in 3-month-old male C57BL/6 mice. Cerebrospinal fluid and blood glucose concentrations were measured at 30-minitue intervals. Serial collections of cerebrospinal fluid were performed via the tube fixed on the dura mater over the cisterna magna. Blood glucose levels were measured by tail-tip sampling. Cerebrospinal fluid and blood were collected from subjects with mild cognitive impairment at the same time after an overnight fast. Blood glucose levels peaked at 30 minutes after glucose loading and returned to baseline by 120 minutes. On the other hand, cerebrospinal fluid glucose levels reached a plateau within 30 minutes and were stable until 120 minutes. The cerebrospinal fluid/blood glucose ratio showed a time-dependent alteration during glucose loading test. The ratio of cerebrospinal fluid/blood

glucose levels, at steady state, was fairly consistent (0.635±0.005, mean±SEM) in subjects with cognitive impairment. We were able to measure cerebrospinal fluid glucose levels in free-behaving mice with a high-temporal resolution. The cerebrospinal fluid/blood glucose ratio was not kept constant following glucose loading in young wild-type mice, while the steady-state ratios in mice and human subjects were maintained at constant levels. These results suggest that there are distinct mechanisms regulating glucose levels in the central nervous system and peripheral circulation.

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Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

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Program #/Poster #: 589.10/P40

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NRF-2016R1D1A3B03934279
KGM4621922

Title: Pine needle extract activates POMC neurons in the hypothalamus

Authors: E. KIM[1], E. BYUN[2], D. KANG[2], S.-G. HONG[2], J. HAN[2], *D. LEE[2];
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Abstract: Prolonged excessive energy intake over the energy consumption leads to obesity which is a major cause of metabolic disease such as type 2 diabetes. The Arcuate nucleus (ARC) of the hypothalamus is the most important brain area to regulate energy balance. The ARC is a major component of the melanocortin system, a regulation center of energy balance in the hypothalamus. Two distinct neuronal types of ARC are anorexigenic POMC (Pro-opiomelanocortin) and orexigenic Neuropeptide Y/Agouti related peptide neurons. Also, the POMC neurons in the ARC are known as an energy expenditure enhancing neurons. In addition, the pine needle contains strong antioxidant polyphenols and has capability of lipolysis and improve elevated blood glucose levels by obesity. However, the role of pine needle extract (PNE) onto the hypothalamic POMC neurons remain unclear. In this study, we use hot water extracted PNE to investigate the role of PNE in regulation of energy balance via hypothalamic POMC neurons. Orally injected PNE (200 mg/kg) increases c-fos expression in the ARC and the paraventricular nucleus of the hypothalamus. Also, PNE increased 20% of c-fos expression in the hypothalamic POMC neurons as compared to control group. And, direct application of PNE

(200 μM) on the brain slice with patch clamp showed that 78% of POMC were depolarized by PNE (200 μM). Moreover, body weight and food intake were decreased by 2 weeks consecutive oral injection of PNE after 12 weeks high fat fed. Simultaneously, PNE improved blood glucose levels after high fat fed as compared to control. Overall, these findings strongly suggest that PNE plays pivotal to regulate energy balance via melanocortin system.

Disclosures: **E. Kim:** None. **E. Byun:** None. **D. Kang:** None. **S. Hong:** None. **J. Han:** None. **D. Lee:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.11/P41

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NRF-2018M3A9G1082609
HI16C1012

Title: Effects of environmental enrichment on ketone metabolism and neurite outgrowth

Authors: ***S. PYO**[1,2,3], S.-Y. SONG[3,1,4], J. YU[3,1], J. SEO[3,1], Y.-K. SHIN[3,1], S. WI[3,1], A. BAEK[5], B.-G. NAM[3,1,4], E. CHO[3,1,2], S. JO[3,2,1], J. HEO[3,4,1], J. CHOI[6], S.-R. CHO[3,1,4];
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Abstract: Environmental enrichment (EE) which contains complex combinations of various physical, cognitive, and social stimuli can induce synaptic plasticity and neurogenesis. However, the exact mechanism underlying EE-mediated changes remains unclear. Previous studies showed that physiological responses and the level of various neurotrophic factors are altered after exposure to EE. Therefore, we attempted to uncover the mechanism of EE based on ketone metabolism and BDNF signaling in various brain regions. At 6 weeks of age, CD-1 mice were randomly assigned either in EE condition or standard cages for two months. After the conditions, the mice were sacrificed and their brain regions (frontal cortex, striatum, hippocampus, and cerebellum) were extracted for molecular works. Quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR) and western blot (WB) were conducted to validate the expression of RNA and proteins associated with neurotrophic factors, G-protein regulated inducer of neurite outgrowth (GPRIN1) and ketone metabolism. The RNA expressions of enzymes associated with ketone metabolism (Monocarboxylase Transporter (MCT); MCT1, MCT2, MCT4, and Beta-hydroxybutyrate Dehydrogenase(BDH); BDH1), neurotropic factors (BDNF, Nerve Growth Factors (NGF) and Neurotrophin-3 (NT-3) were significantly increased

in EE mice compared to control mice. Moreover, the GPRIN1 expression was significantly increased in EE mice as indicated in qRT-PCR and WB analysis. In addition, GPRIN1 is colocalized with early neuronal markers (nestin, DCx, Tuj-1) but not mature neuronal marker NeuN, in the SVZ. In conclusion, the upregulation of GPRIN1 following exposure to an EE is related to neuroblast activation especially in the SVZ of adult brain The beneficial effect of EE was also shown in cognition, motor, and emotion by various behavioral tests. Altogether, the upregulation of the enzymes associated with ketone metabolism and BDNF signaling and GPRIN1 following the exposure to EE and the close interplay among beta-hydroxybutyrate, BDNF, and GPRIN1 may be responsible for the therapeutic mechanism of EE

Disclosures: **S. Pyo:** None. **S. Song:** None. **J. Yu:** None. **J. Seo:** None. **Y. Shin:** None. **S. Wi:** None. **A. Baek:** None. **B. Nam:** None. **E. Cho:** None. **S. Jo:** None. **J. Heo:** None. **J. Choi:** None. **S. Cho:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.12/P42

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Parasympathetic nervous system directly regulate hepatic glucose metabolism

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Abstract: Aim: The role of the neuronal circuity and its function between the nervous system and metabolic organs in the perspective of pathogenesis of obesity and diabetes is poorly understood. To elucidate the direct role of neurons in the DMV region through the parasympathetic nervous system on hepatic both lipid and glucose homeostasis. Method: We injected the virus expressing the hM3Dq DREADD by stereotaxic surgery targeting Dorsal Motor Nucleus of the Vagus (DMV) neurons in the Phox2b-Cre mouse brain. Targeted neurons are activated by intraperitoneal injection of chemogenetic ligand, clozapine-N-oxide (CNO). To exam the effect of neuronal activation on the regulation of liver metabolism, liver tissue is collected for gene expression study and immunohistochemistry analysis. Results: We confirm that our chemogenetic virus and mouse model is working by electrophysiology of DMV neurons showing that CNO activates the neurons. Parasympathetic nervous system and liver are anatomically innervated in not only portal vein region but also hepatocytes. To further dissect the metabolic pathways in the liver by which parasympathetic nervous system controls glucose metabolism, we analyzed gene expression of key hepatic enzymes and present the expression fold change compared to each control including Glucose 6-phosphatase (G6P) and Phosphoenolpyruvate carboxykinase 1 (PCK1). Conclusion and Discussion: In this study, we

show that the parasympathetic nervous system and liver are anatomically innervated. Chemogenetic acute activation of DMV neurons regulate hepatic gene expression indicating the brain-liver neuronal axis is regulating hepatic glucose metabolism gene expression.

Disclosures: W. Song: None. **C. Namkoong:** None. **H. Choi:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

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Program #/Poster #: 589.13/Q1

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NSF CAREER Award 1149446 (awarded to D.M.)

Title: Hyaluronan at the brain-environment interface

Authors: *D. M. THEVALINGAM[1], E. C. JENKINS[1], D. P. MCCLOSKEY[2];
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Abstract: The brain extracellular matrix is composed a diverse set of proteoglycans and lectins with Hyaluronan (HA; Hyaluronic Acid) serving as a primary scaffolding element. The size of the HA molecule can vary across tissue types and species, and recent work has reported functional differences cell signaling and metabolism depending on the size of the HA molecule. The fossorial African naked mole-rat (Heterocephalus glaber; NM-R), a mammal which is capable of tolerating extreme hypoxia and hypercapnia, has been shown to synthesize and sustain a unique high-molecular-mass variant of hyaluronan macromolecule (HMM-HA). This variant may help the NM-R better tolerate the wide environmental excursions experienced between the densely populated underground nest and the fresh air near the burrow surface. Here, we explore the functional consequences of HA size in the NM-R brain. Under acidic and neutral pH conditions, NM-R neuronal viability is enhanced in a concentration-dependent manner when a high-molecular-weight HA species is added exogenously to primary neuron cultures. In addition, analysis of Alcian blue stained paraffin-embedded sections of mouse and NM-R brain tissue illustrates characteristic differences, including unique patterning and variations in expression density, in HA distribution between the two species across multiple brain regions. Together, these findings highlight the contribution of extracellular HA in buffering the NM-R brain against dramatic metabolic shifts, and demonstrate a novel mechanism for the brain to withstand prolonged exposure to extreme environments.

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Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

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Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH grants P01DK049210
Bloomberg Distinguished Professorship.

Title: Effects of hypothalamic cAMP response element binding protein (CREB1) on energy and glucose homeostasis

Authors: *B. TAIB[1], V. FONG[1], J. WEST[1], K. KAESTNER[2], R. S. AHIMA[1];
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Abstract: Type II diabetes is characterized by fasting hyperglycemia and a prolonged increase in the blood glucose level after glucose or meal ingestion. Creb1 has been linked to diabetes through activation of hepatic gluconeogenesis, which has been suggested to be the predominant factor of the fasting hyperglycemia. Studies have also shown that Creb1 is expressed in the hypothalamus and may affect metabolism. The aim of this study is to determine whether Creb1 plays a role in the paraventricular hypothalamus (PVH), a critical integrator of energy homeostasis. Using Sim1-cre mice, we performed a targeted deletion of Creb1 in PVH to generate ($Creb1^{\Delta SIM1)}$ mice and compared them to control (lox/lox) mice. Metabolic parameters were examined in the fed, fasted or refed states or following calorie chronic restriction (CR, 50% energy deficit for 4 weeks). Body composition measured with ^{1}H-MRS was similar in both groups in the fed, fasted and refed states. However, under CR, the $Creb1^{\Delta SIM1}$ mice maintained a higher lean mass. Indirect calorimetry in a Comprehensive Laboratory Animal Monitoring System (CLAMS) revealed that the respiratory exchange ratio (RER) was lower during feeding and refeeding in $Creb1^{\Delta SIM1}$ mice compared to control mice, indicating an increase in fat oxidation. During CR, the VO_2, RER and heat production were significantly lower in $Creb1^{\Delta SIM1}$ compared to control mice. Moreover, $Creb1^{\Delta SIM1}$ mice displayed lower blood glucose levels in the fed and fasted states. Insulin was significantly reduced in fed $Creb1^{\Delta SIM1}$, and the fall in insulin in response to fasting was blunted. Our results highlight novel effects of hypothalamic Creb1 on energy and glucose homeostasis, which may represent a new therapeutic strategy to improve glycemic control in the pathogenesis of Type II diabetes.

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Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.15/Q3

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: The effect of intermittent hypoxia on body weight regulation in diet induced and genetically obese mice

Authors: *K. E. PROPSOM[1], S. N. FRAMNES[1], D. M. ARBLE[2];
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Abstract: Obstructive Sleep Apnea (OSA) is characterized by periodic breathing cessation which results in blood oxygen desaturation. These drops in blood oxygen can be mirrored in animal models using an intermittent hypoxia (IH) protocol. As OSA affects over 50% of the overweight and obese populations, it is hypothesized that IH leads to further impairment of body weight regulation. To determine if insensitivity to leptin, which occurs with obesity, can exacerbate obesity in the context of IH, we utilized lean wild type, diet-induced obese (DIO) wild type, and leptin-deficient *ob/ob* mice. All mice were exposed to 7 days of IH. Preliminary data demonstrate that IH leads to a negative energy balance in WT mice. IH does not alter the food intake of WT lean mice but reduces caloric intake in DIO mice, resulting in weight loss. Interestingly, *ob/ob* mice increase their food intake in response to IH. These results suggest that severe leptin insensitivity combined with IH may increase body weight and food intake homeostatic set points in mice. Clinically, these results help elucidate why an already overweight individual may be at a high risk for becoming obese after developing OSA.

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Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

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Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: CONACYT 284883
DGAPA 204310
CONACYT National Scholarship 273496

Title: Chronic variable stress during adolescence alters the thyroid axis response to voluntary exercise

Authors: *M. A. PARRA-MONTES DE OCA, J.-L. CHARLI, P. JOSEPH-BRAVO;
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Abstract: One of the principal regulators of energy balance is the hypothalamus-pituitary-thyroid (HPT) axis that is activated by energy demands like cold exposure and exercise, the cold-activation is inhibited by a previous stress. We have demonstrated that chronic stress at adulthood blunts HPT axis response to voluntary exercise in a sex dependent manner. Adolescence is considered as a critical development stage when synaptic limbic circuits mature, and is vulnerable to stress situations. We evaluated now the effect of chronic variable stress during adolescence of male and female rats in the response of HPT axis to voluntary exercise. Wistar male and female rats at PND 30 were divided in: a) control group (C) left undisturbed, b) another submitted to chronic variable stress (CVS) where rats received a different type of stress every day during adolescence period (up to PND-60 for females, PND-70 for males). Anxiety-like behavior was evaluated every week by open field test or elevated plus maze; CVS females showed anxious behavior after two weeks of stress and CVS males after four. At PND-74 (females) and PND-84 (males) C and CVS groups were divided in three groups, one placed in a cage with running wheel (Ex) for 14 nights, one sedentary group with food *ad libitum* (Sed), and one sedentary group which was pair-fed (PF) to the amount of food consumed by Ex group. Hormones and mRNA levels were quantified by ELISA, RIA and RT-PCR. Females ran 4x more than males; exercised diminished food intake by 13-17% in males, 30-33% in females, diminished body weight gain in PF compared to Sed of both sexes, but only females lost weight by exercise, more in CVS than C. Exercise reduced retroperitoneal fat mass in C and epididymal fat in CVS males, visceral and subcutaneous in C-females to a greater extent than males. CVS reduced *Trh* mRNA levels in hypothalamic paraventricular nucleus (PVN), without altered concentration of thyroid hormones in both sexes. Expression of *Crh* and *Avp* in PVN was diminished by CVS and diet restriction, more in females than males. *Trh* expression increased in both C and CVS female groups after exercise and TSH in the latter. *Dio2* and *Pgc1a* expression was measured in skeletal muscle (gastrocnemius), that of *Pgc1a* increased considerably by exercise only in C-males. These results suggest that CVS during adolescence affects more female rats than males, modifying the activity of HPT and HPA axis, and their response to voluntary exercise in adulthood.

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Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.17/Q5

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Glut4 expression in relationship with prenatal and postnatal sugared water consumption in rats

Authors: *V. VELÁZQUEZ-OROZCO[1], L. NICOLAS-TOLEDO[2], E. CUEVAS-ROMERO[2], A. ORTEGA-SOTO[3], F. CASTELÁN[4], J. RODRÍGUEZ-ANTOLÍN[2];
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Abstract: Kidneys achieve the elimination of toxic substances from the organism. In this process, they also have to reabsorb important molecules that include glucose. Glucose uptake can be done through up to 14 glucose transporters (GLUTs) expressed in kidneys. One member of this family is the GLUT4 that is located in a specialized tubulovesicular compartment located beneath the plasma membrane. As a response to insulin, this reservoir of GLUT4 is then available to be recruited to the cell surface to raise glucose uptake. The consumption of sugary drinks has been associated with metabolic diseases including type 2 diabetes mellitus that is linked to renal failure. The aim of our present study was to determine whether the consumption of sugared water during pregnancy and lactation alters the expression of GLUT4 in the kidney of adult male offspring. We used female rats that mated and divided in a control group fed with a standard diet and tap water, and the experimental group fed with standard diet and 5% sucrose diluted in tap water (sugared water). At weaning, the 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. Male rats were sacrificed at four months old and the expression of GLUT4 in the left kidney was analyzed. In contrast to the group that consumed plain water, we observed that consumption of sugared water caused a GLUT4 overexpression in males from mothers that consumed sugared water during pregnancy and lactation. Furthermore, the expression of GLUT4 was different renal cortex and medulla. Together, the consumption of sugared water, even in low concentration, modifies the renal expression of GLUT4. In doing this, we advanced in the knowledge of renal outcomes associated with the intake of sugary beverages.

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Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

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Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: AFOSR FA9550-18-1-00

Title: Neuronal mitochondria design principles from mouse cerebellum tomography

Authors: *R. MENDELSOHN[1], T. M. BARTOL, JR[2], C. LEE[4], G. GARCIA[5], E. LIU[3], K. BROCKMEYER[3], E. A. BUSHONG[6], S. PHAN[7], G. PERKINS[6], M. H. ELLISMAN[8], A. SKUPIN[5], T. J. SEJNOWSKI[2], P. RANGAMANI[2];
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Abstract: Understanding of neuron function at the sub-cellular level requires biochemical simulations and membrane architecture analysis, creating a need for highly accurate 3D membrane reconstruction meshes at a nano-meter scale. No structure better exemplifies this challenge than the mitochondria. Especially in the highly dynamic metabolic landscape of a neuron, mitochondria membrane architectures can provide critical insight into the unique energetics of the cell. Theoretical calculations of functional outputs like ATP and heat are often unreliable because mitochondria are represented simply as spheres or ellipsoids. In reality, the mitochondria are glaringly different from simple spheres. The secondary lipid bilayer is riddled with invaginations, known as cristae junctions, which generate complex cristae compartments that intersect the matrix. Cristae form functionally specialized morphologies which differentiate the mitochondria in different cell types, sections of the cell, and metabolic states. 3D tracings of dendritic and axonal mitochondria were constructed using a database of serial TEM tomography images from mouse cerebellum neuropil slices. Watertight meshes were created from the traces using new procedures in 3D rendering softwares (CellBlender and GAMer) in order to produce minimal distortion from the original microscopy at a scale of 1.6 nano-meter isotropic voxel size. Differential geometry methods were then used to quantify the mean and Gaussian curvatures, surface areas, volumes, and membrane motifs which can alter the metabolic output of the organelle. Some reconstructed mitochondria were found to have one continuous cristae compartment, a property that can only be identified in reconstructions. Several mitochondria reconstructions along with custom meshing details and smoothing algorithms that preserve accuracy at high curvature features are presented. This lays the foundation for future studies of the internal mitochondrial physiology and metabolism in neurons.

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Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

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Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: Intramural NIH

Title: Chronic activation leads to neuronal glycolysis

Authors: *A. KSENDZOVSKY[1], M. ALTSHULER[2], M. BACHANI[3], S. WALBRIDGE[3], J. P. STEINER[4], J. HEISS[2], J. KAPUR[5], K. A. ZAGHLOUL[6];
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Abstract: Introduction
The metabolic consequences of neuronal activation are relatively unknown. It is thought that glycolysis supports active neurons as a supplement to mitochondrial respiration in times of high metabolic demand which occurs through the astrocyte neuron lactate shuttle. Recent evidence, however, strongly refutes this claim and argues that acute neuronal stimulation directly leads to neuronal glucose utilization through glycolysis, which becomes the primary source of ATP. Furthermore, the metabolic phenotype of frequently stimulated neurons is also unknown. In this study we show that chronically stimulated neurons switch from aerobic respiration to glycolysis through the AMPK/HIF1a hypoxia pathway.
Methods
We activated neurons cultured on a multielectrode array with low Mg2+ media to probe for lactate dehydrogenase A (LDHA), a marker for glycolysis and to determine neuron's metabolic phenotype after chronic stimulation. We analyzed human tissue for LDHA expression based on electrographic characteristics of overlying subdural electrodes, as determined during intracranial monitoring (epileptic vs normal cortex). Finally, we probed the AMKP/HIF1a pathway to determine its involvement in this metabolic switch.
Results
Treatment of cultured neurons with low Mg^{2+} increased neuronal bursting activity which caused LDHA upregulation. In human tissue, LDHA expression was significantly upregulated in epileptic neurons. Neuronal bursting caused depletion of intracellular ATP and subsequent activation of the AMPK/HIF1a pathway through phosphorylation of AMPK. Furthermore, chronic activation of AMPK led to HIF1a and LDHA upregulation and a subsequent switch from an aerobic to a glycolytic cellular phenotype in neurons.

Conclusion
In this study, we show that chronic neuronal activation leads to up-regulation of LDHA and a metabolic switch from aerobic respiration to glycolysis. This metabolic reprogramming occurs through the canonical AMPK/HIF1a hypoxia pathway.

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Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.20/Q8

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Focused ultrasound treatment of murine non-alcoholic steatohepatitis

Authors: *T. S. HUERTA[1], A. DEVARAJAN[1], T. TSAAVA[1], S. S. CHAVAN[1,2,3], K. J. TRACEY[1,2,3];
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Abstract: Non-alcoholic steatohepatitis (NASH), a progressive form of non-alcoholic fatty liver disease, is closely associated with obesity, hyperlipidemia and insulin resistance. NASH involves hepatic inflammatory changes and apoptosis leading to organ injury and fibrosis, and can ultimately advance to end-stage liver disease including cirrhosis and cancer. Despite the significant burden to the public health system, there are no FDA-approved drugs that are specifically tailored for this condition. Here, we utilize a preclinical model of NASH, which is induced by diet, to study the effectiveness of high-intensity focused ultrasound (HIFU) in modulating specific hepatic neural networks and test HIFU as a therapeutic strategy. Mice were maintained on a high-fat high-carbohydrate (HFHC, 60% kcal from fat) with sugar supplemented water (55%, 45% sucrose) for 16 weeks. The control group was maintained on a low-fat diet (LFD, 10% kcal from fat). After 8 weeks on these diets, animals received daily liver-targeted HIFU or sham stimulation, and were monitored weekly for body weight change (g), blood glucose change (mg/dL) and average food intake (g/week/cage). Exposure to HIFU but not sham stimulation significantly reduced %Δ body weight (HFHC-sham: 154.4 ± 3.9% vs HFHC-stim: 137.1 ± 3.9% $p < 0.0001$) and %Δ blood glucose levels (HFHC-sham: 205.6 ± 18.2% vs HFHC-HIFU: 131.3 ± 6.8 % $p < 0.0001$) at week 16. The HFHC-HIFU group had improved performance in glucose tolerance test and reduced HOMA-IR score. In addition, HIFU attenuated circulating markers linked to metabolic dysregulation. Histological assessment of the liver via H&E staining revealed reduced steatosis and inflammation in the HFHC-HIFU group.

Together, these findings suggest that noninvasive HIFU stimulation targeting liver is a potential therapy for NASH.

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Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

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Program #/Poster #: 589.21/Q9

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Metabolic rewiring in mice with decreased mitochondrial complex I function

Authors: *T. L. EMMERZAAL[1], G. PRESTON[2], B. GRAHAM[3], R. KELLY[4], E. MORAVA[1], R. RODENBURG[5], T. L. KOZICZ[1];
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Abstract: Adaptation to adverse life events is metabolically costly competing for energy with the maintenance of normal homeostatic processes. Although the concept of energy production and consumption as a special case of system vulnerability for the brain has been intensively discussed, our understanding of the impact of abnormal energy flows affecting brain metabolism remains an unmet need. Using a genetically engineered mouse model of SMF (the Ndufs4 deficient mouse), we have previously shown that SMF influences the animals' stress response and impacts various biological domains linked to the pathobiology of depression. We report here that chronic stress causes a complete metabolic rewiring as a function of impaired mitochondrial function. To elucidate the metabolic alterations associated with chronic stress in a mouse model of SMF, and to discover novel biosignatures, we performed targeted high-performance liquid chromatography and gas chromatograph mass spectrometry. We focused on amino acids (AA) and their metabolites, acylcarnitines (AC), as well as tricarboxylic acid cycle (TCA) analytes. We found no alterations in acylcarnitines in mice with SMF whereas stress decreased medium-chain acylcarnitines. Furthermore, we found elevated alanine concentration in the brain, which is often used as a biomarker of mitochondrial dysfunction in individuals with mitochondrial disease. Besides alanine, we also found a profound rewiring of amino acid metabolism; specifically, glutamate, hydroxyproline, and serine were increased in mice with SMF, whereas arginine, cystathionine, histidine, phenylalanine, proline, and tryptophan were decreased. Altered amino acid metabolism is also often observed in other models of mitochondrial dysfunction as well as in individuals with mitochondrial disease. Chronic stress mostly further exacerbated the changes found in Ndufs4def mice, i.e., a more pronounced increase in alanine, serine, and hydroxyproline. In addition to this lysine and threonine were elevated in chronically stressed

mice. In addition to the altered AA metabolites, we found evidence for a reversed flux in the TCA cycle. This reverse was indicated by a decreased citrate, cis-aconitase, and isocitrate concentrations and supported by a decreased citrate/malate ratio, probably as a compensatory mechanism to decrease the NADH/NAD+ ratio caused by the lower mitochondrial electron transport chain activity. From these results, we can conclude that mice with SMF show a substantial metabolic rewiring that could be a mechanism to maintain normal energy flows in the stressed brain to promote successful stress adaptation.

Disclosures: T.L. Emmerzaal: None. **G. Preston:** None. **B. Graham:** None. **R. Kelly:** None. **E. Morava:** None. **R. Rodenburg:** None. **T.L. Kozicz:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.22/Q10

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: 1R01NR017190-01A1

Title: Non-guassian diffusion procedure shows microstructural changes in patients with type 2 diabetes mellitus

Authors: *R. KUMAR[1], C. CABRERA-MINO[2], B. ROY[1], L. EHLERT[1], M. WOO[2], S. CHOI[2]; [1]Anesthesiol., [2]Sch. of Nursing, Univ. of California at Los Angeles, Los Angeles, CA

Abstract: Type 2 diabetes mellitus (T2DM) patients show brain microstructural changes in mood and cognitive regulatory areas, examined with Gaussian diffusion based diffusion tensor imaging (DTI). However, majority of the brain regions follow non-Gaussian diffusion, and tissue injury assessment is needed with non-Gaussian diffusion procedures. In this study, our aim was to examine regional brain tissue changes using non-Gaussian based diffusion kurtosis imaging (DKI) in T2DM over controls. We performed DKI in 32 T2DM (age, 56.6±7.0 years; 18 female; BMI, 29.7±5.8 kg/mm^2), and 19 controls (52.6±7.1 years; 10 male; BMI, 26.1±4.1 kg/mm^2) using a 3.0-Tesla MRI scanner. Using DKI data, mean kurtosis (MK) maps were calculated, normalized, smoothed; the smoothed MK maps were compared between groups using ANCOVA (SPM12; covariates; age, sex; uncorrected-threshold $p<0.005$). Both increased and decreased MK values emerged in various brain areas in T2DM over control subjects. Multiple areas, including the medulla, pons, cerebellar peduncle and vermis, cerebellum, posterior cingulate, frontal and prefrontal cortices, corpus callosum, lingual gyrus, and temporal cortices showed reduced MK values, indicating chronic changes, in T2DM over controls. Brain regions that showed increased MK values included the ventral medial prefrontal cortices, hippocampus, amygdala, putamen, insula, thalamus, anterior and mid cingulate, temporal, and occipital

cortices. T2DM subjects show increased, as well as decreased MK values, indicating acute and chronic tissue changes in those critical brain areas involved in mood and cognition. These data suggest that non-Gaussian diffusion based MK measure can be used to examine brain microstructural changes in T2DM.

Disclosures: R. Kumar: None. **C. Cabrera-Mino:** None. **B. Roy:** None. **L. Ehlert:** None. **M. Woo:** None. **S. Choi:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.23/Q11

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH Grant GM111251
NIH Grant DK113197

Title: Steady-state intracellular ph and the recovery from NH_4^+-induced acidosis in rat hippocampal neurons and astrocytes: A new look on the analysis

Authors: *V. A. RUFFIN[1], W. F. BORON[2];
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Abstract: Hippocampal neurons (HC) neurons involved in memory formation, and their neighboring and astrocytes, presumably require a tightly controlled resting intracellular pH (pH_i). The Na-H exchangers (NHEs) are the major family of acid-base transporter in the absence of CO_2/HCO_3^-. In the present study, we used the pH-sensitive dye BCECF to examine the regulation of steady-state pH_i and the recovery of pH_i from NH_4^+-induced intracellular acid loads in HC neurons and astrocytes, co-cultured from embryonic (E18-20) Sprague Dawley rats, and studied in CO_2/HCO_3^--free HEPES-buffered ("HEPES") solutions. Traditionally, investigators have transferred cells from a CO_2/HCO_3^- incubator to a chamber with flowing HEPES, begun measuring pH_i (checkpoint 1) allowed pH_i to stabilize (checkpoint 2), and reported "initial pH_i" as the value at checkpoint 2 = $(pH_i)_2$. Here we use a twin-NH_4^+-pulse protocol (both pulses in HEPES/21% O_2) to induce two rapid decreases in pH_i, each followed by an exponential pH_i recovery (increase). We find that—after the pH_i recovery from the first acid load—neuronal steady-state pH_i (now at checkpoint 3) is ~0.3 (astrocytes: ~0.15) lower than $(pH_i)_2$. We then impose the second NH_4^+ pulse and observe that—after the pH_i recovery from the second acid load—steady-state pH_i (now at checkpoint 4) is virtually the same as $(pH_i)_3$. We hypothesize that $(pH_i)_2$ is higher than $(pH_i)_3$ because the absence of HCO_3^--dependent acid loaders prevents cells from fully acidifying. For each recovery from an acid load, we use a novel analysis in which plot

pH_i recovery rate (dpH_i/dt) vs pH_i; the data fall on a line, the slope of which is the pH_i recovery rate constant (k, s^{-1}). We bin k values according to $(pH_i)_3$, using pH_i intervals of 0.2. k is not appreciably different from pulse 1 vs pulse 2, but tends to be greater (faster) for astrocytes than neurons. Surprisingly, we find that k tends to be low for cells in the lowest pH_i bins, highest in moderate-pH_i bins (more dramatically for astrocytes), and low again at the highest-pH_i bins. These new analytical approaches may ultimately provide mechanistic insight into cell-to-cell heterogeneity of pH_i regulation in the nervous system

Disclosures: V.A. Ruffin: None. **W.F. Boron:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.24/Q12

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: National Institutes of Health Grant R01 NR017190

Title: Brain microstructural changes in patients with type 2 diabetes mellitus

Authors: *M. LAI[1], L. EHLERT[1], C. CABRERA-MINO[2], B. ROY[1], M. WOO[2], S. CHOI[2], R. KUMAR[1,3,4,5];
[1]Anesthesiol., [2]Sch. of Nursing, [3]Radiological Sci., [4]Bioengineering, [5]Brain Res. Inst., Univ. of California Los Angeles, Los Angeles, CA

Abstract: Type 2 diabetes mellitus (T2DM) patients show gray matter changes in mood and cognitive control sites, functions that are deficient in the condition. However, the nature and extent of brain injury in various sites in T2DM subjects are unclear, which can be examined with diffusion tensor imaging (DTI) based mean diffusivity (MD) measures. Mean diffusivity measures water molecular motion within tissue and shows microstructural changes, with reduced values in acute and increased values in chronic pathological conditions. Our aim was to assess nature and extent of regional brain damage in T2DM over control subjects using DTI procedures. We collected DTI data from 28 T2DM (age, 55.96±7.09 years; BMI, 29.89±5.48 kg/m^2; HbA1C, 7.32±1.37%; 11 males) and 30 healthy controls (age, 54.57±6.72 years; BMI, 27.53±3.83 kg/m^2; 13 males) using a 3.0-Tesla MRI scanner. Whole-brain MD maps were calculated, normalized to a common space, smoothed, and compared between T2DM and control subjects using ANCOVA (SPM12; covariates, age and sex; uncorrected threshold, $p<0.005$). Various brain sites showed increased MD values in T2DM subjects, indicative of chronic tissue changes, in areas including the prefrontal cortices, medulla, cerebellar vermis and cortices, ventral medial prefrontal cortex, cingulate, insula, hypothalamus, mammillary body, frontal, parietal, occipital, and temporal cortices over healthy controls. Decreased MD values, suggestive of acute tissue injury, in T2DM

patients in the thalamus, hippocampus, midbrain, putamen and globus pallidus, cerebellar, and temporal cortices. T2DM subjects show chronic and acute wide-spread microstructural changes in cognition and mood regulatory sites. These data suggest that brain tissue changes can contribute to functional deficits accompanying the condition.

Disclosures: M. Lai: None. **L. Ehlert:** None. **C. Cabrera-Mino:** None. **B. Roy:** None. **M. Woo:** None. **S. Choi:** None. **R. Kumar:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.25/Q13

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: 1R01NR017190-01A1

Title: Regional brain gray matter tissue changes and associations with cognition and mood functions in patients with type 2 diabetes mellitus

Authors: *B. ROY[1], S. CHOI[2], C. CABRERA-MINO[2], L. EHLERT[1], R. MULLER[3], M. J. FREEBY[4], M. WOO[2], R. KUMAR[1];
[1]Anesthesiol., [2]Sch. of Nursing, [3]Med., [4]Diabetes Ctr. of Santa Monica, Univ. of California at Los Angeles, Los Angeles, CA

Abstract: Type 2 diabetes mellitus (T2DM) patients show cognitive and mood symptoms, indicating brain injury in regions that regulate these functions. However, brain tissue integrity in cognition and mood regulatory sites, and associations between brain changes and these functional deficits in T2DM remain unclear. Our aim was to examine gray matter (GM) volume changes in T2DM over healthy controls, and assess any associations between cognition and mood variables and regional brain GM volumes in T2DM subjects. We collected high-resolution T1-weighted images from 28 T2DM (age, 55.6±7.2 years; BMI, 29.9±5.5 kg/m^2; 17 female) and 96 healthy controls (age, 53.3±5.7 years; BMI, 26.4 ±3.7 kg/m^2; 52 male) using a 3.0-Tesla MRI, and examined cognition, depression, and anxiety symptoms with the Montreal cognitive assessment (MoCA), Beck Depression Inventory (BDI-II), and Beck Anxiety Inventory (BAI), respectively. High-resolution T1-weighted images were partitioned into GM and other tissue types; GM maps were normalized, smoothed, and compared between T2DM and controls (ANCOVA, SPM12; covariates, age and sex). Whole-brain GM maps were also correlated with BAI, BDI-II, and MoCA scores in T2DM subjects (Partial correlations; SPM12; covariates, age and sex). Cognition and mood scores between groups were assessed with ANCOVA (covariates, age and sex). No significant differences in age ($p=0.07$) or sex ($p=0.17$) appeared between groups. However, BMI ($p=0.003$) showed significantly higher value in T2DM over controls.

T2DM subjects had significantly increased BDI-II ($p<0.001$), BAI ($p<0.001$), and decreased global MoCA scores ($p = 0.002$) over controls. Multiple brain areas showed reduced GM volumes in T2DM over controls, including the para-hippocampal, cerebellum, insula, cingulate, hippocampus, amygdala, caudate, basal-forebrain, thalamus, prefrontal and frontal, and temporal cortices. Negative associations appeared between anxiety scores and the frontal, cingulate, putamen, thalamus, basal-forebrain, hippocampus, insula, and amygdala, and between depression scores and the frontal, temporal, and occipital sites in T2DM. Global MoCA values showed positive correlations in T2DM with the frontal, prefrontal, temporal, and parietal, insula, hypothalamus, cingulate, hippocampus, and amygdala. T2DM patients show significant brain structural changes in wide-spread areas that are involved in mood and cognition regulation, and associations emerged between functional deficits and these brain regulatory sites. The pathophysiology underlying gray matter changes in T2DM subjects may involve an interplay between endocrinologic, metabolic, and vascular issues.

Disclosures: **B. Roy:** 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.; NHI Grant 1R01NR017190-01A1. **S. Choi:** None. **C. Cabrera-Mino:** None. **L. Ehlert:** None. **R. Muller:** None. **M.J. Freeby:** None. **M. Woo:** None. **R. Kumar:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.26/Q14

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: American Diabetes Association
Helmsley Charitable Trust

Title: Low-grade benzene exposure induces sex-specific metabolic imbalance and hypothalamic ER-stress markers

Authors: *L. K. DEBARBA[1], A. MULKA[2], P. FAKHOURY[1], O. DIDYUK[1], A. AWADA[1], M. HOLLAND[1], I. AYYAR[1], M. SACLA[1], J. B. M. LIMA[1], U. KLUEH[2], M. SADAGURSKI[1]; [1]Biol., [2]Bioengineering, Wayne State Univ., Detroit, MI

Abstract: The current global prevalence of type 2-diabetes mellitus is estimated at 8.4% by the World Health Organization, which represents a fourfold increase over the last four decades. The lifestyle, lack of physical activity, diet and the growing aging population is often used to explain the rise of the diabetes pandemic. However, it is now increasingly accepted that insulin resistance, T2D prevalence and mortality have been associated with long- term exposure to air

and traffic pollution. Benzene is a highly volatile liquid, and a constituent of crude petroleum. Given its ubiquitous utilization in industry as well as consumer products, it is classified as a common airborne pollutant. As such, any exposure to petroleum or its products can result in significant occupational benzene exposure. Notably, benzene exposure from motor vehicle exhaust is higher in inner city populations, which suggests a causative role in the pathogenesis of T2D. We hypothesized that benzene, at levels below carcinogenic, contributes to insulin resistance and inflammatory responses linking persistent organic pollutants (POP) exposure to type 2 diabetes mellitus. For this purpose, C57BL/6 mice in inhalation chambers were exposed to benzene concentration of 50 ppm for 6h/day for 4 weeks. We found that under these conditions, exposure to benzene did not significantly influence mice body weight, neither had it trigger any toxic responses in these animals. Benzene-exposed male mice displayed significantly impaired glucose tolerance, higher fasting glucose and insulin levels. Consequently, we detected a significant elevation of hepatic genes associated with gluconeogenesis, *G6Pase* and *Pck1*, and lipid synthesis, *SREB-1c* and *SREB-2* in male mice as compared to controls. Female mice were completely resistant to the negative metabolic consequences of chronic benzene exposure. Further sex differences were apparent in neuroinflammatory responses, with greater male vulnerability observed in the hypothalamus of benzene- exposed animals. Benzene exposure promoted hypothalamic gliosis and robust neuronal activation in the arcuate, paraventricular, ventromedial, and dorsomedial hypothalamic nucleus; and, significantly upregulated proteins associated with ER stress, IRE-1α, XBP1, CHOP in the arcuate nucleus and IRE-1α, XBP1 in the paraventricular hypothalamus. Our results provide evidence that exposure to benzene induces metabolic imbalance, higher hypothalamic ER-stress markers and severe neuroinflammatory in a sex-specific manner. Persistent ambient benzene exposure may be a heretofore unrecognized contributor to metabolic diseases with male bias.

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Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.27/Q15

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: CIHR

Title: Implications of fatty acid metabolism for bioenergetic and behavioural deficits of NMDAR deficient mice

Authors: *T. V. LIPINA, Y. YAN, L. PEPERA, A. J. RAMSEY;
Univ. of Toronto, Toronto, ON, Canada

Abstract: *Grin1* knockdown (*Grin1*^{KD}) mice have a reduction in NMDA receptors, which causes severe cognitive and social phenotypes. Previous studies indicate deficient glucose uptake and expression of the glucose transporter *Slc2a1* in the brains of *Grin1*^{KD} mice. These findings suggest reduced neuronal glucose transport/utilization, which could contribute to their behavioral deficits. We hypothesize that *Grin1*^{KD} mice rely more on fatty acid utilization to compensate for their impaired glucose-dependent metabolism. Indeed, our previous study found that an omega-3-deficient diet exacerbated cognitive deficits and even increased mortality of *Grin1*^{KD} mice (Islam et al 2017). Hence, the current study further probed the role of fatty acid metabolism in *Grin1*^{KD} mice. First, we asked whether maintenance on a ketogenic diet would prevent *Grin1*^{KD} abnormalities in cell metabolism as well as social and cognitive behaviours. Next, we also assessed effects of beta-hydroxybutyrate (BHB) as a pure metabolite of fatty acids and ketogenic amino acids on behavior, metabolism and mitochondrial function. Behavioural analysis revealed that a ketogenic diet has beneficial effects on *Grin1*^{KD} mice in age-dependent manner, which was given to *Grin1*^{KD} mice and their wild-type (WT) littermates from 3 to 12 weeks of age. In particular, significant improvements in working memory and hyperactivity were detected after five weeks of maintenance on a ketogenic diet without effects on social behavior. However, nine weeks of ketogenic diet corrected deficient social behavior, sensorimotor gating and acoustic startle response in *Grin1*^{KD} mice. To determine whether the beneficial effects of ketogenic diet were due solely to the presence of ketone esters, we also tested behavioral and cellular effects of BHB (60 mg/kg; added in water bottles) given chronically to experimental animals maintained on a normal chow for 9 weeks. In parallel, we probed blood glucose tolerance and glucose levels after exhaustion conditions and found that *Grin1*^{KD} mice fail to elevate blood glucose with exercise, whereas WT animals showed significant raise of glucose after exercise to exhaustion on the treadmill. To directly estimate brain bioenergetics, mitochondrial function was assessed by MitoSox Red in cortical slices from experimental mice. Furthermore, mitochondrial respiration and glycolysis level of primary cortical cells were measured by Seahorse XFe96 analyzer. A comparative analysis of a ketogenic diet and BHB effects on *Grin1*^{KD} mice indicates that fatty acid metabolism plays a critical role to maintain healthy bioenergetics and regulate cognition when NMDARs are hypofunctional.

Disclosures: **T.V. Lipina:** None. **Y. Yan:** None. **L. Pepera:** None. **A.J. Ramsey:** None.

Poster

589. Brain Blood Flow, Metabolism, and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 589.28/Q16

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: CIHR

Title: Vascular changes in the brains of NMDA receptor knockdown mice

Authors: *K. INTSON[1], Y. YAN[1], T. LIPINA[1], L. YU[4], D. EMTYAZI[2], J. G. SLED[4], A. SALAHPOUR[1], A. J. RAMSEY[1,3];
[1]Pharmacol. and Toxicology, [2]Human Biol., [3]Physiol., Univ. of Toronto, Toronto, ON, Canada; [4]Mouse Imaging Ctr., The Hosp. for Sick Children (SickKids), Toronto, ON, Canada

Abstract: NMDA receptor subunit *GRIN1* hypofunctionality has been linked to a spectrum of conditions from schizophrenia, to autism, to intellectual disability with epileptic features. Here, we report features consistent with these disease states in a mouse modeling NMDA receptor hypofunction, the *Grin1*^{KD} mouse. We replicated behavioural findings that *Grin1*^{KD} mice model cognitive features of these disorders, including significant stereotypy, decreased habituation, deficits in social interaction, and disrupted prepulse inhibition (compared to wild-type mice). *Grin1*^{KD} mice also demonstrate spontaneous seizures throughout testing periods. Another disabling aspect of *de novo GRIN1* genetic mutation-induced disorders is muscular hypotonia (Lemcke et al, 2016). Therefore, we also performed the Wire Hang test and find that *Grin1*^{KD} mice have significantly shorter hanging times compared to wild-type mice, indicative that *Grin1*^{KD} mice also model this hypotonia. Given reports of neurovascular changes in the brains of schizophrenia (Lopes et al., 2015) and autism patients (Azmitia et al., 2016), we turned our attention to aspects of blood supply and vascularization in *Grin1*^{KD} mice to investigate why muscular weakness occurs. We analysed vasculature of the brains of *Grin1*^{KD} mice and their wild-type littermates using x-ray microCT and report increased cerebrovascularization. Further, blood-brain barrier (BBB) integrity experiments reveal an increase of *Grin1*^{KD} BBB permeability to Evans Blue dye compared to wild-type. Neovasculogenesis and BBB permeability are regulated by the brain's endothelial cell network (Tang and Conti, 2004; Stamatovic, Keep, and Andjelkovic, 2008). Specifically, NMDA receptors of neuroendothelial cells are proposed to play roles in BBB integrity, glucose uptake, vasodilation, and mitochondrial dysfunction (Hogan-Cann and Anderson, 2016). Our vascular findings, taken together with Agilent Seahorse XF results of increased glycolysis of *Grin1*^{KD} cells (compared to wild-type), suggest that insufficient energy supply leads to muscle weakness in *Grin1*^{KD} mice. Our observations highlight potential therapeutic targets in these disorders. Ongoing experiments examine the system-wide effects of endothelial-specific rescue of NMDA receptors within the global *Grin1*^{KD} mouse.

Disclosures: **K. Intson:** A. Employment/Salary (full or part-time):; University of Toronto. **Y. Yan:** None. **T. Lipina:** None. **L. Yu:** None. **J.G. Sled:** None. **A. Salahpour:** None. **A.J. Ramsey:** None. **D. Emtyazi:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 590.01/Q17

Topic: F.08. Biological Rhythms and Sleep

Support: Marquette University Biological Sciences, Start-Up Funds

Title: Photoperiod affects leptin sensitivity and ventilatory drive in the C57Bl/6J mouse

Authors: *A. A. JONES, N. A. CHAPPELLE, D. M. ARBLE;
Biol. Sci., Marquette Univ., Milwaukee, WI

Abstract: Obstructive Sleep Apnea (OSA) is commonly characterized by a reduction or cessation of breathing during sleep and significantly increases one's risk for heart disease and mortality. Symptoms of OSA are exacerbated in the winter months, suggesting a role of seasonal photoperiod in disordered breathing. However, photoperiodic modulation of breathing is an unexplored topic open to novel therapeutic findings. Photoperiod plays a role in many physiological processes including alterations in leptin sensitivity. Given that our lab has previously shown leptin-mediated modulation of breathing in mice, we investigated the effect of photoperiod on leptin sensitivity and ventilatory drive in a mouse model. Male and female C57Bl/6J mice were housed in one of three photoperiods, long-day (20L:4D), short-day (4L:20D), or a standard 12L:12D day for 3 weeks prior to testing. Leptin sensitivity was assessed by reductions in body mass and food intake during 5 days of daily leptin treatment (i.p. 1 μg/g/day). Breathing and ventilatory drive were quantified using a whole-body plethysmograph. We found that mice housed in long-day photoperiods exhibited a greater reduction in body mass and food intake than those in 12L:12D or short-day photoperiods, indicative of increased leptin sensitivity. Ventilatory drive was also significantly reduced in mice housed on long-day photoperiods. Additionally, mice lacking the melanocortin-4 receptor, an important mediator of leptin signaling and body weight homeostasis, do not exhibit photoperiod-dependent changes in breathing. Taken together, these results suggest that a photoperiod-dependent increase in leptin sensitivity decreases ventilatory drive through a leptin-melanocortin pathway. Overall, these findings represent the first step in understanding the broader implications of light-mediated changes in breathing. Future studies will elucidate the underlying neuronal mechanisms and may prove useful for understanding and treating sleep-disordered breathing in humans.

Disclosures: **A.A. Jones:** None. **N.A. Chappelle:** None. **D.M. Arble:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 590.02/Q18

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant R01NS096151
NIH Grant R21NS101469

Title: Amygdala GABAergic neuron's abnormal activity pattern during cataplexy

Authors: *M. LIU, Y. SUN, E. BENDELL;
Psychiatry and Behavioral Sci., Med. Univ. of South Carolina, Charleston, SC

Abstract: Cataplexy is one of the main symptoms of the sleep disorder narcolepsy. The involvement of strong emotions in the etiology of cataplexy has been confirmed by recent studies showing selective activation of the GABAergic neurons located in the central nucleus of the amygdala (CeA) triggered cataplexy. Nonetheless there is still no direct evidence on CeA GABAergic neurons' real-time dynamic during cataplexy, which would be crucial to understand how cataplexy is triggered. To obtain this direct evidence, we used the deep-brain calcium imaging tool (nVoke, Inscopix) to image the fluctuation of intrinsic calcium transient as the marker of neuronal activity changes in 186 cells from 5 narcoleptic mice (both sexes) by expressing the calcium indicator GCaMP6 into genetically defined CeA GABAergic neurons. GCaMP6 signal were collected and analyzed by Inscopix data acquisition and processing software to obtain the intensity index (ΔF/F), which were further normalized to Z-score (ΔF/F) for statistical analysis with generalized linear mixed model (SPSS). Upon exposure to predator odor, narcoleptic mice displayed intense fear responses and cataplexy bouts. Z-scores (ΔF/F) of 112 recorded cells were significantly increased upon exposure. 74 out of these 112 "activated" cells continued their maximal Z-score (ΔF/F) level into succeeding cataplexy bouts. Furthermore, 2D activity cross correlation analysis demonstrated significantly higher coefficients among these GABAergic neurons during cataplexy bouts when compared to any other brain states including waking, NREMS (non-rapid eye movement sleep) and REMS (rapid eye movement sleep). We conclude that we have unveiled amygdala cataplexy-ON GABAergic neurons in rodent narcolepsy model. We propose that both the abnormal activation and high synchronization of CeA GABAergic neurons trigger emotion-induced cataplexy.

Disclosures: M. Liu: None. **Y. Sun:** None. **E. Bendell:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

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Program #/Poster #: 590.03/R1

Topic: F.08. Biological Rhythms and Sleep

Support: Human Frontier Science Program Fellowship LT000338/2017-L
NIH R01 MH102638
NIH R01 MH087592
NIH R01 MH116470

Title: Adolescent sleep disruption induces long-lasting impairment in social novelty preference

Authors: *W.-J. BIAN, L. DE LECEA;
Psychiatry and Behavioral Sci., Stanford Univ., Stanford, CA

Abstract: Sleep takes one-third of our lives, yet its function is largely unknown. A large proportion of young patients with psychiatric disorders such as autism spectrum disorders (ASDs) and schizophrenia were reported to have sleep problems, including delayed sleep onset, shortened sleep duration and fragmentation of sleep continuity, and a correlation has been found between sleep impairment and defects in social interaction, a shared symptom of these disorders. However, the causal relationship between sleep disruption and social deficits as well as the underlying mechanisms have not yet been established despite their importance in understanding the etiology of these disorders and developing potential therapeutic means. Here we found that developmental sleep disruption (SD) in adolescent mice caused significantly reduced preference towards the novel social stimulus in adulthood in the three-chamber social interaction test without affecting the overall sociality. This social deficit was persistent to at least 1 month after the initial test. Interestingly, SD in adulthood did not induce any social defect, indicating a critical period in adolescence during which sleep shapes social novelty preference. Dopaminergic (DA) neurons in the ventral tegmental area (VTA) are important players in social reward processing and motivation, and they are active during waking but mostly silent during sleep. We found adolescent SD abolished the Ca2+ activity of VTA DA neurons in response to novel social stimuli. Furthermore, adolescent over-excitation of the VTA DA neurons, specifically during the light phase when sleep mostly occurs, led to the loss of social novelty preference similar to that caused by SD, while VTA inhibition concurrent with adolescent SD rescued this social novelty phenotype. Collectively, these results suggest a critical role of adolescent sleep and normal activity level of VTA DA neurons in the developmental shaping of social novelty preference.

Disclosures: W. Bian: None. **L. de Lecea:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

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Program #/Poster #: 590.04/R2

Topic: F.08. Biological Rhythms and Sleep

Support: ANII POS_NAC_2015_1_109643
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Title: Social clock influence on Uruguayan adolescent's sleep and performance

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Abstract: After puberty, sleep time is delayed as adolescents become more evening-oriented. Besides, sleep duration is reduced as eveningness collides with early morning school. This mismatch of internal and external time is a risk factor for cognitive and health outcomes. Many schools in Latin America arrange their activities in multiple shifts. This naturally occurring experiment represents an opportunity to study the influence of scholar and lifestyle schedules on sleep and cognitive performance. Three hundred students aged between 15 and 18 years participated in this study, attending either morning (7:30 to 11:30 AM) or afternoon shift (11:30 AM to 3:30 PM) in a Public High School in Montevideo, Uruguay. After obtaining informed consent, participants answered three questionnaires: an adaptation of the School Sleep Habits Survey (Wolfson & Carskadon, 1998), the Morningness/Eveningness Scale for Children (Carskadon et al., 1993), and a sociodemographic one. A group of students were also evaluated using an adaptation of the Revised Attention Network Test (Fan et al., 2009), at the beginning and at the end of their respective school shift. Sleep timing and duration were studied in relation to time restrictions imposed by school schedule on weekdays vs free days. Sleep restriction and Morningness-Eveningness influence in performance in the three attentional networks was also studied. As expected, in week vs free days sleep was advanced and reduced in duration as wake time is constrained by school schedules, particularly in students attending the morning shift. Synchrony effect between time-of-day and Morningness-Eveningness was explored. Changes in attention performance across time were more pronounced in the morning than in the afternoon shift. This is the first study addressing the time differences in sleep and attention performance using school shifts as social clock variants. Advances in knowledge about predictors of adolescent sleep are relevant for public policies on adolescent health and education, and constitutes important information to schedule family activities.
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Wolfson, A. R., & Carskadon, M. A. (1998). Sleep schedules and daytime functioning in adolescents. *Child Development*, 69, 875-887.

Disclosures: I. Estevan Debat: None. **B. Tassino:** None. **A. Silva:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 590.05/R3

Topic: F.08. Biological Rhythms and Sleep

Title: Is dim light at night a risk factor for exacerbating autistic behavior?

Authors: *H.-B. WANG[1], D. H.-W. LOH[2], Y. TAHARA[2], C. A. GHIANI[3], C. S. COLWELL[2]; [1]Molecular, Cellular, and Integrative Physiol., [2]Psychiatry and Biobehavioral Sci., [3]Pathology, Univ. of California - Los Angeles, Los Angeles, CA

Abstract: Many studies report that 50 to 80% of patients with autism spectrum disorders (ASD) suffer from delayed sleep onset, difficulty in sleep maintenance, and difficulty waking in the morning. These sleep disturbances are indicative of a possible problem with the circadian timing system. In this study, we first examined sleep/wake cycles in the *Cntnap2* KO (contactin-associated protein-like 2 knockout) mouse model of ASD. Mutations and polymorphisms in this gene have been linked to cortical dysplasia as well as autism symptoms in patients and in mouse models. We found that *Cntnap2* KO mice phenocopy the circadian disturbances in patients as they displayed a reduced rhythm strength and increased sleep fragmentation. There is a growing concern that nighttime light pollution may be negatively affecting our health and the nighttime pollution has been broadly linked to dysfunctions of circadian clock, metabolism, and cognition. Noteworthy, ASD patients have been reported to have more exposure to light via electronic screens during the night. As consequence, it is possible that this inappropriate photic environment caused by nighttime exposure to electric lights and light-emitting devices would further disrupt their unstable circadian clocks and exacerbate the autistic behavior. After applying dim light at night (DLaN, 5 lux) for 2 weeks, we confirmed that DLaN not only dampened circadian rhythms in locomotor activity and sleep, but also significantly affected the sociability and repetitive behavior of the mutants. To unravel possible underlying mechanisms, Per2::Luciferase monitoring from cultured tissues and neuroinflammation biomarkers in prefrontal cortex using qPCR were performed. Moreover, we identified strong cFOS expression in amygdala, a region implicated for social behavior and repetitive behavior, evoked by DLaN. Together, this preclinical work evaluates whether even mild circadian rhythm disruption (i.e.

nighttime light pollution) is an environmental risk factor for ASD populations, and suggests new therapeutic interventions aiming to stabilize the circadian timing system may be useful for ASD. Melatonin has been used successfully in the management of patients with autism spectrum disorders. We found that daily treatment with melatonin improved the strength of the daily rhythm and reduced the excessive grooming of the mutant mice to WT levels. Importantly, the beneficial effects were only found when the treatment was given at a phase aligned with the circadian timing.

Disclosures: H. Wang: None. **D.H. Loh:** None. **Y. Tahara:** None. **C.A. Ghiani:** None. **C.S. Colwell:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

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Program #/Poster #: 590.06/R4

Topic: F.08. Biological Rhythms and Sleep

Support: Center for Sleep and Health Research Equipment Research Support
National Institutes of Health (NINR R00NR014369)

Title: Validation of PiezoSleep scoring against EEG/EMG sleep scoring in rats

Authors: I. TOPCHIY[1,2], A. M. FINK[1,2], K. MAKI[1], ***M. W. CALIK**[1,2];
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Abstract: Current methods of scoring sleep in rodents involve invasive surgical procedures to implant EEG and EMG electrodes. Though this an established method of sleep scoring in rodents, there are limitations: postoperative recovery time; infections or mortality from surgery; and issues with misplacement of electrodes or noisy signals. Recently, a new method of measuring sleep, PiezoSleep, has been validated against implanted electrodes in mice. PiezoSleep uses a piezoelectric film to detect the rodent's movements and breathing with high sensitivity and uses an algorithm to automatically score sleep. However, no validation has been completed for rats. Here, we validate PiezoSleep scoring against EEG/EMG implanted electrodes sleep scoring in rats. Adult male Brown Norway, Wistar Kyoto and Long Evans rats were anesthetized and implanted with bilateral stainless steel screws into the skull for EEG and bilateral wire electrodes into the nuchal muscles for EMG. For the Brown Norway rats, the EEG/EMG leads were soldered to a miniature connector and fixed to the skull. For the Wistar Kyoto and Long Evans rats, the EEG/EMG leads were tunneled subcutaneously to a telemetry transmitter implanted in the flank. Rats were allowed to recover from surgery for one week. Brown Norway rats were placed in PiezoSleep cages, and had their headsets connected to a steel

cable for recording EEG/EMG signals, which were then manually scored for sleep in 10-sec epochs. Wistar Kyoto and Long Evans rats were placed in PiezoSleep cages and EEG/EMG signals were recorded using a telemetry system. Sleep was scored automatically in 4-sec epochs using Neuroscore software. PiezoSleep software simultaneously recorded and scored sleep in the rats. Rats implanted with EEG/EMG headsets had 83.6% concurrence with PiezoSleep scoring. Out of 22827 epochs, 6919 (30.3%) wake and 12173 (53.3%) sleep epochs were scored concurrently by the two recording systems. PiezoSleep scored 1060 (4.6%) wake and 2675 (11.7%) sleep epochs when the EEG/EMG headsets scored those epochs as sleep and wake, respectively. Rats implanted with EEG/EMG telemetry had 84.0% concurrence with PiezoSleep scoring. Out of 353391 epochs, 106363 (30.1%) wake and 190481 (53.9%) sleep epochs were scored concurrently by the two recording systems. PiezoSleep scored 40135 (11.4%) wake and 16413 (4.6%) sleep epochs when the EEG/EMG telemetry scored those epochs as sleep and wake, respectively. The accuracy in rats is similar to reports in mice. We show that PiezoSleep is a reliable alternative to EEG/EMG sleep scoring in rat sleep research.

Disclosures: **I. Topchiy:** F. Consulting Fees (e.g., advisory boards); Signal Solutions, LLC. **A.M. Fink:** None. **K. Maki:** None. **M.W. Calik:** F. Consulting Fees (e.g., advisory boards); Signal Solutions, LLC.

Poster

590. Sleep Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 590.07/R5

Topic: F.08. Biological Rhythms and Sleep

Support: PAPIIT, DGAPA IN: 214017

Title: Effect of extremely low frequency electromagnetic fields on locomotor activity rhythm of Wistar rats

Authors: *K. F. ROLDAN-RIZO[1], D. ELIAS-VIÑAS[2], L. VERDUGO-DIAZ[3];
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Abstract: Technological development has involved an increase in environmental electromagnetic fields and its exposure to living organisms. Animals synchronize their activity to external signals, in such a way that locomotor activity recordings become essential for measuring the effects of certain stimuli, such as electromagnetic fields. For this study Wistar rats (n=8) were exposed to a 60 Hz electromagnetic field for 5 days (1 hour daily) using a pair of Helmholtz coils (2.4 mT, 1uA). Animals were housed in constant dark conditions and locomotor

activity was recorded continuously. Results showed that exposure altered animal locomotor activity for a few hours after exposure ended. Data showed significant differences on period (T) comparing animal locomotor activity before, during and after the exposure. The stimulation induced an increase of locomotor activity in adult rats as well as a change in duration of the period. This change was immediate and transitory. Electromagnetic stimulation is perceived by animals as a mild stressor, as has been proposed by other research groups. Further investigation is required to see if similar effects are induced at other times of the circadian rhythm.

Disclosures: **K.F. Roldan-Rizo:** None. **D. Elias-Viñas:** None. **L. Verdugo-Diaz:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

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Program #/Poster #: 590.08/R6

Topic: F.08. Biological Rhythms and Sleep

Support: JSPS KAKENHI Grant Number JP17K08951

Title: Increasing the arousal level may inhibit cisplatin-induced anorexia in mice

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Abstract: Sleep problems are major complaints of cancer patients. These patients often develop anorexia during the course of cancer chemotherapy, and sleep problems can aggravate this. They are not life-threatening symptoms, but their insufficient control reduces the patient's quality of life and become a risk factor for refusal to undergo further therapy. Previous studies proposed orexin OX_2 receptors and histamine H_3 receptors as targets for treating sleep disorders, and reported that OX_2 receptor agonists and H_3 receptor inverse agonists are effective for reducing daytime sleepiness. In this study, we investigated the effects of cisplatin on the change of the arousal level in mice, and the involvement of orexinergic and histaminergic systems in their development of chemotherapy-induced anorexia. Mice were housed in individual cages which were equipped with a sensor that detects pressure changes on the cage floor in response to motion. On the day of the experiment, mice received cisplatin (7.5 mg/kg, i.p.), and their sleep and wake states were discriminate by the changes of signals generated from the sensors. Additionally, mice received cisplatin with or without treatment with YNT-185 (an OX_2 receptor agonist, 20 mg/kg, s.c.), ciproxifan (an H_3 receptor inverse agonist, 1 mg/kg, s.c.), or VUF5681 (an H_3 receptor neutral antagonist, 5 mg/kg, s.c.), then their daily food intake was measured. Finally, we investigated the effect of cisplatin on the hypothalamic expression of prepro-orexin (PPO) mRNA, which encodes precursors of orexin. Cisplatin increased sleep state during the active phase and induced anorexia. The administration of ciproxifan or YNT-185, which was

reported to induce wakefulness in mice, significantly inhibited the cisplatin-induced anorexia. The inhibitory effect of YNT-185 was antagonized by the administration of VUF5681. Furthermore, cisplatin decreased the hypothalamic expression of PPO mRNA and the period of expression decreased in parallel with the onset of anorexia. These results suggest that changes in the arousal level may lead to the development of cisplatin-induced anorexia in mice, and the increase of the arousal level via the activation of the orexinergic and histaminergic pathway is involved in the therapeutic effect against cisplatin-induced anorexia.

Disclosures: K. Yamamoto: None.

Poster

590. Sleep Mechanisms

Location: Hall A

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Program #/Poster #: 590.09/R7

Topic: F.08. Biological Rhythms and Sleep

Support: National Natural Science Foundation of China (31371115, 81527901)
Tsinghua Brain Research and Center for Brain-Inspired Computing Research

Title: The caudal paralaminar thalamus plays a critical role in cortical activation and arousal

Authors: *W. YIWEI[1], M. LIU[2], D. CAI[3], F. XIE[4], L. YOU[1], Y. YUE[1], R. CHEN[1], J. ZOU[1], T. LI[1];
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Abstract: The midline and intralaminar thalamocortical projection system, which is located anteriorly and innervated by brainstem reticular formation nuclei, was considered as the last link of the dorsal pathway of the ascending reticular activating system (ARAS). In human patients, lesions of the midline and intralaminar thalamus cause decreased cortical and behavioral arousal. Surprisingly, earlier animal studies suggested that the dorsal pathway may not be necessary. A more recent study in mice showed that, although the midline thalamus is important for arousal, it might play its role via thalamostriatal rather than thalamocortical projection system. These opposing findings made in animals raised a fundamental question, namely, whether the dorsal pathway is indeed involved in arousal and, if it is, how. We lately characterized the whole-brain connectivity pattern of a caudal paralaminar thalamic region (CPT), mainly composed of the medial part of medial geniculate body (MGBm), the posterior intralaminar thalamus (PIN) and the peripeduncular nucleus (PP), which was traditionally considered as part of the higher order auditory processing thalamus. We found that the CPT receives direct inputs from both monoaminergic and cholinergic centers of brainstem reticular formation and projects to the

superficial layer of a wide range of temporal cortices, suggesting its involvement in sensation-related arousal. Using fiber photometry and EEG/EMG recordings, we found that the activities of CPT VGluT2-positive (VGluT2+) neurons were high during wakefulness and REM sleep and low in NREM sleep, and increased before cortical activation at the sleep-to-wake transition. Optogenetic activation of CPT VGluT2+ neurons with low light power rapidly and reliably awoke mice from sleep and elicited cortical activation during general anesthesia, and chemogenetic activation led to prolonged wakefulness, indicating that the activation of CPT VGluT2+ neurons strongly promotes cortical and behavioral arousal. On the other hand, optogenetic inactivation of CPT VGluT2+ neurons greatly reduced the probability of awakening by acoustic stimulation of various intensities. The ablation of CPT VGluT2+ neurons led to decreased wakefulness and increased REM sleep in 24 hours, but had little effect on NREM sleep. Furthermore, the activation of the CPT-to-cortex pathway was sufficient to evoke both cortical and behavioral arousal, and this pathway was critical for sound-elicited sleep-to-wake transition. Our study identified a new thalamic region important for arousal control and provided strong support for the dorsal pathway hypothesis.

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Poster

590. Sleep Mechanisms

Location: Hall A

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Program #/Poster #: 590.10/R8

Topic: F.08. Biological Rhythms and Sleep

Support: KAKENHI grant 18J21663

Title: Hypothalamic MCH neurons contribute to forgetting of hippocampus dependent memory during REM sleep

Authors: *S. IZAWA[1,2], S. CHOWDHURY[1], D. ONO[1], T. MIYAZAKI[1,2], Y. MUKAI[1,2], R. INOUE[1], T. S. KILDUFF[3], A. YAMANAKA[1,4];
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Abstract: Sleep is thought to both consolidate and impair memory, however, the underlying neural mechanisms are unknown. Here, we found that melanin-concentrating hormone (MCH)-producing neurons in the hypothalamus contribute to forgetting of hippocampal memory. Retrograde-transported beads injection into the hippocampus revealed that MCH neurons densely innervated the dorsal hippocampus. MCH neurons are known to synthesize and release a

variety of neuropeptides/transmitters that are involved in REM sleep regulation. To reveal the role of MCH neurons in hippocampus-dependent memory, the novel object recognition, Morris water maze and contextual fear memory tests were performed in mice. Pharmacogenetic activation of MCH neurons impaired memory in all these tests, whereas inhibition or ablation of these neurons improved memory. These results suggested that MCH neuron activity was involved in hippocampus-dependent memory impairment. Optogenetic activation of MCH neurons during the retention period, but not during the encoding or retrieval periods, impaired memory. To reveal the mechanism of memory impairment, slice patch clamp recordings from hippocampal pyramidal neurons were performed. Optogenetic stimulation of MCH nerve terminals in the hippocampus hyperpolarized and decreased the firing frequency of hippocampal pyramidal neurons. Finally, we tested whether the activity of MCH neurons during REM sleep is involved in memory impairment. MCH neurons were silenced in a vigilance state-dependent manner (wakefulness, REM sleep, and Non-REM sleep) for 14 hr of the memory retention period. Optogenetic silencing during REM sleep but not during wakefulness or Non-REM sleep significantly improved memory, suggesting that MCH neurons impair memory particularly during REM sleep. Taken together, our results demonstrate that MCH neurons impair memory by inhibiting hippocampal pyramidal neurons during REM sleep, a mechanism that could effectively save memory resources by erasing memories that are not important for survival.

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Poster

590. Sleep Mechanisms

Location: Hall A

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Program #/Poster #: 590.11/R9

Topic: F.08. Biological Rhythms and Sleep

Support: NIA K01AG048259
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Title: Right putamen functional connectivity is associated with chronic pain and sleep quality in older adults

Authors: *S. MONTESINO GOICOLEA, P. A. VALDES-HERNANDEZ, Y. CRUZ-ALMEIDA;
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Abstract: Sleep disturbances and chronic pain are common co-morbidities in older adults tied to significant reductions in quality of life. The potential mechanisms underlying sleep disturbances in the presence of chronic pain are not understood. An understudied factor is the detrimental effect of chronic pain on cerebral circuits needed for sleep generation and maintenance. In the present study, we explored associations between sleep quality with resting state functional MRI connectivity (FC) of brain regions involved in sleep and pain in cognitively healthy older adults (60-83, M=72.3±6.3, n=47) enrolled in the NEPAL study. Participants reported presence of pain during the past 3 months (55%, n=26), completed the Pittsburgh Sleep Quality Index (PSQI) and underwent MRI. The fMRIs were preprocessed and denoised using CONN and normalized to MNI using DARTEL. ROI-to-ROI FC was calculated with Fisher-transformed Pearson correlations. Based on the sleep and pain literature, we placed seeds in medial prefrontal cortex, anterior cingulate cortex, middle/inferior frontal gyri, pre/postcentral gyri, supplementary motor areas, paracingulate gyri, precuneus, frontal orbital cortex, basal ganglia, insula, thalami, hippocampi, amygdalae, opercula, right Heslch's gyrus and brain stem. General Linear Model was used to investigate the effect of pain presence, PSQI and their interaction, controlling for age, sex and handedness. FC was FDR corrected (q&lt0.05) for multiple comparisons across whole brain targets, and size/intensity of the resulting networks were FDR corrected (q&lt0.05) using Network-Based Statistics across seeds. As expected, those with chronic pain reported significantly lower sleep quality (p&lt0.05). We found a significant negative interaction on the FC of the right putamen with supplementary motor areas, pre/post central gyri, lateral occipital cortex, bilateral parietal opercula, language areas (right Heslch's gyrus and bilateral planum temporale), right inferior frontal gyrus pars opercularis and left central operculum. To our knowledge, this is the first examination of resting state FC at the intersection of sleep and chronic pain in older adults. Such associations may explain the reported bidirectional relationships between sleep disturbances and chronic pain.

Disclosures: S. Montesino Goicolea: None. **P.A. Valdes-Hernandez:** None. **Y. Cruz-Almeida:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 590.12/R10

Topic: F.08. Biological Rhythms and Sleep

Title: Differential change of light and deep NREM sleep by thalamic PLCβ4

Authors: *J. HONG[1], G. HA[1], H. KWAK[1], Y. LEE[1], H. JEONG[1], P.-G. SUH[2,3], E. CHEONG[1]; [1]Yonsei Univ., Seoul, Korea, Republic of; [2]Sch. of Life Science, Unist of Sci. and Technol., Ulsan, Korea, Republic of; [3]Korea Brain Res. Inst., Daegu, Korea, Republic of

Abstract: Sleep consists of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep is further divided into light (slow wave sleep 1, SWS1) and deep (slow wave sleep 2, SWS2) NREM sleep, which are characterized by frequent occurrence of sleep spindle and delta waves, respectively. Both brain rhythms are thought to be mediated in the thalamocortical circuit, consisting of the cortex and thalamus. The thalamus is further dissected into thalamic reticular nuclei (TRN) and thalamocortical (TC) nuclei which reciprocally project each other. Among many inputs to TC neurons, the corticothalamic pathway from cortical neurons in layer VI send massive glutamatergic inputs. The activation of corticothalamic input have been considered to regulate the firing properties of TC neurons, which affect thalamocortical oscillations. However, the function of which on regulating light and deep NREM sleep is unclear. Here, we investigated that the changes of dynamics in light and deep NREM sleep using TC-specific PLCβ4 knock-out (KO) mice.

Disclosures: J. Hong: None. **G. Ha:** None. **H. Kwak:** None. **Y. Lee:** None. **H. Jeong:** None. **P. Suh:** None. **E. Cheong:** None.

Poster

590. Sleep Mechanisms

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Topic: F.08. Biological Rhythms and Sleep

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Title: Sleep quality meaning and its association with the Pittsburgh sleep quality index (PSQI): A population base study across the adult lifespan

Authors: *L. AMORIM[1,2,3], A. SOUSA[4], T. C. CASTANHO[1,2,3], N. SOUSA[1,2,3], N. C. SANTOS[1,2,3];
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Abstract: Sleep is a complex, dynamic and multidimensional phenomenon, with proven effects on health and well-being. However, while dimensions such as 'sleep quantity' are clearly defined, that does not apply to the 'sleep quality' construct. In fact, different conceptualizations

of it have led to a high variability in the methodologies used. Herein, we searched for the meaning of a good sleep quality and its stability across the adult lifespan, as well as the association between sleep quality self-ratings and the Pittsburgh Sleep Quality Index (PSQI). For this purpose, adult community-dwellers were randomly and consecutively invited to participate in the study (n=340; age range: 18-87 years), and asked to provide their interpretation of a good sleep quality and a good night of sleep. Self-ratings of sleep quality, sleep patterns and habits and information on psychological variables were also collected. Content analysis was performed with the qualitative data and the obtained parameters were considered as to their frequency; an exploratory network analysis was also used. Associations between self-rated sleep quality and PSQI were determined and the predictors of good/poor sleep quality explored. Results showed that while the most frequently reported parameters for a 'good sleep quality' are 'sleep continuity', 'sleep characteristics' and a dyad involving these two, for a 'good night of sleep' the most reported information focused on the dyad 'sleep duration'-'sleep continuity' and on 'sleep duration' and 'sleep continuity' individually. From the exploratory network analysis, the strongest association occurred between 'sleep continuity' and 'waking up feelings' but strong associations were also found between 'sleep continuity' and 'sleep characteristics' and 'sleep continuity' and 'sleep duration'. Results also indicated that self-rated sleep quality measures and PSQI are correlated and no differences were found across the lifespan in the distribution of these parameters. In the one-year follow-up, 52% of the invited individuals maintained the definition that they provided in first assessment. Overall, our results point to the need to consider not only sleep information when addressing sleep quality, but also aspects related to the feelings when waking up. Additionally, our results also point to the need of developing a new tool to address sleep quality that goes beyond PSQI that is framed by a clinical context. Overall, our results contribute to the clarification of the meaning of 'a good sleep quality', and provide a relevant framework for future studies addressing the complaints and sleep changes across lifespan.

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Poster

590. Sleep Mechanisms

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Program #/Poster #: 590.14/R12

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant R56NR017435
NIH Grant R01HL135562
NIH Grant NR013693

Title: Inspiratory muscle training may increase gray matter volume in obstructive sleep apnea

Authors: *P. M. MACEY[1], A. PAL[2], A. AGUILA[2], M. SARMA[3], A. SAUCEDO[3], A. M. THOMAS[3], R. S. AYSOLA[4];
[1]Nursing; Brain Res. Inst., [2]Nursing, [3]Radiology, [4]Med-Pulm & Critical Care, Univ. of California at Los Angeles, Los Angeles, CA

Abstract: Introduction: Obstructive Sleep Apnea (OSA) is a sleep disorder present in more than 10% of the adult population. One approach to reduce the sleep-disordered breathing is to improve muscle tone through Inspiratory Muscle Training (IMT). We and a group in Tucson found in pilot studies of OSA patients that IMT leads to more than improved respiratory function, with lower reduced blood pressure and improvement in psychological symptoms observed. These changes suggest improvement in brain function, so our objective was to assess regional gray matter volume before and after IMT to assess evidence of improvement in brain structure.
Methods: Five OSA patients perform an IMT intervention over 10 weeks (2 females; age 47-74, mean 62±5 years). Each day, patients performed a set of 30 inspiratory breaths against a resistance of 65% of maximum inspiratory capacity. At pre and post time points, we assessed brain structure with voxel-based morphmetry, a measure of regional gray matter volume (GMV), based on high resolution T1-weighted anatomical scans (0.8mm voxel size). We compared GMV before and after IMT in SPM12 software.
Results: Twelve regions of increased GMV appeared post-IMT ($p<0.001$). Regions of increases included multiple subregions of the bilateral precuneus, bilateral middle occipital gyrus, and left superior parietal-occipital cortex, the right posterior insula, right hippocampus, and left medial prefrontal cortex. No areas showed volume decreases.
Discussion: The findings illustrate an increase in GMV in multiple regions, several of which are associated with common symptoms in OSA. The increase in GMV could reflect a reduction in vascular content or learning-related dendritic growth.

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Poster

590. Sleep Mechanisms

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Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant R56NR017435
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Title: Inspiratory muscle training reduces inflammation markers in brain of obstructive sleep apnea patients

Authors: *A. PAL[1], A. P. AGUILA[1], M. SARMA[2], A. SAUCEDO[2], R. S. AYSOLA[3], A. M. THOMAS[2], P. M. MACEY[4];
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Abstract: Introduction: Obstructive Sleep Apnea (OSA) affects over 10% of the adult population and is characterized by airway muscle collapse. One approach to prevent this collapse is to improve muscle tone through Inspiratory Muscle Training (IMT). We and another group in Tucson have shown in pilot OSA studies that IMT leads to not only improved respiratory function but also reduced blood pressure and lower psychological stress. Since brain function is associated with these symptoms, we aimed to determine if in OSA IMT leads to brain changes, specifically changes in structure related to reduced inflammation.Methods: We conducted a 10 week IMT intervention study in 5 untreated OSA participants (2 females; age 47-74, mean 62±5 years). The intervention consisted of daily set of 30 inspiratory breaths against a resistance of 65% of maximum inspiratory capacity. At pre and post time points, we assessed brain structure with Diffusion Tensor Imaging (DTI) indices of Mean Diffusivity (MD) and Fractional Anisotropy (FA). These indices are sensitive to changes in inflammation amongst other phenomena. We assessed IMT related changes using a repeated measures linear model in SPM12 software. Results: Post IMT we found significantly ($p<0.001$) increased MD in several brain regions. There were no areas where MD decreased, and we did not find any change in FA. Areas with MD increases included the prefrontal lobe (left cerebral white matter and posterior ventral orbital gyrus); occipital lobe (right lingual gyrus white matter); bilateral temporal poles; and bilateral ventral diencephalon.Discussion: The findings are consistent with IMT causing a reduction in inflammation in brain areas associated with autonomic and stress regulation. The increased MD could reflect decreased cell size, and the lack of FA changes suggests the effects were not due to white matter alterations.

Disclosures: **A. Pal:** None. **A.P. Aguila:** None. **M. Sarma:** None. **A. Saucedo:** None. **R.S. Aysola:** None. **A.M. Thomas:** None. **P.M. Macey:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 590.16/R14

Topic: F.08. Biological Rhythms and Sleep

Support: GIST Research Institute (GRI) grant funded by the Gwangju Institute of Science and Technology (GIST) in 2018

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Institute of Information & Communications Technology Planning & Evaluation (IITP) grant funded by the Korea government (No. 2017-0-00451)

Title: Acoustic pink noise stimulation after sleep spindle may enhance the procedural memory consolidation

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Abstract: Slow wave and sleep spindle activity are well-known components associated with memory consolidation during sleep. Positive effects of acoustic or electrical stimulations on memory consolidation to modulate slow wave sleep or sleep spindles have been reported. On the other hand, there is a suggestion that temporal matching of slow waves and sleep spindles is an important feature of memory integration mechanisms. In this study, we hypothesized that adjusting the slow wave after sleep spindle activity may improve the memory consolidation effect. To verify this hypothesis, we built a closed-loop feedback system that delivers pink noise stimuli (50 ms, 62dB SPL) whenever sleep spindle activity is detected. We set up SHAM condition (no acoustic stimulation) and STIM condition (nap with acoustic stimulation after spindle detection) to investigate the effects of acoustic stimulation on memory consolidation and neurophysiological characteristics. We recruited thirteen healthy male subjects (mean ± SD age: 26.3 ± 2.4 years, right-handed). Subjects proceeded to SHAM and STIM conditions in pseudo-random order after adaptation nap; two conditions were separated at least 2 weeks. All subjects requested to perform word-pair memorization task and finger tapping tasks before and after the nap. We found phase-locked slow wave activities after spindle detection (acoustic stimulation) during the STIM condition. STIM condition yielded a greater improvement in finger tapping task than SHAM condition ($p = 0.014$). Additionally, it was observed that there was a marginal correlation between declarative memory performance change and theta activity change from SHAM to STIM ($r=0.53$, $p=0.059$). In addition, we found that there was no procedural memory consolidation enhancement among subjects who showed larger auditory evoked potential (AEP) than spontaneous slow wave activity. From these findings, it is believed that individual sound amplitude optimization considering individual sensitivity of sound is of great importance to introduce procedural memory consolidation enhancement.
*****This work was supported by the GIST Research Institute (GRI) grant funded by the Gwangju Institute of Science and Technology (GIST) in 2018 and the National Research Foundation of Korea under Grant NRF-2016R1A2B4010897 and by the Institute of Information & Communications Technology Planning & Evaluation (IITP) grant funded by the Korea government (No. 2017-0-00451).

Disclosures: **J. Choi:** None. **S.C. Jun:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 590.17/R15

Topic: F.08. Biological Rhythms and Sleep

Support: ANPCyT, FONCyT: PICT 2015 0844
MINDEF, PIDDEF 14/17

Title: Sleep consolidation of visuomotor adaptation: Differential effects on memory retention and persistence

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Abstract: Adaptation is a type of learning that allows maintaining precise motor control in face of environmental and/or internal perturbations. Like other types of learning, adaptation may lead to interference or facilitation depending on the level of congruency of sequentially learned materials. We have previously shown that adaptation to opposing visual rotations, A and B, impairs the ability to learn in B and long-term memory measured 24 hours later. Here, we examined the impact of sleep on the retention and persistence of visuomotor adaptation memories, in the presence or absence of a conflicting perturbation. To this aim, we carried out two experiments in which we manipulated the proximity between training and sleep. We hypothesized that if sleep participates in the consolidation of visuomotor adaptation, then there should be a benefit of the promixity of sleep on memory retention and/or persistence. To examine this possibility we carried out two experiments: in Experiment 1 (n=26), subjects performed a visuomotor adaptation task (30 deg CW perturbation); in Experiment 2 (n=31), a different set of participants performed the same task but under a protocol of anterograde interference in which they adapted to two opposing visual rotations (30 deg CCW followed by 30 deg CW) separated by a 5 min interval. In each experiment one group of subjects performed the task in the morning and the other group at night, just before going to sleep. All subjects participated in a whole-night polysomnographic study in the sleep lab, and returned to the lab 24h and 2 weeks post training to measure memory retention and persistence, respectively. In agreement with our previous work, we found that anterograde interference reduced the overall level of memory retention by about 70% ($p<0.001$). Yet, the magnitude of this effect differed depending on the proximity between learning and sleep ($p=0.045$). Specifically, the group that learned ~12 hours before sleep showed a reduction in the level of retention at 24 hs, whereas the group that trained immediatly before sleep was impaired only at 2 weeks. Our findings provide

evidence in favor of a role of sleep in the stabilization of visuomotor adaptation, which may be reflected in the persistence of long-term memories.

Disclosures: **A. Solano:** None. **L.A. Riquelme:** None. **D. Pérez-Chada:** None. **V. Della-Maggiore:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 590.18/R16

Topic: F.08. Biological Rhythms and Sleep

Title: Potential role of gut microbiota in neurobehavioral deficits induced by simulated shift work condition in mice

Authors: *S. SHIYANA[1], K. KONDEPUDI[2], M. BISHNOI[2], K. CHOPRA[1];
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Abstract: Shorter sleep hours along with altered circadian rhythm may meet the societal needs but impairs the normal physiological responses thus resulting into many gastrointestinal and neuronal pathologies. That's why the population engaged in night shifts e.g. security personnel, nurses, flight crew have gastrointestinal and neuronal abnormalities as the most common phenotypes. Moreover, the interplay between sleep and gut microbiota is evidenced in the recent literature. However, the impact of gut microbiota on chronic sleep deprivation induced neurobehavioral deficits in a simulated shift work condition is not explored. Therefore, the current study was designed to mimic the night shift work condition. Female Laca mice were divided into four groups: control, sleep deprived (SD), antibiotic treated (Ab+NPD) and fecal microbiota transplanted (Ab+NPD+FMT). In SD group, the sleep deprivation was produced using modified multiple platforms model for eight hours daily from 9:00 am to 5:00 pm from Monday to Friday with weekend as sleep recovery period. In Ab+NPD, the cocktail of three non - absorbable antibiotics neomycin, bacitracin and pimaricin was administered orally for seven days along with normal pellet diet (NPD) for the depletion of microbiota. The fecal matter from sleep deprived group was transplanted to the Ab+NPD+FMT following the antibiotic treatment. All the animals were assessed for locomotor activity using actophotometer, stereotype and aggressive behavior, pain parameters using tail immersion test and Von frey test. Fecal samples were collected and analyzed for the selected gut microbiota by polymerase chain reaction**.** The results elucidated the occurrence of mania like behavior and decreased pain threshold in SD animals. The gut microbiota transplantation also induced the similar mania like behavior and decreased pain threshold in antibiotic treated animals. Furthermore, the fecal microbiota analysis showed altered Bacteriodetes to Firmicutes ratio. Hence, the current study substantiates the

adverse modulation of gut microbiota in chronic sleep deprivation and its potential role in resultant neurobehavioral deficits.

Disclosures: **S. Shiyana:** None. **K. Kondepudi:** None. **M. Bishnoi:** None. **K. Chopra:** None.

Poster

590. Sleep Mechanisms

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Program #/Poster #: 590.19/R17

Topic: F.08. Biological Rhythms and Sleep

Support: PAPIIT-UNAM IG-200314
CONACyT 239403

Title: Activation of orexigenic neurons induced by binge eating of sugar or fat and sleep delay in a model of night eating syndrome

Authors: *E. ESPITIA-BAUTISTA, L. UBALDO-REYES, C. ESCOBAR;
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Abstract: Night eating syndrome (NES) is an eating disorder, characterized by a delayed circadian pattern of food intake to late at night; it includes night binge episodes (BE) and sleep disorder like insomnia. Sleep and food intake are both controlled by orexigenic neurons (ORX) in the lateral hypothalamus (LH). This neuronal system is also associated with appetite for palatable food. Loss of circadian or homeostatic control in this system may lead to compulsive eating behaviors (CEB), overweight and metabolic syndrome (MSyn). Palatable food contains high levels of sugar and fat. A high sugar diet (HSD) or a high fat diet (HFD) undergo differences in digestion and absorption and stimulate brain systems in a differential manner. This study aimed to investigate two experimental models of NES, food intake into the sleep phase and food combined with sleep deprivation In both conditions we explored the contribution of a HFD or HSD.. We evaluated BE, effort behaviors, MSyn and the activation of ORX neurons. Rats were housed with chow and water *ad-libitum* and were randomly assigned to*:* 1) Control, 2) HSD, 3) HFD, 4) Sleep delay (SD), 5) SD+HSD and 6) SD+HFD. Four hours after starting the rest phase rats exposed to NES had 1 hour restricted access to the diet. Animals with SD were exposed to a slow rotating wheel the first 4h of their rest phase. Experimental protocols lasted 4 weeks. General activity, body weight and food intake were recorded. At the end of the study effort behaviors and metabolic variables were assessed and brains were collected to evaluate c-Fos activation in ORX in the perifornical area (PFA) and the LH. Results indicate that HSD and HFD animals present a delayed peak time (acrophase) of daily activation of ~1.5h and 0.5h, respectively. SD induced a delay of ~3h, SD+HSD of ~2.5h and SD+HFD of ~3.5h, suggesting circadian misalignment. All groups exposed to palatable diet developed effort behaviors to

obtain the diet. HFD and SD+HFD groups developed more BE than HSD, SD+HSD, SD or Control groups; and developed glucose intolerance, high insulin, triglycerides and leptin. Animals exposed to SD were less heavy and accumulated less fat. All groups exposed to SD showed a decrease in the activation of ORX in the LH, as compared with their non-sleep deprived groups. However, in the PFA SD only reduced the ORX of HFD rats. We conclude that a HFD as compared with HSD is a stronger stimulus for producing BE and metabolic syndrome in experimental conditions of NES. The protocol for SD disrupted the circadian phase in general activity, as observed with the acrophases, while the diet alone produced a minimal change. We demonstrate that NES is a risk factor to develop CEB and MSyn, reducing the ORX activation.

Disclosures: **E. Espitia-Bautista:** None. **L. Ubaldo-Reyes:** None. **C. Escobar:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

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Program #/Poster #: 590.20/R18

Topic: F.08. Biological Rhythms and Sleep

Support: NSF Grant 1652060
NIH Grant DK105510

Title: Asprosin administration promotes wakefulness and blunts torpor bouts in mice

Authors: *E. M. COHN, K. ODENIGBO, F. GULAMALI, S. J. SWOAP, M. CARTER; Dept. of Biology, Program in Neurosci., Williams Col., Williamstown, MA

Abstract: Hormones that cause an increase in food intake can prioritize feeding behavior over competing behavioral states such as sleep. Furthermore, in small mammals including mice, hormones that affect feeding can also affect torpor, brief (6-8 hours) states of metabolic dormancy characterized by low body temperature and heart rate. Asprosin is a recently discovered peptide hormone released from white adipose tissue that causes an increase in glucose release from the liver and a corresponding increase in food-seeking behavior. We tested the hypothesis that asprosin administration is sufficient to promote wakefulness over other sleep states and to blunt the depth and length of torpor bouts in mice. We found that administration of asprosin caused a reversible increase in wakefulness and increased latency from states of wakefulness to states of sleep. Additionally, we found that asprosin reduced the duration and depth of torpor bouts. Taken together, these data suggest that asprosin negatively regulates states of sleep and torpor, prioritizing food intake over competitive homeostatic and metabolic states that limit food-seeking behavior.

Disclosures: **E.M. Cohn:** None. **K. Odenigbo:** None. **F. Gulamali:** None. **S.J. Swoap:** None. **M. Carter:** None.

Poster

590. Sleep Mechanisms

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Program #/Poster #: 590.21/R19

Topic: F.08. Biological Rhythms and Sleep

Support: University of Michigan, Department of Anesthesiology

Title: Tetrodotoxin-mediated inactivation of the prefrontal cortex decreases wakefulness and increases the time to emergence from sevoflurane anesthesia in rat

Authors: *E. R. TRAMMEL, A. PARKAR, T. GROENHOUT, L. SHARBA, A. BOOTWALA, T. LIU, G. A. MASHOUR, D. PAL;
Dept. of Anesthesiol., Univ. of Michigan, Ann Arbor, MI

Abstract: There is an ongoing debate on the role of prefrontal cortex (PFC) in consciousness. We recently showed that cholinergic stimulation of PFC in sevoflurane-anesthetized rats induced a wake-like state (Pal et al., 2018 Current Biol. 28:2145-2152.e5). In this study, using a within-group design, we tested the hypothesis that inactivation of PFC will reduce wakefulness and increase anesthetic potency. Four adult male Sprague Dawley rats were instrumented for sleep-wake recordings and PFC inactivation through bilateral infusion of tetrodotoxin [TTX: low (15.6μM, TTX-L) and high (156μM, TTX-H) dose]; sterile saline (CTRL) infusion into PFC served as the control group. All injections (500nL) were done 1h before the onset of dark phase. Thereafter, sleep-wake states were recorded through 12h of dark (7pm-7am) and light (7am-7pm) phases. In another set of experiments, 6 rats (4 male) were exposed to sevoflurane anesthesia (2.5%) two hours after bilateral TTX-H or CTRL infusion (500nL) into PFC. Thereafter, the time to loss of righting reflex (LORR), a surrogate for unconsciousness in rodents, was measured. Sevoflurane anesthesia was stopped after 45 minutes and the time to return of righting reflex (RORR), a surrogate for return of consciousness in rodents, was quantified. The injections were counterbalanced, and 5-7 days were allowed between injections. Sleep-wake states were analyzed in 10 second bins into wakefulness, slow wave sleep (SWS), and rapid eye movement sleep (REMS). The data are reported as mean ± standard deviation. Time to LORR/RORR was compared using a paired t-test. The immediate 12h period after TTX infusion into PFC (dark phase) was characterized by decrease in wake state (63.7±11.3% TTX-L and 53.8±22.9% TTX-H vs. 64.7±3% CTRL) and REMS (3.5±2.1% TTX-L and 2.9±0.74% TTX-H vs. 7.3±1.6% CTRL) while the time spent in SWS increased (32.8±10.8% TTX-L and 43.3±23.2% TTX-H vs. 28.0±3.6% CTRL). The overall trend continued as such in the next 12h period (light phase): decrease in wakefulness (44.1±6.3% TTX-L and 43.4±19.4% TTX-H vs.

55.9±8.5% CTRL) and increase in SWS (48.8±4.3% TTX-L and 54.8±20.1% TTX-H vs. 39.5±7.8% CTRL). REMS after TTX-H also showed a similar trend (1.8±1.1% vs. 4.6±2.2% CTRL) but there was an increase in REMS after TTX-L (7.03±2.4% vs. 4.6 ±2.2% CTRL). TTX infusion into PFC produced a significant increase in the time to emergence from sevoflurane anesthesia (13.5±2.6 min after TTX vs. 9.1± 2.6 min after saline infusion, p =0.001). These data further support a causal contribution of PFC in regulating level of consciousness.

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Poster

590. Sleep Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 590.22/R20

Topic: F.08. Biological Rhythms and Sleep

Support: 6-FY18-529
1 RO1 GM102525

Title: Neonatal exposure to isoflurane alters sleep architecture and cognition in adolescent rats in a sex-specific manner

Authors: *F. M. MANZELLA[1], B. F. GULVEZAN[1], Y. H. RAOL[2], V. JEVTOVIC-TODOROVIC[1], S. M. TODOROVIC[1];
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Abstract: Objective & Rationale
Exposure to general anesthetics (GAs) is neurotoxic to the developing rodent and primate brains and is associated with neurocognitive impairment later in life. Yet, little is known about its effect on other behavioral outcomes, such as sleep and exploratory behavior. Sleep plays a major role in cognition, especially during adolescence. Thus, the goal of this research was to understand how neonatal exposure to GAs affects sleep quality and to see if changes in sleep quality are similarly reflected in a cognitive exploratory task.
Methods
At postnatal day (P) 7, male and female Sprague Dawley rat pups were exposed to either six hours of continuous 1.5% isoflurane (ISO) or to compressed air alone (SHAM). At weaning age (P21-P23), rats were implanted with a cortical EEG electrode, and sleep recordings were obtained at P35. Sleep architecture and power spectra were analyzed from six hours of the light cycle and six hours of the dark cycle, for a total of 12 hours of analysis. Sleep stages were categorized as Wake, NREM, REM, or Total Sleep. Following sleep recording, rats were given an object exploration task in which they were allowed to explore one of three objects in

sequential order for 10 minutes.

Results

We found no changes in sleep architecture during the light cycle. However, during the dark cycle, ISO males had more NREM episodes (p=0.027), shorter Wake episodes (p=0.023), and more transitions between sleep stages compared to SHAM males (p=0.024). Moreover, there were no differences in total time spent in each stage. Changes persisted when light and dark cycles were combined. Again, ISO males had more NREM episodes compared to SHAM males (p=0.039). Unlike the dark cycle alone, there were no differences in duration of wake episodes; instead, ISO males had shorter NREM episodes (p=0.029). There were no changes in the total amount of time spent in each stage. For power spectra analysis, there were no changes between ISO and SHAM groups. Finally, for the exploration task, we found that ISO males spent less time exploring all objects compared to SHAM males (p=0.011).

Conclusions

Our results suggest that adolescent males are vulnerable to disturbances in sleep architecture after neonatal exposure to GAs. Specifically, GAs affect sleep quality as manifested as destabilized NREM sleep, and not quantity, as there were no changes in overall time spent in each sleep stage. Moreover, these results are reflected in deficiency seen in a cognitive exploration task, in which ISO males were more greatly affected. Because sleep quality can affect cognition, we propose that sleep deficits associated with neonatal GA exposure may perpetuate cognitive impairments later in life.

Disclosures: F.M. Manzella: None. **B.F. Gulvezan:** None. **Y.H. Raol:** None. **V. Jevtovic-Todorovic:** None. **S.M. Todorovic:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 590.23/S1

Topic: F.08. Biological Rhythms and Sleep

Title: Sleep fragmentation increases alcohol sensitivity and alcohol-induced mortality in *drosophila*

Authors: *L. C. LYONS, A. K. DE NOBREGA, C. L. CAMARILLO, E. J. NOAKES; Biol. Science, Program in Neurosci., Florida State Univ., Tallahassee, FL

Abstract: Alcohol abuse is a major global health problem causing individual health consequences and adverse economic impacts on society. Individuals with sleep disorders are more likely to have an alcohol use disorder with increased incidence of alcohol-related pathologies observed in populations prone to sleep disruption including shift workers and older individuals. Sleep disorders affect approximately 70 million Americans resulting in mood

disorders, cognitive impairments, and metabolic disorders. While the effects of alcohol abuse on sleep quality have been well-studied, little is known about the converse effect of sleep loss on alcohol pathologies. *Drosophila* is an excellent model for studies of sleep and alcohol neurobiology providing a model for disentangling the underlying molecular and neural mechanisms of sleep and alcohol interactions. Recently, our lab characterized the effect of 24 hours of total sleep deprivation on alcohol sensitivity and toxicity in *Drosophila* finding that sleep deprivation increased alcohol toxicity and suppressed long-term alcohol tolerance. As sleep fragmentation with decreased sleep quality represents a common sleep problem for millions of individuals, in our current study we investigated the effect of sleep fragmentation on alcohol toxicity. *Drosophila* sleep occurs mostly during the night with sleep bouts averaging approximately 40 minutes. Daytime sleep bouts are less numerous and shorter averaging 27 minutes. Previously, researchers found that deeper sleep states occurred in *Drosophila* approximately 15 and 30 minutes after inactivity (van Alphen et al., 2013). Consequently, as a first step we used a mechanical sleep fragmentation protocol in which young flies (7 days old) were subjected to mechanical rotation and startle for 3 minutes out of every 10 minutes. We found that four days (96 hours) of sleep fragmentation increased behavioral sensitivity to alcohol-induced sedation as well as alcohol-induced mortality in young flies. Ongoing experiments are investigating additional sleep fragmentation paradigms and the amount of recovery sleep necessary to restore baseline alcohol responses.

Disclosures: L.C. Lyons: None. **A.K. De Nobrega:** None. **C.L. Camarillo:** None. **E.J. Noakes:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 590.24/S2

Topic: F.08. Biological Rhythms and Sleep

Title: Investigation novel-sleep related genes in *Drosophila melanogaster*: A follow up on KOMP2 identified genes in *Mus musculus*

Authors: *R. GUERRIERO[1], D. A. HARRISON[1], P. SHAW[2], B. F. O'HARA[1,3];
[1]Univ. of Kentucky, Lexington, KY; [2]Neurosci., Washington Univ. Sch. of Med. In St. Louis, Saint Louis, MO; [3]Signal Solutions LLC, Lexington, KY

Abstract: Sleep is well-conserved across phylogeny, yet the function of sleep and its underlying mechanisms are currently poorly understood. Novel-sleep related genes were previously identified by our lab as part of the Knockout Mouse Phenotyping Program (KOMP2). This international effort generated *Mus musculus* single-gene knockouts on a C57BL6/NJ background and proceeded to gather data on over 200 phenotypes, including five days of sleep and wake

parameters. This sleep data was gathered using the non-invasive, high-throughput PiezoSleep System (Signal Solutions, LLC.), which uses piezoelectric films to gather movement data which can be assigned as wake or sleep. These data identified 122 novel genes that influence sleep phenotypes such as sleep duration and bout length. Homologous proteins were identified in flies and a subset of these genes are under investigation in *Drosophila melanogaster,* including myosin heavy chain (Mhc) and spinophillin (Spn). Using both genetic mutants and RNAi knockdowns, the effect of gene reduction on activity profiles and sleep were analyzed. Conditional mutants/ knockdowns were also made for the central nervous system and subsets of the CNS that are known to impact sleep and circadian rhythms. Sleep and activity data were recorded using DAM2 monitors (TriKinetics Inc.) while being maintained on a 12:12 light dark cycle. Preliminary data analysis show that whole body aberrations in Mhc and Spn impact sleep percentage. Both Mhc and Spn are known to be involved in structure and development of synapses. Spn is involved in the neurexin scaffolding of presynaptic neurons and also help with maintaining these synapses once formed. Synaptic reorganization and regulation is known to take place during sleep, showing a potential connection of these proteins and sleep. Since removal of both of these genes impact sleep in *D. melanogaster* and in *M. musculus,* this may show evidence of the conservation of underlying sleep machinery across many phyla.

Disclosures: R. Guerriero: None. **D.A. Harrison:** None. **P. Shaw:** None. **B.F. O'Hara:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Signal Solutions LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Signal Solutions LLC, GISMO Therapeutics. F. Consulting Fees (e.g., advisory boards); GISMO Therapeutics.

Poster

590. Sleep Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 590.25/S3

Topic: F.08. Biological Rhythms and Sleep

Title: Deprivation of ‘sleep-like’ inactivity in an annelid worm disrupts neural mechanisms, but not metabolism

Authors: *M. J. ZORAN, L. H. JORDAN;
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Abstract: Many invertebrate animals undergo periods of rest or ‘sleep-like’ inactivity, but the function of these behavioral states is not clear. The aquatic annelid worm, *Lumbriculus variegatus,* exhibits a circadian-regulated inactivity, which involves a ventilatory posture that

facilitates gas exchange. *Lumbriculus* is nocturnal, active at night, and its inactive phase is expressed during the day and subjective day when in constant conditions (n=31). Using physiological (neural and metabolic) recordings, together with behavioral monitoring, the hypothesis that the inactive 'sleep-like' state of this worm functions to enhance both neural and metabolic deficits accrued over a day's activity was tested. Both physical disruption (agitation) and pharmacological treatment (caffeine) were used to deprive animals of inactivity. Deprivation of daily inactivity, and consequently ventilatory behavior, disrupted plasticity associated with regenerative morphallaxis (n=18 per group) and increased the onset of asexual fragmentation (n=13 per group), two mechanisms dependent on neural signaling. In contrast, whole-animal metabolic rate was not detectably impacted by disruption of daily inactivity. Still, chronic deprivation of inactivity with agitation (n=7 per group) or caffeine (n=5 per group) caused a prolonged rebound period of inactivity and an increase in ventilatory behavior. Using specific wavelengths of LED light to entrain the worm's activity rhythms (n=12 per group), we find that inactivity deprivation reduces the threshold for light-evoked escape responses. Our results suggest that *L. variegatus* possesses a 'sleep-like' resting state that when disrupted leads to broad deficits in neural-regulated development and behavior, including escape reflexes.

Disclosures: M.J. Zoran: None. **L.H. Jordan:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 590.26/S4

Topic: F.08. Biological Rhythms and Sleep

Support: MH088176

Title: Zebratrack: A remanent imaging behavior quantification platform

Authors: P. R. MARTINEAU[1], L. C. LEUNG[2], ***P. MOURRAIN**[3];
[1]Martineau and Associates, Menlo Park, CA; [2]Psychiatry and Behavioral Sci., [3]Stanford Univ., Stanford, CA

Abstract: We present Zebratrack: a darkfield-illuminated, Remanent Imaging platform for high accuracy behavioral analysis. Our analytics simultaneously reveal individual and population measures from short timescales, to daily cycles, and potentially to entire organismal lifetimes. Recording objects of various sizes from larval to adult animals as well as sub-pixel microorganisms aid in studying feeding and social interactions. Our platform, verified with the popular zebrafish model, can be extended to other aquatic models.

Disclosures: P.R. Martineau: None. **L.C. Leung:** None. **P. Mourrain:** None.

Poster

590. Sleep Mechanisms

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Topic: F.08. Biological Rhythms and Sleep

Support: Programa UNAM-DGAPA-PAPIIT IA207316
Programa UNAM-DGAPA-PAPIIT IN224417

Title: Cardiorespiratory activity and sleep deprivation in crayfish

Authors: *M. OSORIO-PALACIOS, L. MONTIEL-TREJO, Z. PEÑA-LEAL, I. OLIVER-DOMÍNGUEZ, J. HERNÁNDEZ-FALCÓN, K. MENDOZA-ÁNGELES;
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Abstract: In vertebrate and invertebrate animals, sleep is necessary for survival. For example in rats, after two to three weeks of sleep deprivation animals loss weight despite a strong increase in food intake, if deprivation continues they finally die. In crayfish, 24 hours of deprivation are enough to cause death. Sleep deprivation in mammals elicit changes in the structure of EEG and disregulation of cardiorespiratory activity. However, we do not know if this occurs also in invertebrates, particularly in crayfish. The main aim of this work was to analyze brain electrical activity and cardiorespiratory rate of adult crayfish *Procambarus clarkii* in order to compare the dynamic of these variables in control conditions and after sleep deprivation. We used male animals in intermolt, synchronized to light-dark cycles 12:12. In cold anesthetized animals we implanted electrodes on deutocerebrum, both gills chambers and cardiac sinus. After two days of recovery, we recorded, simultaneously, behavioral and electrical activity during 8 continuous hours in two different conditions: 1. control and 2. after one hour of sleep deprivation. For behavioral records, we defined two body positions of the animal: walking and lying on one side, and associated each one with the time of recording. To analyze brain electrical activity and cardiorespiratory rate we used no-linear techniques. We found that brain electrical activity from control sleeping animals showed a decrease in power at 30 Hz, as compared to walking animals that had high power in the entire frequency band analyzed, 0-60 Hz. Sleep-deprived animals presented even lower power in all EEG frequencies even when they were allowed to sleep. Both conditions are accompanied by oscillations in cardiorespiratory frequency. To summarize, sleep deprivation modify the dynamic of brain electrical activity and cardiorespiratory regulation in crayfish.

Disclosures: M. Osorio-Palacios: None. **L. Montiel-Trejo:** None. **Z. Peña-Leal:** None. **I. Oliver-Domínguez:** None. **J. Hernández-Falcón:** None. **K. Mendoza-Ángeles:** None.

Poster

590. Sleep Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 590.28/S6

Topic: F.08. Biological Rhythms and Sleep

Support: Ministry of Science and ICT, E0164503-04

Title: Standardized rice bran supplement enhances non-rapid eye movement sleep in mice through histamine H1 receptors

Authors: *M. UM[1,2], M. YOON[1], J. JUNG[1], J. LEE[1], S. CHO[3];
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Abstract: We investigated the effect of rice bran on sleep and the mechanism underlying this effect. Electroencephalography was used to evaluate the effects of standardized rice bran supplement (RBS) and doxepin hydrochloride (DH), a histamine H1 receptor (H1R) antagonist used as a positive control, on sleep in mice. The mechanism of RBS action was investigated using knockout (KO) mice and ex vivo electrophysiological recordings. Oral administration of RBS and DH significantly decreased sleep latency and increased the amount of non-rapid eye movement sleep (NREMS) in mice. Similar to DH, RBS fully inhibited H1R agonist-induced increase in action potential frequency in tuberomammillary nucleus neurons. In H1R KO mice, neither RBS nor DH administration led to the increase in NREMS and decrease in sleep latency observed in WT mice. These results indicate that the sleep-promoting effect of RBS is completely dependent on H1R antagonism. RBS decreases sleep latency and promotes NREMS through the inhibition of H1R, suggesting that it could be a promising therapeutic agent for insomnia.

Disclosures: M. Um: None. **M. Yoon:** None. **J. Jung:** None. **J. Lee:** None. **S. Cho:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.01/S7

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant DK083452
NIH Grant DK052849

Title: Leptin increases postsynaptic NMDA receptor-mediated currents and synaptic throughput in LepR neurons of the NTS

Authors: *D. M. NEYENS, N. J. HUSTON, R. C. RITTER, S. M. APPLEYARD;
Integrative Physiol. and Neurosci., Washington State Univ., Pullman, WA

Abstract: Leptin signaling within the nucleus of the solitary tract (NTS) is necessary for appropriate control of food intake and body-weight regulation. Injections of leptin into the NTS reduce meal size and increase the efficacy of vagus-mediated satiety signals to reduce food intake. Leptin receptors (LepRs) are expressed in both vagal afferents and in some NTS neurons, and loss of LepRs in either increases food intake and weight-gain. However, while selective knockdown of LepRs in NTS neurons induces hyperphagia and stimulates weight-gain in rats, LepR-expressing neurons of the NTS are not well-characterized and the mechanism by which leptin acts within the NTS to control food intake is unclear. Previous work from our lab has shown that NMDA-type glutamate receptors (NMDARs) help maintain the fidelity of vagal-NTS synaptic transmission, and our recent data suggests that NTS LepR neurons express larger NMDAR currents compared to other NTS populations. This is noteworthy since NMDARs are requisite mediators for excitatory actions of leptin in other brain regions, such as the hippocampus. To study electrophysiological outcomes of leptin in the NTS, we used patch-clamp techniques guided by LepR-Cre X Rosa-tdTomato fluorescence in a horizontal brain slice preparation that allows for stimulation of the vagus-containing solitary tract. We found that LepR neurons are located throughout most of the NTS, including regions known to be involved in control of food intake, and they receive both direct and indirect glutamatergic input following stimulation of the vagus-containing solitary tract. When compared to unlabeled NTS neurons, LepR neurons had comparable synaptic AMPAR currents but nearly two-fold larger NMDAR currents during a high frequency (50Hz) stimulus train ($p < 0.001$, two-way ANOVA). Interestingly, bath application of 100 nM leptin increased the size of evoked NMDAR currents in LepR neurons but not AMPAR currents (1.3 fold-change, $p < 0.001$, two-way ANOVA). Furthermore, leptin increased synaptic throughput from ~0.25 to above 1.0 ($p < 0.001$, two-way ANOVA) and total charge transfer (1.55 ± 0.21 fold increase; $p < 0.01$, Mann-Whitney) within fifteen minutes. These effects were blocked by NMDAR antagonists; either bath application of 10 uM DCPP-ene or including MK801 (1 mM) in the recording pipette to selectively block post-synaptic NMDARs. Finally, injection of a DCPP-ene (20 ng in 100 nl) into the NTS also blocked the effects of intra-NTS leptin on overnight food intake. Taken together, these findings suggest leptin decreases food intake by enhancing postsynaptic NMDAR function thus increasing the sensitivity of NTS neurons to vagal input.

Disclosures: D.M. Neyens: None. **N.J. Huston:** None. **R.C. Ritter:** None. **S.M. Appleyard:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.02/S8

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant RO1 DK047320-22
NIH Grant RO1 DK047320-22S2
NIH Grant U54MD007601

Title: Role of selenium utilization in hypothalamic control of energy metabolism

Authors: *D. TORRES, M. W. PITTS, A. C. HASHIMOTO, M. J. BERRY;
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Abstract: Selenium (Se), an essential trace element known mainly for its antioxidant properties, is critical for proper brain function and may also play an important role in whole-body energy metabolism. Dietary Se is incorporated into selenoproteins in the form of the unique amino acid selenocysteine (Sec), which requires its cognate selenocysteine-tRNA (Trsp) to be synthesized. Whole-body knockout (KO) of Sec lyase (Scly), a critical participant in selenium recycling, increases susceptibility to developing metabolic syndrome (MetS) in mice, a phenotype more strongly displayed by male mice. Scly KO mice also have decreased expression of several selenoproteins in the hypothalamus, a key regulator of energy homeostasis. The purpose of this project is to elucidate the mechanisms underlying the link between disrupted hypothalamic selenium utilization and the associated metabolic disturbances. Agouti-related peptide (Agrp)-positive neurons, which reside in the arcuate nucleus (Arc), are a nutrient-sensing hypothalamic sub-population that promotes positive energy balance. Resistance to the anorexigenic hormone leptin in Agrp neurons has been linked to energy dyshomeostasis and may result from oxidative stress. We generated a mouse line with Cre-driven Agrp neuron-specific Scly KO (Scly-Agrp KO mice) to determine the contribution of these neurons to the sexually dimorphic MetS phenotype observed in whole-body Scly KO mice. Unexpectedly, Scly-Agrp KO mice had decreased body weight and adiposity as well as heightened sensitivity to glucose compared to controls when fed a high-fat diet. While control mice displayed leptin resistance in the Arc, a known consequence of a high-fat diet regimen, Scly-Agrp KO mice maintained sensitivity to leptin. While no changes in food intake were observed, Scly-Agrp KO mice showed signs of increased brown adipose tissue thermogenesis. We also generated Trsp-Agrp KO mice to evaluate ablation of selenoprotein synthesis within these neurons. Female Trsp-Agrp KO mice had reduced body weight and higher levels of energy expenditure, while male mice exhibited no phenotype. This study sheds light on the important roles of Se utilization and selenoproteins in metabolic disease pathology, provides new information on the interplay between the central

nervous system and whole-body energy metabolism, and may help identify key targets of interest for preventative strategies or therapeutic treatments for metabolic disorders.

Disclosures: D. Torres: None. **M.W. Pitts:** None. **A.C. Hashimoto:** None. **M.J. Berry:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.03/S9

Topic: F.10. Food Intake and Energy Balance

Support: NIH T32 2T32DK076540
Salary Savings
Purdue Institute for Integrative Neuroscience
Purdue Executive Vice President for Research and Partnerships

Title: A chemogenetic analysis of the nucleus solitary tract role in satiation

Authors: *K. GILLAND, E. A. FOX;
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Abstract: Excitation of cells during consumption of a meal in the caudal 2/3 of the nucleus solitary tract (cNTS) of the brainstem are thought to produce satiation. It is unknown how excitation of these cells inhibits feeding. A major obstacle has been the inability to selectively manipulate these cells without affecting intermixed cells that mediate other autonomic functions. Our method uses inducible, activity-dependent chemogenetics to test if artificial excitation of cNTS cells activated during satiation can reduce food intake, an effect that could help prevent or reverse obesity. Food intake was measured in 3-month old male and female c-Fos-tTA mice while maintained on standard chow for five days and were then switched to chow containing doxycycline (Dox). Mice increased their food intake over five days on Dox from regular chow ($p<0.05$), demonstrating mice will consume enough Dox throughout experiments and is likely not causing malaise in mice. c-Fos-tTA mice were injected with an AAV-hM_3D_qvirus into the cNTS. Mice were maintained on 40mg/kg Dox chow from the time of injection to prevent hM_3D_qreceptor expression until the start of the meal training. Mice were trained to eat a large meal (Fox, AJP Regu2013;305:11). Mice increased body weight and the daily large meal increased over the course of the meal training (both $p<0.01$). During the large meal training, 1/2 of the mice were taken off Dox which allowed for activation of the c-Fos promoter to produce tTA, and thus activated hM_3D_qexpression. Data demonstrated mice kept on Dox throughout meal training do not express the hM_3D_qreceptor. Mice taken off Dox through meal training expressed the hM_3D_q receptor in the cNTS. Clozapine-N-oxide (CNO) was administered at .8mg/kg to activate the hM_3D_q receptor and c-Fos expression was seen in a proportion of cells expressing the

hM_3D_q receptor. This suggests CNO activated cells expressing the hM_3D_qreceptor. Further behavioral experiments will be conducted to determine if the excitation of the cNTS cells by CNO will result in decreasedfood intake, thus confirming the role of these neurons in satiation, the first step in identifying, characterizing and determining how these neurons produce satiation.

Disclosures: K. Gilland: None. **E.A. Fox:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.04/S10

Topic: F.10. Food Intake and Energy Balance

Support: NIH grant DK053903

Title: Leptin receptor activity in the nucleus of the solitary tract increases forebrain leptin sensitivity

Authors: *R. B. HARRIS;
Physiol., Med. Col. of Georgia, Augusta, GA

Abstract: We previously reported that fourth ventricle infusions of leptin that cause weight loss are associated with an increase in hypothalamic phosphorylation of signal transducer and activator of transcription 3 (pSTAT3), a marker of leptin receptor (ObRb) activation, implying an integrated response to central leptin. This study tested the impact of ObRb activity in the nucleus of the solitary tract (NTS) on sensitivity to leptin in the forebrain. Leptin-Saporin (Lep-Sap) injections were used to delete ObR-expressing neurons in the NTS of 300g male Sprague Dawley rats. Controls were injected with Blank-Saporin (Blk-Sap). Loss of NTS ObR was confirmed with RNAScope *in situ* hybridization and pSTAT3 response to peripheral leptin in representative Lep-Sap rats. Experimental rats were fitted with 3rd ventricle (3V) guide cannula 12 days after Lep-Sap or Blk-Sap injections. Nine days later cannula placement was tested with Angiotensin II and rats were adapted to calorimeter cages for 4 days. Lep-Sap had no effect on body weight. To test leptin responsiveness rats were food deprived for 5 hours and at 5 p.m. they received 3V injections of 0, 0.05, 0.1, 0.25 or 0.5 μg leptin. Food was returned at 6 p.m., the start of the dark period. Each rat received the injections in random order at 4 day intervals. At the end of the experiment NTS pSTAT3 was used to confirm efficacy of Lep-Sap injections. Seven Lep-Sap and 6 control Blk-Sap rats completed the experiment. There was a dose-dependent inhibition of food intake in Blk-Sap rats, but only 0.5 μg leptin inhibited intake of Lep-Sap rats. Intake was inhibited during the 24 hours following injection and was not compensated for so that cumulative intake was inhibited for 60 hours post-injection. Energy expenditure was not different between groups and respiratory exchange ratio tended to follow food intake. These data suggest that

leptin-induced inhibition of food intake is mediated by an integrated network involving both the forebrain and hindbrain and that activation of NTS ObRb lowers the threshold for leptin responsiveness in the forebrain.

Disclosures: R.B. Harris: None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.05/S11

Topic: F.10. Food Intake and Energy Balance

Support: NIH MH62044
Rainin Innovator Award
GSU Brains and Behavior Seed Grant

Title: Consumption of dietary emulsifiers alters gene expression in the amygdala, paraventricular nucleus, and arcuate nucleus of mice

Authors: *A. R. ARNOLD, K. L. HUHMAN, B. CHASSAING;
Neurosci. Inst., Georgia State Univ., Atlanta, GA

Abstract: As obesity, inflammatory disease, and stress disorders continue to rise in western society, the assessment of factors contributing to the increase in these debilitating diseases becomes critically important. The western diet is one such factor contributing to the etiology of these disorders. Food additives, such as emulsifiers, are commonly added to highly processed western foods and have recently been shown to promote gut dysbiosis, low grade inflammation, metabolic disease and alterations in feeding and anxiety-like behavior in mice. However, very little is known about the impact of dietary emulsifiers on brain regions that modulate stress responses and feeding behavior. We investigated here the effect of two broadly used dietary emulsifiers, polysorbate 80 (P80) and carboxylmethycellulose (CMC), on gene expression in the amygdala, paraventricular nucleus, and arcuate nucleus of the hypothalamus using next generation RNA sequencing (RNA-Seq). RNA extracted from brain micro-punches of C57BL/6 male mice treated with 1% P80 or CMC in drinking water for 12 weeks were compared to regular water treated controls. As a quality control measure, quantitative polymerase chain reaction (qPCR) was performed on selected genes of interest to validate the RNA-Seq dataset on a new cohort of animals. Differential gene expression analysis revealed altered expression of immune regulatory genes in each brain area investigated, altered expression of HPA-axis regulatory genes in the amygdala and PVN, and altered expression of obesity-associated genes in the PVN and arcuate nucleus in emulsifier treated animals. Interestingly, P80 and CMC treatment affected different genes within each of these gene categories, suggesting that each

emulsifier acts through different molecular mechanisms to produce similar behavioral phenotypes. Altogether, these data reveal that these commonly used food additives may potentially negatively impact feeding and anxiety-like behaviors by modulation of gene expression in key brain areas. [Supported by NIH MH62044 to KLH and a Rainin Innovator Award to BC as well as a GSU Brains and Behavior Seed Grant.]

Disclosures: **A.R. Arnold:** None. **K.L. Huhman:** None. **B. Chassaing:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.06/S12

Topic: F.10. Food Intake and Energy Balance

Support: UNAM-DGAPA-PAPIIT: IN216119
CONACyT: 255635

Title: Leptin and glucose-sensing neurons in the hypothalamic arcuate nucleus of the rat

Authors: *D. E. GARCIA-DIAZ, J. GARDUÑO, I. ARENAS, J. BRAVO-MARTINEZ, H. CASTRO, K. BERMEO;
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Abstract: Arcuate nucleus (ARC) has been involved in the regulation of feeding behavior and energy expenditure. It has been thought to be comprised of two main populations of neurons. NPY neurons are supposed to be orexigenic and their activation promotes food intake conversely to POMC neurons. In this work we sought to investigate the response of rat ARC neurons to leptin and glucose concentration changes. We used patch clamping methods and biochemical reagents in freshly dissociated neurons and brain slices. Leptin (30 nM) response in NPY/orexigenic neurons induces calcium current inhibition on specific L-type calcium channel population (~50%). Only the amplitude of the current is decreased indicating a lower number of calcium-conducting channels in the absence of kinetic changes. Interestingly, rapamycin diminishes leptin responses suggesting a mTOR-mediated pathway. Rapamycin has been shown to inhibit NPY and AgRP release in ARC neurons. On the other hand, low-glucose exciting neurons (LGE) exhibit higher firing frequencies, little adaptation and higher input resistance compared to low-glucose inhibiting (LGI) neurons. LGE neurons were labeled with an anti-NPY antibody indicating that they are NPY/orexigenic neurons. LGI neurons may represent anorectic POMC cells which are inhibited and excited with low and high concentrations of glucose, respectively. These results advance our understanding on the role of ARC in the modulation of food intake and energy homeostasis.

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Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.07/S13

Topic: F.10. Food Intake and Energy Balance

Support: R01 DK102918
F32 DK120298

Title: AgRP neuronal disinhibition is driven by KCC2 dysregulation in obese mice

Authors: *A. C. KORGAN, W. WEI, K. C. GRAHAM, S. L. A. MARTIN, K. M. S. O'CONNELL;
The Jackson Lab., Bar Harbor, ME

Abstract: In the arcuate nucleus of the hypothalamus (ARH), neurons co-expressing the neuropeptides agouti-related peptide (AgRP) and neuropeptide Y (NPY) are essential for maintaining life by driving appetitive behavior and food intake. Consistent with their role in energy balance, their activity is tightly correlated with nutritional status: increased activity is associated with hunger while decreased activity is associated with satiety. AgRP neuronal activity responds quickly to food cues; this response does not require ingestion, suggesting there is strong “top-down” synaptic modulation of AgRP neurons. Our lab has demonstrated that AgRP neuronal activity is sensitive to diet, implicating high-fat diet (HFD)-induced plasticity and alterations to synaptic inputs to AgRP neurons as a potential causal factor in the development of obesity. We have shown that chronic HFD feeding was associated with a significant increase in inhibitory GABAergic input, suggesting an uncoupling of AgRP neurons from these inputs. Because the transporter KCC2 is required for the inhibitory action of GABAergic inputs, we hypothesized that aberrant KCC2 function may contribute to decreased GABA-mediated inhibition of AgRP neurons. Consistent with this, we found that the equilibrium potential of the $GABA_AR$-mediated Cl^- current was significantly depolarized in AgRP neurons from chronic HFD-fed mice. Further, the impact of optogenetic activation of inhibitory presynaptic inputs on inhibitory post-synaptic currents as well as pharmacological activation of KCC2 (CLP 257) or antagonism of NKCC1 (bumetanide) will elucidate the impact of diet on KCC2 efficacy in hyperpolarizing $GABA_AR$-mediated Cl^- currents. Ongoing work using RNAScope and scRNAseq will quantify transcriptional alterations of Cl^- transporters in arcuate neurons, including AgRP neurons. Further, we will validate AgRP disinhibition in intact, unperturbed neurons using *in vitro* imaging of genetically encoded voltage-sensors. Overall, we have shown that chronic HFD feeding is sufficient to reduce GABA-mediated inhibition in

AgRP neurons and that this disinhibition is linked to altered KCC2 functionality. Thus, obesity may result from failure of postsynaptic AgRP neurons to efficiently integrate incoming synaptic information following long-term HFD feeding.

Disclosures: A.C. Korgan: None. **W. Wei:** None. **K.C. Graham:** None. **S.L.A. Martin:** None. **K.M.S. O'Connell:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.08/S14

Topic: F.10. Food Intake and Energy Balance

Title: Relation of oxidative stress and phosphorylation of AMPK hypothalamic with the feeding behavior in diabetic rats

Authors: *J. M. MENDOZA-BELLO[1], M. I. BARRAGAN-BONILLA[1], Y. A. FLORES-CORTEZ[1], A. MILLAN-VEGA[2], B. ILLADES-AGUIAR[3], M. RAMIREZ[4], M. ESPINOZA-ROJO[1];
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Abstract: Introduction. The AMP-dependent kinase (AMPK) is an important protein to regulate the energy balance in the body. In the hypothalamus, AMPK regulates signals that induce appetite and satiety. The increase in glucose level causes a high production of reactive oxygen species (ROS), which results in a state of oxidative stress (OS), an important factor for diabetic complications. At the level of hypothalamus little has been studied about the relationship between oxidative stress and its effect on phosphorylation of AMPK and food intake in animal models of DM. **Methodology.**To investigate this, Wistar rats were used, diabetes was induced with streptozotocin (60 mg/kg of BW). The animals were divided into 3 independent groups, 7, 14 and 28 days DM (7D, 14D and 28D) each with their respective control group (C). In each of the groups the increase in food intake was calculated (% of change) and at the end of each of the times, the hypothalamic tissue was extracted to evaluate the oxidative stress (malonaldehyde and the activity of glutathione peroxidase) by spectrophotometry , and the phosphorylation of AMPK by Western blot. **Results.**There was a significant increase ($p < 0.05$) in the consumption of food in the groups with DM in comparison with control group(C: 85%, 7D: 120%, 14D: 130%, 28D: 145%). We find that the MDA level decreased to 66%, in group 7D, but in the group 28D this level increased to 190%, these results are significant ($p < 0.05$) compared to group C. On the other hand, the activity of glutathione peroxidase was found to be increased in group 7D (170%) and decreased in group 28D (65%), both significant in comparison with group C.

Phosphorylation of AMPK increased significantly (p. <0.05) in group 28D (168%), compared to group C.**Conclusion.** At 7, 14 and 28 days of diabetic condition, the animals shown an increased in food intake, which is related with increases ofOS and phosphorylation of AMPK, in hypothalamus.

Disclosures: J.M. Mendoza-Bello: None. **M.I. Barragan-Bonilla:** None. **Y.A. Flores-Cortez:** None. **A. Millan-Vega:** None. **B. Illades-Aguiar:** None. **M. Ramirez:** None. **M. Espinoza-Rojo:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.09/S15

Topic: F.10. Food Intake and Energy Balance

Title: Effect of curcumin on NPY and POMC expression in the arcuate nucleus of the hypothalamus in diabetic rats

Authors: *M. I. BARRAGAN-BONILLA[1], M. RAMIREZ[2], J. M. MENDOZA-BELLO[1], B. ILLADES-AGUIAR[3], P. AGUILERA[4], M. ESPINOZA[1];
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Abstract: Neuropeptide Y (NPY) and proopiomelanocortin (POMC) are neuropeptides expressed in the arcuate nucleus (Arc) of hypothalamus and play a key role in the control of food intake behavior by stimulating appetite or satiety, respectively. Arc is an area that integrates metabolic signals and thus regulates the glucose homeostasis. In diabetic models the hyperphagia is associated with increased NPY and decreased POMC expression level in Arc. It is known that hyperphagic behavior contributes to poor glycemic control. On the other hand, in diabetes the treatments with antioxidants can attenuate or improve several alterations including diabetic hyperphagia, however, it is not known if that effect is associated to changes in NPY and POMC expression levels in Arc. Therefore, the aim of this study was to evaluate the effect of curcumin on NPY and POMC expression in Arc of diabetic rats related to diabetic hyperphagia, blood glucose and oxidative stress markers. For this purpose, male Wistar rats two days old were injected with streptozotocin (70mg/kg bw), after weaning, they were supplemented with 10 % sucrose-sweetened-beverage for 4 weeks. At 10 weeks-of-age, diabetes was confirmed, and we administered the treatments: metformin [MET (100mg/kg)] and curcumin [CUR (50mg/kg)] for 28 days orally; we also included a pair feed group (PF). Food intake and body weight was measured daily, blood glucose and oxidative stress markers such as malondialdehyde (MDA),

carbonyl groups, glutathione peroxidase (GPx) and glutathione S tranferase (GST) enzymatic activity were evaluated at the end of the treatment. Finally, the rats were transcardiacally perfunded to obtain brain and detect NPY and POMC in Arc by immunofluorescence. In our study model, diabetic rats showed hyperglycemia, a low body weight gain, hyperphagia, and a tendency to increase GPx activity and MDA level in blood. In addition, they showed a high NPY and a low POMC level expression in Arc. After 28 days of treatment, MET was incapable to reduce blood glucose, while CUR and PF caused a decreased in blood glucose of diabetic rats. On the other hand, treatment with CUR diminished MDA level in blood. In relation to food intake, none treatment was able to avoid the diabetic hyperphagia, however, our preliminary results showed that treatment with MET and CUR in diabetic groups induced changes in NPY and POMC expression level in Arc, we observed a low and increase of these neuropeptides, respectively. These results suggest that a chronic treatment with CUR could attenuate diabetic hyperphagia in rats and probably it will be related to changes in NPY and POMC expression in Arc.

Disclosures: M.I. Barragan-Bonilla: None. **M. Ramirez:** None. **J.M. Mendoza-Bello:** None. **B. Illades-Aguiar:** None. **P. Aguilera:** None. **M. Espinoza:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.10/S16

Topic: F.10. Food Intake and Energy Balance

Support: R01 DK102918
F32 DK120298

Title: Sexual dimorphism in the onset of diet-induced obesity is dependent on AgRP-neuronal excitability

Authors: *K. C. GRAHAM, A. C. KORGAN, W. WEI, S. L. A. MARTIN, K. M. S. O'CONNELL;
The Jackson Lab., Bar Harbor, ME

Abstract: The hypothalamus contains several sexually dimorphic nuclei that have clear structural and functional differences between males and females. One such sexually dimorphic area is the arcuate nucleus, which is essential for the control of energy homeostasis and feeding behavior. When activated under normal feeding conditions, neurons expressing agouti-related peptide (AgRP) in the arcuate nucleus respond to peripheral cues of negative energy balance to elicit food-seeking behavior and are then rapidly suppressed once food is presented. In contrast, our laboratory has shown that when male mice are fed an obesogenic diet, regardless of the

length of time on the diet, AgRP neurons in the arcuate rapidly and persistently increase in intrinsic excitability, suggesting that the diet itself may reinforce hyperphagia and promote the development of obesity. Here, we show that, in females, AgRP neurons also increase in excitability in response to high-fat diet (HFD) but not as rapidly or persistently as in males with female mice being more resistant to development of obesity and leptin insensitivity. Additionally, when we measured synaptic inputs to AgRP neurons following long-term HFD we observed an increase in inhibitory post-synaptic current frequency that is consistent with what we find in neurons from male mice; however, unlike in males, there is no shift in the reversal potential of GABA-evoked Cl^- current in AgRP neurons from female mice, suggesting that Cl homeostasis and synaptic signaling mechanisms remain intact in response to HFD exposure. Taken together, these data suggest a potential compensatory mechanism in female AgRP neurons for control of feeding behavior and energy homeostasis that contributes to resistance to diet-induced obesity. Ongoing research will utilize RNA-sequencing techniques to examine the potential for gene or pathway expression that may elucidate this compensatory mechanism.

Disclosures: K.C. Graham: None. **A.C. Korgan:** None. **W. Wei:** None. **S.L.A. Martin:** None. **K.M.S. O'Connell:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.11/S17

Topic: F.10. Food Intake and Energy Balance

Support: NIH R01 DK102918
NIH F32 DK120298

Title: Elevated dietary sucrose consumption induces AgRP neuronal circuit dysregulation and leptin resistance without altering body weight

Authors: A. C. KORGAN[1], K. ABREU[3], K. GRAHAM[1], W. WEI[1], S. L. A. MARTIN[2], *K. M. S. O'CONNELL[2];
[1]Res., [2]The Jackson Lab., Bar Harbor, ME; [3]Superior Inst. of Biomed. Sci., State Univ. of Ceara, Fortaleza, Brazil

Abstract: The role of agouti-related peptide (AgRP) expressing neurons has been well documented in the context of hunger, satiety, and response to metabolic stress (e.g. fast, high-fat diet). However, the response of AgRP neurons to long-term increases in dietary sucrose, independent of increased dietary fat have not been detailed. While this neuronal population has a canonical role in appetitive behavior, it also serves as a regulator of fat deposition, substrate utilization, and nutrient partitioning. We previously reported that consumption of a high-fat diet

was associated with hyper-excitability of AgRP neurons and subsequent alterations to feeding behavior. In the current study, we aimed to examine the effects of long-term sucrose consumption on AgRP neuronal excitability and synaptic dynamics in addition to changes in peripheral metabolic phenotypes and behavior. Sucrose was provided via the drinking water while feeding the identical diet as controls. We found that similar to mice fed a high-fat diet, AgRP neuronal excitability was increased despite an increase in the frequency of inhibitory synaptic inputs. Further, we found that AgRP neurons from sucrose-fed mice were leptin-resistant. However, unlike HFD, acute sucrose consumption had no effect on AgRP neuronal excitability. Thus, the deleterious effects of sucrose consumption may be related to a non-canonical role of AgRP neurons and/or feedback from peripheral consequence of chronic sucrose consumption, as body weight was not increased after 14 weeks of sucrose consumption despite impairments in both glucose and insulin tolerance. Ongoing work will examine the pattern and penetrance of AgRP dendritic outputs and the effects that these have on feeding behaviors. Altogether, these results suggest that AgRP neurons are involved in mediating specific, diet-dependent, alterations and future studies will focus on circuit specific effects of diet manipulation on metabolic and behavioral outcome.

Disclosures: K.M.S. O'Connell: None. **A.C. Korgan:** None. **K. Abreu:** None. **K. Graham:** None. **W. Wei:** None. **S.L.A. Martin:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.12/S18

Topic: F.10. Food Intake and Energy Balance

Support: NRF 2016R1C1B2007319
NRF 2017M3C7A1043845
NRF 2016R1A4A1010796
KHIDI HI17C2665
KHIDI HI15C2887

Title: A neural circuit mechanism for mechanosensory feedback control of ingestion

Authors: *M. KIM[1,2], D.-Y. KIM[1,3], G. HEO[1], H. KIM[1], S. JUNG[1,3], M. AN[1,2], J. PARK[1], H.-E. PARK[1], M. LEE[1,2], S.-Y. KIM[1,2,3];
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Abstract: Negative sensory feedback from the digestive tract to the brain is critical for limiting food and water intake. Mechanosensory detection of ingesta is a major source of the signaling, but the underlying gut-brain communication pathways and mechanisms for reducing appetite remain unclear. Here we identify an excitatory subpopulation in the parabrachial nucleus as a key circuit node for mechanosensory monitoring and feedback control of ingestion. By recording calcium dynamics in vivo, we show that the neurons respond to the intake of either fluids or solids regardless of the composition, and the response strength scales with the ingestion rate. Furthermore, this population is activated by mechanical stimuli applied to any parts of the upper digestive tract, but not modulated by taste, osmolality or temperature of ingesta. Activating these neurons suppresses both feeding and drinking, by transmitting sustained negative-valence signals that discourage the initiation of intake bouts. In contrast, inhibiting the same population induces pathological overconsumption, only if a drive for ingestion exists, signifying that these neurons transmit negative feedback signals. Together, our findings provide a neural mechanism underlying mechanosensory monitoring of ingestion and inhibition of intake behaviors upon aversive digestive tract distension.

Disclosures: **M. Kim:** None. **D. Kim:** None. **G. Heo:** None. **H. Kim:** None. **S. Jung:** None. **M. An:** None. **J. Park:** None. **H. Park:** None. **M. Lee:** None. **S. Kim:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.13/T1

Topic: F.10. Food Intake and Energy Balance

Support: EMBO

Title: Modulation of hypothalamic hunger circuits by an ascending catecholamine pathway

Authors: *D. ATASOY[1], I. AKLAN[1], N. SAYAR[1], Y. YAVUZ[2];
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Abstract: Hunger is a hard-wired behavioral state essential for survival. Hunger sensitive agouti-related protein (AgRP)-expressing neurons of arcuate hypothalamic nucleus (ARC) play central role in feeding, yet the signals that modulate AgRP neuron activity are poorly understood. We discovered that tyrosine hydroxylase (TH)-expressing neurons from nucleus of solitary tract (NTS) project densely to the hypothalamus, and their local activation elicit voracious feeding through bidirectional regulation of AgRP and proopiomelanocortin (POMC)-expressing neurons. Neuroanatomical tracing results suggested that ARC projecting orexigenic NTS^{TH} neurons comprise a largely distinct subpopulation than those parabrachial nucleus (PBN)-projecting anorexigenic NTS^{TH} neurons. Finally, optogenetic and chemogenetic analyses showed that

norepinephrine (NE)-signaling from NTS^{TH} terminals in the ARC is critical for appetite stimulation. Collectively, we describe a circuit organization in which an ascending neuromodulatory pathway from brainstem coordinates key appetite neurons in hypothalamus for rapid regulation of hunger.

Disclosures: D. Atasoy: None. **I. Aklan:** None. **N. Sayar:** None. **Y. Yavuz:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.14/T2

Topic: F.10. Food Intake and Energy Balance

Title: Effects of vagotomy and lesions of the area postrema on nausea induced by tranexamic acid

Authors: *M. FUJITA, Y. HIRAI, K. HISADOME, M. FUNAHASHI;
Hokkaido Univ., Hokkaido, Japan

Abstract: The aim of the present study is to clarify the mechanism of emetogenic effects of tranexamic acid (TXA) that is offen used as an drug for accidental ingestion of animals in the field of veterinary medicine. TXA is an artificial amino acid that can block the binding of plasmin and plasminogen to fibrin. Therefore TXA is well known as antibleeding, antiallergic and anti-inflammatory drugs. However, we can not explain the mechanism of emetogenic effects of TXA based on the antiplasmin activity. To investigate the details of TXA-induced nausea, we performed the following experiments. Male Sprague Dawley rats (body weight 200~350 g) were used as experimental animals. Since rats are animals that do not vomit, conditioned taste aversion (CTA) was used as an index for evaluating the presence or absence of nausea. 0.1% saccharin was used as a conditioned stimulus, nausea induced by TXA injection (1.5g/kg, 15 ml/kg, i.p.) was used as an unconditioned stimulus. CTA to saccharin was evaluated using the 1-bottle method. Experimental period was for 15 days with same daily cycle of scheduled drinking and voluntary feeding. The training period was the first 7 days (day 0~6). The conditioning was performed at day 7. After recovery period at day 8, saccharin intake was measured at day 9~14. The scheduled drinking protocol consists of water deprivation for 20 h, voluntary drinking for 20 min (measurement period), water deprivation for 40 min, and voluntary drinking for 3 h. On the conditioning day, rats had a first chance of saccharin intake for 20 min instead of distilled water and the saccharin intake obtained this day was used as a control value. We performed measurement of CTA in 3 groups: rats received no operation (control), bilateral subdiaphragmatic vagotomy (VX), and lesions of the area postrema (APX). Saccharin intake was significantly reduced in the control and the VX on the day 9~10 as compared to the conditioning day, indicating that both groups acquired CTA for saccharin as a result of induction of nausea by

TXA. CTA acquisition was suppressed in 2 cases in the APX. These results suggest possible role of the area postrema neurons in the mechanism for inducing nausea by TXA.

Disclosures: **M. Fujita:** None. **Y. Hirai:** None. **K. Hisadome:** None. **M. Funahashi:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.15/T3

Topic: F.10. Food Intake and Energy Balance

Support: The Saban Research Institute Core Pilot Program

Title: Impact of early life gut microbial environment on energy homeostasis, vagal development, and CCK-induced satiety

Authors: *A. K. KAMITAKAHARA[1], V. MAGALONG[1], P. R. LEVITT[1,2];
[1]Children's Hosp. Los Angeles, Los Angeles, CA; [2]Keck Sch. of Medicine, Univ. of Southern California, Los Angeles, CA

Abstract: The vagus nerve directly connects the brain and gastrointestinal tract and is able to sense and fire action potentials in response to microbial signals. However, a critical knowledge gap exists in understanding whether early life microbiome disruption affects vagal development and metabolic function. To this end, we used a mouse model of perinatal antibiotic exposure: [1)] control mice receiving no antibiotics, [2)] mice receiving penicillin 1 week prior to birth through the end of the study (ABX^{Life}), and [3)] mice receiving penicillin 1 week before birth through 4 weeks of age, after which they were maintained on water with no antibiotics (ABX^{Early}). At 12 weeks of age, ABX^{Life} mice (male mean 24.363g, SEM 0.639g; female mean 19.080g, SEM 0.675) tended to weigh less than control mice (male mean 26.837g, SEM 0.907g; female mean 20.528g, SEM 0.270), while ABX^{Early} mice (male mean 28.896g, SEM 0.478g; female mean 21.855, SEM 0.303) tended to weigh more. In addition, body composition analysis revealed that both ABX^{Life} and ABX^{Early} mice exhibited a trend toward increased fat mass compared to controls. To exacerbate these differences in body weight and body composition, a separate cohort of mice underwent the same antibiotic treatment paradigm, followed by weaning onto a high-fat diet. Interestingly, both the differences in body weight and body composition were mitigated by high-fat diet exposure. To assess vagal signaling in early life, control and antibiotic treated pups were injected with choleocystokinin (CCK) on postnatal day 7. CCK is secreted by enteroendocrine cells in the gut and acts largely through the vagus to signal satiety to the central nervous system. Control pups exhibited a robust CCK-induced cfos neuronal activation response in the nucleus of the solitary tract, where vagal afferents connect. In contrast, pups receiving antibiotics exhibited blunted CCK-induced cfos responses, suggesting that satiety signaling via

the vagus nerve may be impaired developmentally. Increased sample number is required to demonstrate statistical significance, but these preliminary data suggest that early life antibiotic exposure may impair vagal afferent signaling of satiety.

Disclosures: A.K. Kamitakahara: None. **V. Magalong:** None. **P.R. Levitt:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.16/T4

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant GM109817
NIH Grant GM127251
NIH Grant DK081937

Title: Atlas-based spatial analysis of rat hindbrain regions that display rapid activation in association with glycemic challenge

Authors: *G. P. TAPIA[1], L. J. AGOSTINELLI[2,3], S. D. CHENAUSKY[1], J. BARNES[1], D. D. MOLINA[1], A. M. KHAN[1,2];
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Abstract: It has been hypothesized that hypoglycemia unawareness may result, in part, from a failure of hindbrain glucosensing neurons to respond effectively to changes in circulating glucose. Subpopulations of hindbrain-originating epinephrine and norepinephrine neurons are necessary to prompt the glucose counterregulatory response (CRR) that protects against hypoglycemic conditions, but the precise atlas-based distribution of glucosensing neuronal populations remains unclear. To assess this distribution, hindbrain regions were re-examined carefully in glucoprivic (2-deoxyglucose, 250 mg/kg, i.v.) and control rats that had been previously processed to identify single- and double-labeled neurons using antibodies against phospho-ERK1/2 (phosphorylated forms of MAP kinase), dopamine β-hydroxylase, and choline acetyltransferase. Wide field epifluorescence images of these immunlabeled tissue sections were aligned with those of an adjacent series of Nissl-stained tissue that served as a cytoarchitectural reference, enabling the data to be mapped to a rat brain atlas (Swanson, *Brain Maps 4.0*, 2018). In glucoprivic animals, we had previously found increased cellular activation in hindbrain noradrenergic and cholinergic regions, suggesting that activation of these areas may be associated with rapid responses to glycemic challenge. Our new mapping analysis shows that, in the anterior hindbrain (e.g., Swanson Atlas Levels (L) 46-53), phospho-ERK1/2+ neurons were distributed in the locus ceruleus, subceruleus, and parts of the parabrachial nucleus. More

caudally (e.g., L54-62), activation was observed in cholinergic cell groups and in the vicinity of the facial nucleus and ambiguus nucleus. At the most caudal hindbrain atlas representations (e.g., L69-72) activation was observed in the nucleus of solitary tract and near the central canal. These initial atlas assignments are a critical step for our ongoing atlas-based mapping of hindbrain glucosensing regions and will facilitate more precise targeting of neural circuitry related to glucosensing in the future.

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Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.17/T5

Topic: G.03. Emotion

Support: NIH R01MH105447

Title: Examining the effect of antibiotic treatment on emotional health: Comparable findings in rats and humans

Authors: *M. E. GLOVER[1], I. A. KERMAN[2], S. M. CLINTON[1];
[1]Neurosci., Virginia Tech. Univ., Blacksburg, VA; [2]Carilion Clin., Roanoke, VA

Abstract: Gastrointestinal disorders are highly comorbid with emotional disorders such as Major Depression, and changes within the gut microbiome have been linked to a variety of brain disorders. Gut microbiota are essential for healthy gastrointestinal function, but also broadly influence organismal health through effects on the immune and central nervous systems. Several environmental factors can influence microbiome composition, including stress exposure and treatment with drugs such as antibiotics. Stress has well-known negative impacts on emotional behavior and recent evidence suggests that antibiotics, although widely prescribed, may also negatively affect mental health. To further investigate the potential relationship between antibiotic use and altered emotional behavior, we first conducted a study where experimental rats that were bred for emotional behavior differences were treated with antibiotics. High Novelty Responder (HR) / Low Novelty Responder (LR) rats were selectively bred based on their locomotor response in a novel environment. Breeding for this trait behavior leads to consistent behavioral differences in rodent emotionality. HRs exhibit increased aggression, impulsivity, and proclivity to take drugs of abuse while LRs exhibit high levels of anxiety-like behavior, passive stress coping, and susceptibility to chronic stress. Because it was unknown whether HR/LR rats exhibit differences in microbe communities, we used 16S rRNA sequencing to compare the microbiome of HR and LR rats. At baseline, adult HR and LR rats did not exhibit microbiome

differences; however, treating them with broad-spectrum antibiotic cocktails reduced microbe community diversity and exacerbated some of their behaviors, including increasing anxiety-like behaviors in LRs and active coping in both rat strains. These findings prompted us to investigate whether antibiotic use in a human population also increases the risk of mental illness as few population-based studies have interrogated this relationship. To do so, we conducted retrospective studies of patient electronic medical records in the TriNetX database to determine if antibiotics were associated with an increased risk of new mental illness diagnoses. We hypothesized that antibiotic treatment may lead to an increased risk of new mental illness diagnoses. In this analysis, we first investigate the risk associated with 1) any antibiotic class or 2) specific classes with various mental health diagnoses including MDD, anxiety disorders, Bipolar Disorder, and Schizophrenia. The results of this study will help elucidate the relationship between antibiotic-induced dysbiosis and mental health.

Disclosures: **M.E. Glover:** None. **I.A. Kerman:** None. **S.M. Clinton:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.18/T6

Topic: G.03. Emotion

Support: Exploratory Research for Advanced Technology (JPMJER1801)
Precursory Research for Embryonic Science and Technology (JPMJPR1785)

Title: Relationship between vagus nerve spikes and physiological signals of central and peripheral organs in a freely moving rat

Authors: *T. OKONOGI[1], Y. SHIKANO[2], Y. NISHIMURA[1], A. YAMANAKA[3], Y. IKEGAYA[1], T. SASAKI[1,4];
[1]Grad. Sch. of Pharmaceut. Sci., The Univ. of Tokyo, Tokyo, Japan; [2]Sch. of Med., Keio Univ., Tokyo, Japan; [3]Res. Inst. of Envrn. Medicine, Nagoya Univ., Nagoya, Japan; [4]JST PRESTO, Saitama, Japan

Abstract: The vagus nerve serves as a major pathway for communication between the central and peripheral organs. Despite traditional knowledge of vagus nerve functions, detailed neurophysiological dynamics of the vagus nerve in naïve behavior remain to be understood. In this study, we developed a method to record spiking patterns from the cervical vagus nerve while simultaneously monitoring central and peripheral organ bioelectrical signals in a freely moving rat. When the rat transiently elevated its locomotor activity, the frequency of vagus nerve spikes correspondingly increased, which was retained for several seconds after an increase in running speed. During high frequency sniffing behavior, vagus nerve spikes were nearly absent. During

stopping behavior, the vagus nerve spike patterns varied depending on external contexts and peripheral activity states associated with cortical arousal levels. Electrical stimulation of the vagus nerve altered rat's running speed and cortical arousal states depending on running speed. These observations represent a new step to uncover the physiological dynamics of the vagus nerve modulating the visceral organs such as cardiovascular, respiratory, and gastrointestinal systems. In addition, we recently developed a method to activate vagal afferent or efferent fibers by using a transgenic mouse line in which channelrhodopsin2 is selectively expressed in a fiber specific manner. We present preliminary data showing how photoactivation of these fibers could alter emotion and memory function.

Disclosures: T. Okonogi: None. **Y. Shikano:** None. **Y. Nishimura:** None. **A. Yamanaka:** None. **Y. Ikegaya:** None. **T. Sasaki:** None.

Poster

591. Food Intake and Energy Balance: Integration of Peripheral Signals

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 591.19/T7

Topic: F.10. Food Intake and Energy Balance

Support: IUSM Center for Diabetes and Metabolic Diseases

Title: Altered spinophilin interactions in the hypothalamus and pancreas of a leptin receptor mutant (db/db) model of obesity

Authors: *K. C. STICKEL[1], D. S. WATKINS[2], A. J. BAUCUM II[3];
[1]IUPUI, Indianapolis, IN; [2]Indiana Univ. Sch. of Med., Indianapolis, IN; [3]Biol., Indiana University-Purdue Univ. Indianapolis, Indianapolis, IN

Abstract: Spinophilin is a multi-domain scaffolding protein that targets protein phosphatase 1 (PP1) to myriad downstream signaling proteins in order to modulate synaptic activity. Little is known about how spinophilin acts in both neuronal and non-neuronal cell types, such as the arcuate nucleus and beta cells of the pancreatic islets, to modulate feeding and glucose homeostasis. Previous studies established that spinophilin KO mice have decreased fat mass and increased lean mass and improved glucose tolerance. Yet, how spinophilin acts in specific cell types to modulate the above metabolic parameters is unclear. In addition to its high expression in the brain (and expression in feeding centers of the brain such as the hypothalamus), we observed spinophilin expression in mouse pancreas. Using proteomics-based approaches we identified multiple putative spinophilin interacting proteins isolated from intact pancreas, including: PP1, the spinophilin homolog neurabin, and myosin-9. We have found that the associations of PP1, neurabin, and myosin-9 with spinophilin were regulated in obese, *db/db* mice as early as 6 weeks. We have also found associations of spinophilin, neurabin, myosin 9, and PP1 in isolated

pancreatic islets and are currently delineating if the alterations in interactions are occurring specifically in islets. Ongoing studies are utilizing a recently developed *floxed* spinophilin mouse line to delineate if loss of spinophilin in pancreatic beta cells specifically improves whole body glucose tolerance and if loss of spinophilin expression in AgRP neurons of the hypothalamus inhibit feeding behaviors.

Disclosures: K.C. Stickel: None. **D.S. Watkins:** None. **A.J. Baucum II:** None.

Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 592.01/T8

Topic: G.02. Motivation

Support: DA015188
MH063649
DA047738
DA007281

Title: Excitation and inhibition of limbic corticotropin releasing factor neurons modulates motivation

Authors: *H. M. BAUMGARTNER[1], L. L. HUERTA SANCHEZ[1], J. SCHULKIN[2], K. C. BERRIDGE[1];
[1]Psychology, Univ. of Michigan, Ann Arbor, MI; [2]Dept. of Neurosci., Georgetown Univ., Washington, D.C., DC

Abstract: Corticotropin releasing factor (CRF) is known as the brain's master stress molecule, but also plays a role in reward seeking. Previous pilot work from our lab suggested that optogenetic excitation of CRF neurons in either nucleus accumbens (NAc) or central nucleus of amygdala (CeA) of CRH-Cre rats can amplify and bias incentive motivation to earn and consume natural sucrose rewards, an appetitive motivation effect similar to optogenetic stimulation of general neuronal populations in CeA. By contrast, we find that stimulation of CRF neurons in bed nucleus of stria terminalis (BNST) causes rats to avoid the laser-paired sucrose option and instead choose the alternative sucrose-alone option, and in a progressive ratio task suppresses motivation to work for sucrose rewards. Here, we assess whether optogenetic inhibition of CRF neurons in these areas through halorhodopsin oppositely has negative-valence effects on motivation, causing rats to avoid the NAc or CeA CRF neuron laser-paired sucrose option, while rats receiving BNST CRF neuron inhibition may prefer this laser-paired option. Additionally, we will assess whether CRF neuron laser-inhibition alone will have negative- or positive-valence effects through self-stimulation tasks, and whether CRF neuron excitation can

similarly influence motivation for other salient stimuli (i.e., intravenous cocaine rewards or aversive shocks). Together, these data suggest that CRF neurons in NAc or CeA can focus and influence incentive motivation for natural rewards, whereas BNST CRF neurons may suppress incentive motivation or have aversive effects.

Disclosures: H.M. Baumgartner: None. **L.L. Huerta Sanchez:** None. **J. Schulkin:** None. **K.C. Berridge:** None.

Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 592.02/T9

Topic: G.02. Motivation

Support: NIDA Grant 084564
NIMH Grant 088403

Title: Comparing reward roles of D1 neurons vs D2 neurons in accumbens and amygdala

Authors: *S. ABTAHI[1], E. M. RODBERG[2], K. C. BERRIDGE[1];
[1]Dept. of Psychology, [2]Neurosci. Grad. Program, Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Dopamine projections reach mostly separate populations of medium spiny neurons (MSNs) expressing either D1 receptors or D2 receptors within striatal-like structures. Here we sought to examine the role in reward motivation of D1 MSNs and D2 MSNS in the medial shell of nucleus accumbens (NAc) and in the central nucleus of the amygdala (CeA), which shares some striatal features. Past work on D1-Cre or D2-Cre mice found both mice will work for optogenetic channelrhodopsin (ChR2) laser self-stimulation in NAc shell (Cole et al., 2018). However, D2-Cre results are complicated by the fact that D2 receptors are also expressed by acetylcholine neurons in NAc. Here we compared a D1-Cre line to an A2-Cre line of rats, both developed by C. Ferrario and J. Berke labs. Adenosine-2 (A2) receptors are co-expressed by NAc or CeA MSNs that have D2 receptors, but acetylcholine neurons lack A2 receptors. Thus, an A2-Cre approach may more more selectively target D2 MSNs in NAc or CeA than a D2-Cre approach, for better comparison to D1 MSNs. Our preliminary self-stimulation results using D1-Cre rats indicates robust levers laser self-stimulation of D1 MSNs can be obtained in both medial shell of NAc and in CeA. Our results so far on A2-Cre rats indicate at least moderate levels of positive laser self-stimulation of D2 MSNs in NAc shell, and possibly also in CeA, can similarly be obtained. This supports the hypothesis that selective excitation of D2 MSNs, as well as of D1 MSNs in NAc or CeA, can support positive reward motivation at least under some conditions.
Note: We thank Carrie Ferrario and Joshua Berke for allowing us to use their lines of D1-Cre and A2-Cre rats.

Disclosures: **S. Abtahi:** None. **E.M. Rodberg:** None. **K.C. Berridge:** None.

Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 592.03/T10

Topic: G.02. Motivation

Support: NIH Grant DA015188
NIH Grant MH63649
NIH Grant DC00011

Title: Cortical optogenetic stimulation of 'liking' and ventral pallidum inhibition for 'disgust'

Authors: *I. MORALES, K. C. BERRIDGE;
Dept. of Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: Research in our lab has identified a number of hedonic hotspots that can magnify the hedonic impact, or 'liking' reactions to a taste sensory stimulus. These generators of intense pleasure are small subregions in nucleus accumbens (NAc), ventral pallidum (VP), parabrachial nucleus (PBN), orbitofrontal cortex (OFC), and insula where microinjections of mu-opioid or orexin receptor agonists causally amplify orofacial reactions to sucrose by 200-300%. Of the known hedonic hotspots, the ventral pallidum appears to be especially important for normal hedonic function. It's the only known structure where lesions or temporary inactivations generate intense disgust so that even normally 'liked' sucrose becomes 'disgusting'. Here we study brain causation of 'liking' and 'disgust' reactions using optogenetics by directly controlling the activity of neurons within the hedonic hotspots in anterior medial orbitofrontal cortex, posterior insula, and caudal ventral pallidum. We excited neurons in cortical hotspots, and conversely inhibited neurons in the ventral pallidum. Optogenetic excitation of neurons in anterior-medial OFC hotspot and posterior insula hotspot amplified 'liking' reactions to sweet taste and increased consumption of palatable M&M candies. However, posterior insula, but not OFC stimulation appears to be rewarding on its own and supported laser self-administration as a reward on its own for some animals. We also inhibited neurons ventral pallidum using the inhibitory chloride conducting opsins SwiChR++ and iC++ and tested animals on taste reactivity, food intake, and conditioned place preference tasks. We found optogenetic inhibition of the posterior ventral pallidum may simultaneously reduce hedonic 'liking' reactions to a neutral water taste stimulus and increase negative 'disgust' reactions to both water and bitter quinine. The same optogenetic manipulations also decreased palatable M&M intake, and promoted avoidance of a laser-paired compartment in a conditioned place-avoidance test. Overall, our results suggest that both cortical and subcortical structures are important for generating intense

positive and negative affective responses to taste stimuli. Our experiments may extend our understanding of hedonic dysfunction in psychiatric affective disorders.

Disclosures: I. Morales: None. **K.C. Berridge:** None.

Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 592.04/T11

Topic: G.02. Motivation

Support: MH063649
DA015188
DA007268
DCD00011

Title: Optogenetic excitation of the ventral pallidum and lateral hypothalamus promotes 'wanting' but only the posterior ventral pallidum enhances 'liking'

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Abstract: The ventral pallidum (VP) and lateral hypothalamus (LH) are subcortical structures whose connectivity with other limbic circuitry makes them ideally positioned to influence reward-related behaviors. Accordingly, previous studies have demonstrated that pharmacological excitation of these areas can enhance food 'wanting' (motivation). Although early investigations implicated the LH in modulating 'liking' (pleasure), subsequent examinations have revealed that only the neighboring posterior VP (pVP), not the LH, contains an opioid/orexin hedonic 'hotspot' that mediates 'liking' enhancements. The aim of the present study was to extend upon earlier neurochemical findings by investigating if direct optogenetic depolarization of the LH, VP, or LH neurons projecting to the pVP (LH-VP) via channelrhodopsin under a nonspecific neuronal promoter (hSyn-ChR2) enhances 'wanting' and 'liking' toward a natural reward. Additionally, we sought to identify the neurochemical mechanisms of VP 'wanting' enhancements using GAD-Cre rats with a Cre-inducible ChR2 virus to selectively target GABAergic neurons of the VP. Findings thus far indicate that hSyn-ChR2 photoexcitation at all sites across the VP is able to amplify and focus incentive motivation for a sucrose reward. Similar excitation of LH or LH-VP projections failed to impact sucrose 'wanting'. However, VP, LH, and LH-VP hSyn-ChR2 stimulation increased food intake. Additionally, laser self-stimulation in the absence of an external reward was reinforcing in only some VP and LH rats.

What is more, activation of the pVP via hSyn-ChR2 enhanced 'liking' reactions to oral sucrose whereas similar excitation of the aVP may suppress 'liking' reactions. Interestingly, although laser stimulation of the LH did not alter 'liking' reactions, stimulation of LH-VP neurons amplified 'liking'. Finally, selective stimulation of GABAergic neurons of the VP in GAD-Cre rats similarly amplified and focused incentive motivation for a sucrose reward, but did not enhance food intake. Photoactivation of VP GABA neurons in these rats promoted robust laser self-administration. Together, these data confirm previous findings that 'wanting' is widely distributed throughout the brain while substrates that mediate 'liking' are restricted to a few subregions.

Disclosures: J.J. Olney: None. **D.C. Castro:** None. **K. Urstadt:** None. **A.A. Kotian:** None. **K.C. Berridge:** None.

Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

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Program #/Poster #: 592.05/T12

Topic: G.02. Motivation

Support: NIH Grant DA015188
NIH Grant MH63649

Title: Dangerous desire: Paired central amygdala photostimulation can turn fear into desire

Authors: *E. E. NAFFZIGER[1], S. M. WARLOW[3], K. C. BERRIDGE[2];
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Abstract: Here we show that pairing optogenetic stimulation of central amygdala (CeA) in rats with an electrified "shock" rod that delivers shocks to paws or snout when touched turns fearful defensive burying into attracted approach. In this experiment, rats received bilateral stimulation each time they were within 2 cm of the electrified shock rod protruding into the Plexiglas chamber. While control rats contacted the electrified rod at least once and then avoided or buried the rod, rats with the excitatory opsin, channelrhodopsin (ChR2), repeatedly approached, sniffed, touched or even chewed on the rod, receiving repeated shocks. Furthermore, in a test of conditioned reinforcement in which rats could work for an auditory cue previously paired with shock rod encounters (CS+), CeA ChR2 rats worked on a nosepoke task to earn their shock rod associated CS+. In additional follow-up experiments, it was found that systemic dopamine injections of flupentixol suppressed CeA ChR2 shock rod attraction and CeA ChR2 rats were also willing to overcome an experimenter-imposed obstacle to access the rod when occluded. Histological analyses of distant c-fos indicated that mesocorticolimbic circuitry was activated

during CeA ChR2 shock rod attraction. These data emphasize a role of CeA in transforming even a fear-evoking stimulus into an incentive via recruitment of mesolimbic circuitry.
See: Dangerous Desires: Focusing intense pursuit onto sugar, cocaine, or pain. *(In preparation)*

Disclosures: E.E. Naffziger: None. **S.M. Warlow:** None. **K.C. Berridge:** None.

Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 592.06/T13

Topic: G.02. Motivation

Support: NWO VIDI grant to I.W. (864.14.010, 2015/06367/ALW)
ERC Starting Grant to I.W. (ERC-2014-STG 638013)

Title: Cortico-striatal circuits mediate compulsive behavior in schedule-induced polydipsia

Authors: *T. ARBAB[1,2], D. DENYS[2], I. WILLUHN[1,2];
[1]Netherlands Inst. For Neuroscience, Royal Netherlands Acad. of Arts and Sci., Amsterdam, Netherlands; [2]Dept. of Psychiatry, Amsterdam UMC, Univ. of Amsterdam, Amsterdam, Netherlands

Abstract: Compulsive behavior is implicated in psychiatric aberrations such as addiction and obsessive-compulsive disorder, and is characterized by excessive, repetitive actions that persist despite adverse consequence. Dysregulation of cortico-striatal neural circuits correlates with symptom severity. However, the specific contributions of the underlying neural mechanisms remain elusive, and the efficacy of current treatment is limited. Thus, it is imperative to study the specific contribution of cortico-striatal circuits to compulsive behavior.
We employ schedule-induced polydipsia (SIP), a rat model of escalated drinking, to study how cortico-striatal circuits mediate the development and expression of compulsive behavior. In SIP, food-restricted rats are placed daily in an operant box, where they are presented food pellets at a time interval, with free access to water. In between pellet deliveries, some rats develop excessive water consumption (high drinkers), whereas others do not (low drinkers). Water intake is quantified as a measure of compulsivity.
We find that lesions of the prefrontal cortex escalate acquisition and elevate expression of excessive drinking in SIP, which suggests that under normal circumstances, these regions exert control over compulsivity. Preliminary data shows that excessive drinking in lesioned animals is reflected in their affective self-reports (ultrasonic vocalizations). Additionally, we find excessive drinking in SIP is modulated by glutamate signaling and affected by behavioral manipulations that alter the motivational state of the rat. Finally, high-drinking animals maintain their excessive drinking throughout experimental manipulations that link adverse consequences water intake. All

these effects are specific to compulsive drinking in SIP, without affecting general activity or homeostatic drinking of the animals.
We pursue these initial observations of cortico-striatal mediation of compulsive behavior in SIP with multi-tetrode recordings in freely moving rats during this paradigm, characterizing the underlying single unit and local field activity in cortex and striatum. Altered function of these circuits in high-drinking animals identifies neural substrates of compulsivity as potential targets for treatment.

Disclosures: T. Arbab: None. **D. Denys:** None. **I. Willuhn:** None.

Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

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Topic: G.02. Motivation

Support: National Natural Science Foundation (Grant Nos. 31800963, 81621003)
Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT, Grant No. IRT16R52) of China
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American CMB Distinguished Professorship Award (Award No.F510000/G16916411)

Title: Neurostructural substrates underlying dispositional optimism in late adolescence

Authors: *H. L. LAI, S. WANG, Q. GONG;
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Abstract: As a hot subject for positive psychology researches, dispositional optimism reflects one's generalized positive expectancies for future outcomes, and has been considered to be closely related to personal life outcomes and health. However, the neurostructural substrates underlying dispositional optimism in adolescents remains large unknown. Here, to examine this issue, we conducted a whole-brain voxel-based morphometry (VBM) study to identify neuroanatomical basis of dispositional optimism in 231 healthy adolescents and explored whether extraversion could be an essential personality factor for dispositional optimism development via mediation analysis. Specifically, behavioral measures, including Revised life orientation test (LOT-R), NEO Five-Factor Inventory (NEO-FFI) and Raven's advanced progressive matrix (RAPM), were first employed to obtain each participant's dispositional optimism, extraversion and general intelligence score. Then, MRI data of each participant was collected and processed. To identify brain gray matter correlates of dispositional optimism, whole-brain multiple regression analyses were performed and revealed that dispositional

optimism was positively associated with rGMD in the bilateral putamen (left putamen: $r = 0.28$, $p < 0.001$; right putamen: $r = 0.25$, $p < 0.001$). No other significant cluster was identified. Moreover, to investigate whether the identified optimism-related brain regions were stable and robust, prediction analyses using machine-learning approach were performed and showed that dispositional optimism was reliably predicted by the rGMD in the left putamen [$r_{(predicted, observed)} = 0.25$, $p < 0.001$] and the right putamen [$r_{(predicted, observed)} = 0.21$, $p < 0.001$]. More importantly, to explore whether extraversion could explain the effect of brain anatomy on dispositional optimism, a mediation analysis was conducted and showed that extraversion independently played an important mediating role in the association of rGMD of the putamen with dispositional optimism. Additionally, all findings remained significant even when removing the effect of nuisance covariates including gender, age, general intelligence and total gray matter volume. Taken together, the current findings provide a fresh evidence for neurostructural basis of dispositional optimism, demonstrating that the putamen may be a pivotal neuroanatomical site linking extraversion to dispositonal optimism, and give fresh light on the selection of targeted brain regions for dispositional optimism interventions.

Disclosures: **H.L. Lai:** None. **S. Wang:** None. **Q. Gong:** None.

Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

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Topic: G.02. Motivation

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ERC Starting grant to I.W. (ERC-2014-STG 638013)

Title: Deep-brain stimulation of the internal capsule has distinct effects on neuronal activity in different nodes of cortico-striatal circuits

Authors: *B. J. G. VAN DEN BOOM[1,2], A. ALONSO-ANDRES[1], D. DENYS[2], I. WILLUHN[1,2];
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Abstract: Obsessive-compulsive disorder (OCD) is characterized by obsessions (unwanted thoughts) and compulsions (repetitive, stereotyped behaviors), and is often accompanied by anxiety. Aberrant activity in cortico-striatal circuits is considered a neural correlate of OCD. Some evidence indicates that normal cortico-striatal function can be restored in otherwise treatment-resistant patients using deep-brain stimulation (DBS) of the internal capsule (IC).

Here, we examined the effects of DBS on compulsive-like behavior and brain-network activity in SAPAP3 knock-out mice (SAPAP3$^{-/-}$), a model for OCD that exhibits compulsive grooming, increased anxiety, and deficits in cortico-striatal circuit function. Using miniaturized fluorescent one-photon microscopy (miniscope) in freely behaving mice, we measured DBS-induced changes in single-cell calcium dynamics in cortico-striatal regions. The calcium indicator GCaMP6f was delivered via virus injection into the secondary motor cortex (M2), the dorsal striatum (DS), or the nucleus accumbens (NAc). GCaMP6f fluorescence, indicative of neuronal activity, was captured with the miniscope via a GRIN relay lens implanted above the target region.

We found that DBS of the IC rapidly reduced excessive grooming and vice versa, similar to OCD patients, 'symptoms' quickly returned after discontinuation of DBS. This therapeutic effect of DBS was accompanied by instantly increased neuronal activity in all cortico-striatal circuits monitored: M2, DS, and NAc. However, this effect was not uniform throughout these regions. The DBS-induced activity in the NAc returned to baseline almost momentarily, whereas it only tapered off slowly in the DS. Importantly, in the M2, this increase was sustained throughout the DBS period, thus, potentially providing neuromodulation involved in suppression of compulsive-like grooming.

Our results support the idea that IC-DBS effectively reduces excessive grooming in SAPAP3$^{-/-}$ via recruitment of cortico-striatal circuits. We found that DBS modulates cortical and striatal regions differently, with changes in M2 activity reflecting sustained effects of IC-DBS. Thus, M2 may be involved in the generation of compulsive behavior or at least may represent a brain locus that supports anti-compulsory effects of DBS in OCD.

Disclosures: B.J.G. Van Den Boom: None. **A. Alonso-Andres:** None. **D. Denys:** None. **I. Willuhn:** None.

Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

Location: Hall A

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Program #/Poster #: 592.09/T16

Topic: G.02. Motivation

Support: NIMH (R01MH062646)
NIMH (R37NS031373)

Title: Activation of the metabotropic glutamate receptor 1 attenuates behavioral deficits in NMDA hypofunction models

Authors: *J. GALBRAITH[1], S. YOHN[1], E. RIETH[1], A. J. RAMSEY[2], C. K. JONES[1], C. W. LINDSLEY[1], P. J. CONN[1];
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Abstract: Schizophrenia is a devastating disorder that consists of a complex set of positive, negative and cognitive symptoms. Evidence suggests that disruptions in the normal signaling N-methyl D-aspartate (NMDAR) may underlie many of the symptoms associated with schizophrenia. NMDA subunit GluN1 knockdown (NR1-KD) mice have a global reduction in NMDA receptors, which results in a spectrum of altered behaviors that are similar to those induced by NMDA receptor antagonists. Development of ligands that selectively target the metabotropic glutamate 1 (mGlu1) subtype represents an important approach for modulating NMDAR function and could lead to potential therapeutic interventions for schizophrenia. NR1-KD mice were evaluated in behavioral assays associated with positive, cognitive, and negative behavioral assays. Interestingly, administration of the mGlu1 positive allosteric modulator (PAM) VU6004909 attenuated hyperlocomotor activity in NR1-KD mice. The hyperlocomotor response observed in NR1-KD mice was associated with elevated dorsal striatal dopamine (DA) levels, an effect which can be restored to levels similar to littermate controls following administration of the mGlu1 PAM. Additionally, administration of the mGlu1 PAM improved cognitive performance in novel object recognition (NOR), spontaneous alterations in the Y-maze, social interaction discrimination index, and object locomotion memory in littermate controls and NR1-KD mice. Taken together, these findings provide important novel insights into the role of mGlu1 under conditions of chronic NMDAR hypofunction. These findings also confirm and extend accumulating evidence for the broader therapeutic utility for mGlu1 PAMs in the treatment of schizophrenia.

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Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

Location: Hall A

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Topic: G.02. Motivation

Support: National Institute of Mental Health (MH062646)
National Institute of Neurological Disease and Stroke (NS031373)

Title: Activation of the M1 muscarinic acetylcholine receptor modulates nucleus accumbens dopamine release and increases motivational responding

Authors: *S. E. YOHN[1], J. GALBRAITH[2], E. G. RIETH[2], I. WETZKA[2], C. W. LINDSLEY[2], P. J. CONN[2];
[1]Pharmacol., [2]Vanderbilt Univ., Nashville, TN

Abstract: Motivational symptoms are debilitating features of several neuropsychiatric disorders and are highly correlated with problems in social function, employment and long-term treatment outcomes. Current neuropsychiatric medications do not have efficacy on motivational phenotypes, and, in many cases, can induce or exacerbate these symptoms. While the neural basis of motivational dysfunctions is still being characterized, it has been suggested that there may be common mechanisms across different disorders, and considerable evidence implicates central dopamine (DA) and microcircuitry of the basal ganglia. A powerful modulator of DA signaling is the cholinergic system, which consists of nicotinic (nAChRs) and muscarinic (mAChRs) acetylcholine receptors. mAChRs belong to the superfamily of G-protein coupled receptors (GPCRs) that either activate or inhibit signaling pathway systems through intracellular second messengers. M1 receptors are densely expressed in the nucleus accumbens (NAc), where they have long been suggested to influence DA release. Previous data suggests that M1 activation could regulate NAc DA release and dependent behaviors. However, the data are contradictory due to poor ligand selectivity. To circumvent this problem, our laboratory has developed highly selective compounds that act at allosteric sites. Through use of highly selective M1 preferring compounds and M1 knockout mice, we now report that activation or potentiation of M1 increases effort-related progressive ratio (PR) choice behavior as well as attenuates deficits induced by the DA D2 antagonist haloperidol. Additionally, through use of *ex* and *in vivo* fast scan cyclic voltammetry (FSCV) we report that activation of M1 increases NAc DA release in a drug naïve state or following haloperidol challenge. Taken together, these findings suggest that activation of M1 may be therapeutic for the treatment of motivational dysfunctions.

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Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

Location: Hall A

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Program #/Poster #: 592.11/T18

Topic: G.02. Motivation

Support: BDA training grant T32 DA07268.
Research grant R01-DA-039952

Title: The role of the indirect pathway in sex differences in the formation of preference for cocaine over food in rats

Authors: *M. KALYANI, H. EPSTEIN, N. GUREVICH, J. B. BECKER;
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Abstract: Women progress through the landmark stages of addiction, from initial use to dependence, at a faster rate than males. Rodents exhibit similar sex differences in their addiction-like behaviors. Female rats acquire drug-taking behaviors more rapidly, progress to addiction-like behavior more rapidly, and are more likely to prefer cocaine over a palatable food pellet compared to male rats. The aim of this study was to investigate the role of the DLS indirect pathway in sex differences in the formation of preference for cocaine over food in rats. We did this using designer receptors exclusively activated by designer drugs (DREADDs) to selectively attenuate activity in the indirect pathway of the DLS. We hypothesized that inhibition of the indirect pathway in the DLS, using DREADDs, would enhance the escalation of cocaine taking and more rapid preference formation in both males and females. Male and female rats received DIO hM4Di DREADDs into the DLS. Second, an AAV-Cre viral vector was infused into the globus pallidus external (GPe) of the same rats. At least 2 weeks after the viral vector infusions, the rats were fitted with indwelling catheters for self-administration (SA) of cocaine. Animals were tested in a 7-week choice SA paradigm, to examine their drug-taking behavior in the presence of an alternative, palatable food reward. Their motivation for food and cocaine rewards was also tested under a concurrent progressive ratio (PR) schedule during weeks 3 and 7. Before testing, rats were injected intraperitoneally with Clozapine-N-oxide (CNO; 2 mg/kg) to activate the DREADDs. Immunohistochemistry was used to confirm selective expression of the DREADDs. In addition, c-Fos expression was examined to confirm the activation of the DREADDS by CNO throughout the 2.5-hour SA paradigm. Control females showed an increasing trend in cocaine infusions during the cocaine-only and choice sessions as compared to DREADDs treated group with no significant difference. None of the male rats showed an increase in cocaine infusions. There was no change in pellet intake during the pellet-only session regardless of sex and treatment. The data obtained from the PR schedule showed that the motivation for pellets was not significantly different during early and late SA sessions in either males or females. This suggests that motivation for food was not affected by the DREADDs. By the end of SA, motivation for cocaine was greater in control males and females. These trends suggest that treatment with DREADDs enhanced the motivation for pellets rather than inducing a shift to cocaine preference, regardless of sex.

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Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

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Topic: G.02. Motivation

Support: 1K99DA045758
4T32ES007148-30
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DA016511

Title: Sex differences in motivation for cocaine: Role of progesterone and oxytocin

Authors: *A. S. KOHTZ[1,2], B. LIN[1], H. E. DAVIES[1], A. SHUMYATSKY[1], G. S. ASTON-JONES[1];
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Abstract: There are substantial sex and gender differences in drug abuse that influence susceptibility to, subjective experience of, and relapse propensity for, drugs of abuse. A key feature of drug abuse is pathologically high motivation for cocaine. We investigated the role of ovarian hormones on demand for cocaine in female rats using a within-session threshold behavioral economics (BE) procedure. We quantified demand elasticity (α, inverse motivation) and free consumption (Q_0, hedonic setpoint) in female rats across the estrous cycle and in ovariectomized (OVX) and hormone-replaced female rats. Female rats showed lower demand elasticity (greater motivation) for cocaine compared to males. When female rats were in proestrous, they showed greater demand elasticity (lower motivation) for cocaine compared to all other cycle phases. Hormonal cycle phase accounted for 70% of the variance between data points, obscuring individual differences in demand. High serum progesterone (P4; e.g. in proestrous) predicted decreased cocaine motivation, whereas serum estradiol (E2) correlated to greater intake (Q_0). In OVX females the distribution of α was similar to that previously shown in males, revealing high and low demand female rats. Hormone replacement in OVX females with either E2 (0.09 mg/kg; 44-48 hr prior to testing) and/or P4 (4.0 mg/kg; 4-6 hr prior to testing) showed that E2 increased motivation in females, while P4 decreased motivation. Thus, hormonal milieu, in particular P4, impacts initial motivation for cocaine (e.g. estrus cycling or OVX). We then investigated whether long-term cocaine self-administration altered estrous cyclicity. By 13 weeks, proestrous epochs are no longer observed, and cocaine demand was potentiated by permanent estrous. Finally, we investigated the effects of oxytocin (0.1 mg/kg; 0.3 mg/kg) to reduce cocaine demand. Oxytocin was effective in reducing demand for cocaine in female rats, and also restored proestrous epochs in previously acyclic females. Thus, P4 signaling is a key modulator of cocaine demand in females that may underlie previously observed sex differences

in addiction phenotypes, and oxytocin may be a relevant therapeutic. Supported by grants 1K99DA045758 and 4T32ES007148-30 to ASK and R01-DA006214 and DA016511 to GAJ.

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Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

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NARSAD Award 2017 YI26050
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Title: Differential control of behavior by cocaine and morphine cues: Role of locus coeruleus and auditory brainstem plasticity

Authors: *M. A. PRESKER, Jr.[1], D. SULLIVAN[1], S. TOMBOKAN[1], K. M. BIESZCZAD[2], G. S. ASTON-JONES[1];
[1]Brain Hlth. Inst., [2]Psychology, Behavioral and Systems Neurosci., Rutgers Univ., Piscataway, NJ

Abstract: A major obstacle in treating addiction is the high propensity for relapse. Stimulus-driven drug seeking occurs despite efforts to remain abstinent, and competes with ongoing alternative preferred behaviors such as occupational or social activities. Noradrenergic locus coeruleus (LC) neurons project throughout the neuraxis, and modulate sensory processing and attention to orient organisms to sensory stimuli. Previous work shows that LC activity is altered acutely and chronically by both morphine and cocaine, and by reward-associated stimuli. This supports a role for LC in mediating stimulus control of behavior by drug cues. However, few studies have examined whether morphine- or cocaine-associated stimuli activate LC or exert control over non-drug-seeking behaviors or how this may differ between drug types. Here we implement a behavioral paradigm specifically designed to examine the effects of morphine-paired, cocaine-paired, and saline-paired auditory stimuli (tones) on operant responding for a natural reinforcer (water) in rats. We found that morphine- and cocaine-paired tones exert control over multiple behaviors and these effects differ between drugs. We also collected tissue to assess Fos expression in LC of rats exposed to each tone type. LC Fos expression will be compared with behavioral measures to determine whether they correlate. Furthermore, we will analyze changes in auditory brainstem responses (ABRs) to each tone over the course of conditioning to identify potential changes in auditory processing of a cocaine- or morphine-associated tone

compared to control tones. We previously found a relationship between LC activity and behavioral response to cocaine tones as well as cocaine-induced changes in ABR. This study will establish whether control of behavior by an opioid-associated cue is also encoded in LC activity, and also whether morphine alters auditory processing. Given the role of cues in relapse to opioids and cocaine, identifying a common neural substrate of attentional control by such stimuli may provide a target for therapeutic intervention. Supported by PHS grant R01-DA006214, F31-DA047068-01A1, & NARSAD 2017 YI-26050

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Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

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Topic: G.02. Motivation

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PHS award- K99DA045765
NMHRC CJ Martin 1072706
K12 GM093854

Title: Orexin1 receptor signaling in ventral tegmental area attenuates motivation for cocaine with drug-paired cues

Authors: *C. PANTAZIS[1], M. H. JAMES[1,2], N. SHIN[1], J. E. FRAGALE[1], G. S. ASTON-JONES[1];
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Abstract: Orexin neuropeptides have been linked to motivation for drugs of abuse. Ventral tegmental area (VTA) is an important target for orexin's effects on addiction-like behaviors, as orexin-1 receptor signaling in VTA drives high effort and cue-dependent drug seeking. To investigate the role of orexin-1 receptor signaling in VTA during motivated drug taking, we infused the orexin-1 receptor antagonist SB-334867 (SB) into VTA prior to a within-session behavioral economics (BE) test. In this paradigm, the duration of cocaine infusions decreases in successive 10-minute bins. Demand curves are fitted to individual lever-pressing data to determine two measures of cocaine demand: demand elasticity (alpha; motivation) and low-effort consumption (Q0). We found that SB reduced motivation for cocaine (increased demand elasticity; alpha) without impacting low-effort consumption of cocaine, general locomotor

activity, fixed ratio-1 (FR-1) responding for sucrose, or high-effort sucrose consumption. We also investigated whether orexin's role in motivation was dependent on the presence of drug-associated cues. SB was only effective at reducing motivation in the BE paradigm when animals were trained to associate cues with drug delivery during FR-1 training and were tested with cues during BE. When cues were removed from the BE paradigm, such that lever-pressing resulted in drug delivery without cues, SB did not attenuate motivation. Finally, we microinjected the retrograde tracer CTb into VTA to determine the source of orexin inputs and found that VTA receives orexin input from all subregions of the orexin cell field. However, a greater proportion of lateral hypothalamus (LH) orexin cells project to VTA than those in perifornical/dorsomedial hypothalamus (Pef/DMH). Collectively, these studies indicate that orexin-1 receptor signaling in VTA is necessary for cue-dependent motivation for cocaine, and that the LH orexin to VTA circuit in particular may be important for orexin's effect on motivation.

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Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 592.15/U2

Topic: G.02. Motivation

Support: PHS award R01-DA006214
NHMRC CJ Martin Award 1072706
K99DA045765
Rutgers Brain Health Institute Pilot Grant Scheme
F31DA042588

Title: Enhanced food motivation following binge-like eating in female rats is dependent on orexin (hypocretin) input to ventral tegmental area

Authors: *M. H. JAMES[1,2], S. LIU[1], K. FERNANDOPULLE[1], C. B. PANTAZIS[1], H. E. BOWREY[1], N. T. BELLO[1], G. ASTON-JONES[1];
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Abstract: *Introduction:* Binge eating disorder (BED) is characterized by a progressive escalation of intake of highly palatable food and increased responsivity to food-associated cues. Studies of drugs of abuse indicate that the orexin (hypocretin) system is critically important for motivated behavior. Chronic drug exposure increases the number of orexin neurons and enhances reliance on orexin-1 receptor (Ox1R) signaling. Moreover, orexin inputs to ventral tegmental area (VTA)

augment glutamate-mediated dopaminergic release, and blockade of orexin-1 receptor (Ox1R) signaling in VTA reduces motivated responding for cocaine. Here, we sought to characterize the role of the orexin system and its inputs to VTA in a rat model of BED. *Methods*: Lean and obese (8wk ad libitum high fat diet [HFD]) female Long-Evans rats (n=47) were assessed for baseline sucrose motivation using a behavioral economics paradigm. Binge-like eating was induced by exposing rats to sweetened fat (vegetable shortening/10% sucrose) for 30 min, twice/wk for 4wk; economic demand for sucrose was then reassessed. One group was treated with the Ox1R antagonist SB-334867 (SB; 0,10,30mg/kg, ip) prior to binge-eating or economic demand sessions. In a second group of rats, we chronically silenced orexin neurons that provide input onto VTA by injecting a retroAAV-shOrexin (or scrambled control) virus into VTA prior to the binge-like eating paradigm. In a final group, the effect of binge-like eating on the number of orexin-expressing neurons was investigated using immunohistochemistry. *Results:* Binge eating increased sucrose demand only after HFD-exposure. SB reduced sucrose demand in both lean and obese rats but was effective at lower doses in obese rats following binge. Silencing of VTA-projecting orexin neurons prevented the escalation of intake during binge and the increase in sucrose demand observed following binge. A history of high-fat diet was associated with increased orexin-expressing neurons and this was further augmented by binge experience. *Conclusions:* Our findings reveal an interaction between binge-like eating and excessive weight gain with respect to motivation for food. This is associated with an increase in orexin cell numbers, enhanced reliance on Ox1R signaling and orexin input to VTA. Together, these findings highlight the orexin system as a potential novel target for pharmacotherapies for controlling overeating episodes in individuals with obesity.

Disclosures: M.H. James: None. **S. Liu:** None. **K. Fernandopulle:** None. **H.E. Bowrey:** None. **N.T. Bello:** None. **G. Aston-Jones:** None. **C.B. Pantazis:** None.

Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 592.16/U3

Topic: G.02. Motivation

Support: NIH NIDA Grant R01DA039952

Title: Sex differences in effects of GPER1 activation on preference for cocaine in male and female rats

Authors: *J. A. QUIGLEY, J. B. BECKER;
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Abstract: There are sex differences in susceptibility to addiction and drug-taking behaviors. A higher percentage of female rodents prefer cocaine to natural rewards than males do and females are more motivated than males to attain drugs of abuse. Research from the Becker Laboratory has shown that these heightened addiction-like behaviors in females are modulated by estradiol, where estradiol potentiates cocaine-induced dopamine levels in the dorsal striatum (dSTR). The role of estradiol receptor (ER) activation on addiction-like behaviors in males, however, has not been investigated extensively. The current experiment used the ERα & ERß antagonist, but GPER1 agonist, ICI 182,780 (ICI), and the GPER1 antagonist, G1, to manipulate ERs in the dSTR. The first experiment used a conditioned place preference paradigm (CPP) to determine whether ER manipulation alters preference for 10 mg/kg cocaine in male or female rats. We found that treatment with ICI or G1 into the dSTR of male rats blocked the formation of CPP for cocaine. Neither treatment altered female's formation of CPP. These data suggest that GPER1 regulates preference for cocaine in males only. The second experiment utilized qPCR to investigate potential sex differences in ER expression within the dSTR. There were no differences discovered in ERα, ERß or GPER1. Together, these data suggest that GPER1 activation decreases the rewarding effects of cocaine in males, but not females. Furthermore, there are sex differences in the effect of ER activation on motivation for drugs of abuse, enhancing motivation in females while attenuating motivation in males, that are regulated by mechanisms down-stream from the receptors.

Disclosures: J.A. Quigley: None. **J.B. Becker:** None.

Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 592.17/U4

Topic: G.02. Motivation

Support: NIDCD R03

Title: Graded control of pupil dilation and cortical neuromodulation using selective and parametric stimulation of the mouse vagus nerve

Authors: *Z. H. MRIDHA[1], J. DE GEE[1], Y. SHI[1], R. ALKASHGARI[2], J. WILLIAMS[2], A. SUMINSKI[2], M. WARD[3], W. ZHAMG[1], M. MCGINLEY[1];
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Abstract: The vagus nerve relays information about brain state to the body. Vagus nerve stimulation (VNS) is thought to 'back fire' neuromodulatory centers (such as locus coeruleus), releasing neuromodulators (such as norepinephrine) throughout the brain. The neuromodulatory

effects of VNS are thought to mediate its clinical benefits, in for example the treatment for refractory epilepsy, tinnitus, or depression. Furthermore, VNS enhances auditory learning in healthy individuals, hypothetically by boosting cortical plasticity via the same neuromodulators (Engineer et al., 2015). A major challenge in using VNS, for therapeutic purposes or cognitive enhancement, is that there is no known readout of nerve engagement or subsequent neuromodulatory impact. As a result, stimulation parameters are chosen and optimized, largely through trial-and-error and feedback from patients about symptoms and side effects. We have previously shown that the size of the pupil tracks neuromodulatory brain state and its influence on auditory physiology and behavior (McGinley et al., 2015; Reimer et al., 2016). Here, we developed a VNS preparation for awake, head-fixed mice and test if pupil dilation can serve as a biosensor of VNS and associated cortical neuromodulation. We adapted an implanted cuff design from prior work in rats (Ward et al., 2015). Stimulation via our cuff is well-tolerated by mice for up to several months. We performed an extensive search across a VNS parameter space of 4 pulse widths (0.1-0.8 ms), 5 amplitudes (0.1-0.9 mA), and 3 rates (5-20 Hz; 10 s trains), while monitoring pupil size and other eye and facial movements. We found consistent pupil dilation that parametrically increased with increasing pulse width, amplitudes or rate. Experiments with proximal (or proximal and distal) cut of the nerve confirm that the pupil dilation results from selective activation of the vagus nerve. Using two-photon imaging of axons in auditory cortex, we observed that cortical neuromodulation was phasically boosted during VNS, and then decayed back to a stable baseline. We also found that care with grounding and current spread is necessary to avoid major off target effects such as small phase-locked eye movements and further pupil dilation. Taken together, our results provide a foundation for carefully controlled VNS, and pupil dilation as its readout, for the enhancement of auditory learning and other applications requiring closed-loop, graded control of brain state. References: McGinley et al. (2015), Neuron, 87. Reimer, McGinley, et. al. (2016), Nature communications, 7. Engineer et al. (2015), Brain Stimulation, 8. Ward et al. (2015), IEEE Trans Neural Syst Rehabil Eng, 23.

Disclosures: Z.H. Mridha: None. **J. de Gee:** None. **Y. Shi:** None. **R. Alkashgari:** None. **J. Williams:** None. **A. Suminski:** None. **M. Ward:** None. **W. Zhamg:** None. **M. McGinley:** None.

Poster

592. Subcortical Circuitry Motivation, Compulsive Behavior, and Psychostimulants

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 592.18/U5

Topic: G.08. Drugs of Abuse and Addiction

Support: DA003906
DA12513

Title: The modulation of excitation and inhibition by neuropeptides in the ventral pallidum is cell type specific

Authors: *D. NEUHOFER[1], J. A. HEINSBROEK[3], E. DERESCHEWITZ[2], P. W. KALIVAS[4]; [2]Neurosci., [1]MUSC, Charleston, SC; [3]Med. Univ. of South Carolina, Charleston, SC; [4]Neurosci. Res., Med. Univ. S Carolina, Charleston, SC

Abstract: The ventral pallidum (VP) is an integral component of the reward circuitry and is a major target of GABAergic innervation of both D1 Medium spiny Neurons (MSNs) and D2 MSN from the nucleus accumbens. Although the majority of VP neurons are GABAergic (VPGABA), the VP also contains a significant population of glutamatergic (VPGlu) neurons. It was recently demonstrated that VPGABA drive positive reinforcement, whereas VPGlu drive behavioral avoidance. Also MSN afferents in the VP exert opponent control over behavioral reinforcement with activation of D1 MSN afferents promoting and D2 afferents inhibiting reward seeking. However, the innervation pattern onto VP neurons cannot conclusively explain behavioral output, because D1 and D2 MSN afferents innervate overlapping neuronal populations in the VP. How this afferent specific and cell type specific control of reward seeking is established mechanistically remains elusive.In addition to being segregated according to the expression of D1 versus D2 receptors, the two subpopulations of MSNs segregate according to co-expressed neuropeptides, with D1 MSNs expressing substance P and dynorphin (activating NK1 receptors and kappa opioid receptors respectively), and D2 MSNs co-expressing enkephalin and neurotensin (activating mu opioid receptors and neurotensin receptors respectively). Earlier studies show that administration of these neuropeptides or analogues into the VP alters appetitive behavior and cocaine seeking. To test whether neuropeptides differentially modulate VPGlu and VPGAT Neurons, we bred Ai6lsl-zsGreen with Vglut2-IRES-Cre or VGat-IRES-Cre mice to generate Ai6::VPGlu or Ai6::VPGAT reporter respectively. Using whole cell patch clamp recordings, we quantified the relative strength of excitatory and inhibitory inputs (E/I Ratio) onto VPGlu and VPGAT Neurons and how this E/I Ratio changed after pharmacological activation of neuropeptidergic target receptors in the VP. We found that activation of NK1R does not affect E/I ratio in VPGAT Neurons but decreases E/I ratios in VPGlu neurons via inhibition of glutamate transmission. Activation of MOR increase E/I ratios in VPGlu via inhibition of GABA transmission but no clear effect on VPGAT neurons. These results could provide a circuit-based model to explain the antagonistic effect of D1 and D2 MSN afferents in the VP on reward behavior. Future experiments will complete the characterization of this cell type specific neuropeptidergic modulation and will examine whether it is changed after exposure to drugs of abuse such as cocaine and heroin.

Disclosures: D. Neuhofer: None. **J.A. Heinsbroek:** None. **E. Dereschewitz:** None. **P.W. Kalivas:** None.

Poster

593. Emotion: Neurocircuitry

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 593.01/U6

Topic: G.03. Emotion

Support: MEXT KAKENHI, Grant Number JP24240060 (KN)

Title: Monkey anterior cingulate cortex: Topography and laminar pattern of corticocortical connections indicate hierarchical organization

Authors: H. SAKATA, Y. KIM, M. NEJIME, N. KONOIKE, *S. MIYACHI, K. NAKAMURA;
Primate Res. Institute, Kyoto Univ., Inuyama, Japan

Abstract: The anterior cingulate cortex (ACC) has long been implicated in emotion. The region is functionally divided into three subregions, namely, the dorsal, perigenual, and subgenual regions (dACC, pgACC, and sgACC, respectively). The dACC is more related to cognitive functions and expression of emotional behavior, whereas the pgACC and sgACC are more related to regulation of emotion. Recent studies have suggested that the pgACC and sgACC are involved in mood disorders in contrasting manners: activity of the sgACC is correlated with the severity of depression, whereas the pgACC activity is correlated with the effectiveness of antidepressant and/or positive affect. Anatomically, the ACC has rich connections with other emotion-related areas including the amygdala, the medial temporal cortex, and the temporal pole (TP). To understand the neuroanatomical basis of the functional differences between the ACC subregions, we injected neuronal tracers into the pgACC, sgACC, and dACC and compared the afferent connections. Previously, we analyzed the afferent projections from the amygdala, and found a distinct pattern for the sgACC. In the present study, the distribution of the retrogradely labeled neurons were analyzed in the temporal pole and medial temporal areas. After injections in the sgACC, many neurons were labeled in the TP and the subiculum, an output station of the hippocampal formation. In the TP, a majority of the labeled neurons was found in the superficial layers (“feedforward” type projections). Injections in the pgACC labeled neurons mainly in the deep layers of the TP (“feedback” type projection). In the medial temporal areas, labeled neurons were found in the entorhinal cortex and the parahippocampal cortex, which are known to relay cortical inputs to the hippocampus. In each area, a majority of the labeled cells were in the deep layers (“feedback” type projection). Within the ACC, the projections from the sgACC to the pgACC originated predominantly in the deep layers (“feedback” type projection). These data suggest that the sgACC ranks higher than the pgACC in the hierarchy of the emotional system.

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Poster

593. Emotion: Neurocircuitry

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 593.02/U7

Topic: G.03. Emotion

Title: Oxytocin signaling in the central amygdala modulates emotion discrimination in mice

Authors: *F. MALTESE[1], V. FERRETTI[1], G. CONTARINI[1], M. NIGRO[1], A. BONAVIA[1], H. HUANG[1], V. GIGLIUCCI[2], G. MORELLI[1], D. SCHEGGIA[1], F. MANAGO[1], G. CASTELLANI[1], A. LEFEVRE[3], L. CANCEDDA[1], B. CHINI[2], V. GRINEVICH[3], F. PAPALEO[1];
[1]Inst. Italiano di Tecnologia, Genova, Italy; [2]CNR, Inst. of Neurosci., Milan, Italy; [3]Schaller Res. Group on Neuropeptides, German Cancer Res. Ctr., Heidelberg, Germany

Abstract: Recognition of other's emotions influences the way social animals interact and adapt to the environment. The neuropeptide oxytocin (OXT) has been implicated in different aspects of emotion processing. However, the role of endogenous OXT brain pathways in the social response to different emotional states in conspecifics remains elusive. Here, using a combination of anatomical, genetic and chemogenetic approaches, we investigated the contribution of endogenous OXT signaling in the ability of mice to discriminate unfamiliar conspecifics based on their emotional states. We found that OXT-ergic projections from the paraventricular nucleus of the hypothalamus (PVN) to the central amygdala (CeA) are crucial for the discrimination of both positively and negatively-valenced emotional states. In contrast, blocking PVN OXT release into the nucleus accumbens, prefrontal cortex, and hippocampal CA2 did not alter this emotion discrimination. Furthermore, silencing each of these PVN OXT pathways did not influence basic social interaction. These findings were further supported by the demonstration that virally-mediated enhancement of OXT signaling within the CeA was sufficient to rescue emotion discrimination deficits in a genetic mouse model of cognitive liability. Our results indicate that CeA OXT signaling plays a key role in emotion discrimination both in physiological and pathological conditions.

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Poster

593. Emotion: Neurocircuitry

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 593.03/U8

Topic: G.03. Emotion

Support: NIMH Grant R01MH110425
Purdue Research Fellowship
Purdue Bilsland Dissertation Fellowship

Title: Learning-related changes in infralimbic cortical activity during conditioned inhibition of fear

Authors: *K. H. NG[1,2], S. SANGHA[1,2];
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Abstract: Expressing fear behavior in the absence of a threat is maladaptive because it decreases an organism's opportunity to seek life-sustaining substances. Learned safety signals can rescue the organism from this immobilizing state to resume exploratory behaviors. The infralimbic (IL) region of the prefrontal cortex is known to be critical for consolidating fear extinction and for suppressing fear in the presence of a safety cue. IL neurons have also been shown to increase activity to an extinguished fear cue during the recall of fear extinction. We thus hypothesized that IL neurons also encode for safety signals that are actively suppressing fear behavior in a situation that may be perceived as potentially dangerous.
We recorded from IL neurons using multi-array electrodes during a safety-fear-reward cue discrimination paradigm that is well established in our laboratory. We monitored multiunit activity to assess global changes in IL activity, and single-unit activity to assess changes in recruitment of individual neurons encoding for safety. During the discrimination task, rats learn that the reward cue results in sucrose delivery and the fear cue results in footshock, but when the fear cue is simultaneously presented with the safety cue as a compound cue (fear+safety cue), there is no footshock. To control for sensory modality effects, we also trained a separate group of animals with the modalities (auditory vs visual) counterbalanced for the fear and safety cues. Male rats showed high freezing to the fear cue and significantly lower freezing to the fear+safety cue, regardless if the fear cue was an auditory or visual cue. Our multi-unit data demonstrated increasing IL neuronal firing to the combined fear+safety cue across learning sessions, matching the magnitude of fear suppression to the fear+safety cue. This learning-related increase was not seen to the fear, safety or reward cues across learning sessions and did not depend on cue modality. These data suggest the IL is engaged when a behavioral fear response is actively regulated during conditioned inhibition.

Disclosures: **K.H. Ng:** None. **S. Sangha:** None.

Poster

593. Emotion: Neurocircuitry

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 593.04/U9

Topic: G.03. Emotion

Support: CCTS Pilot Grant 2017-01

Title: Capture and modulation of emotion regulation inferred from connectivity analysis

Authors: *R. SHEPARD, L. STEWART, M. XING, A. LEOW, O. AJILORE;
Psychiatry, Univ. of Illinois at Chicago, Chicago, IL

Abstract: Introduction: Individuals with anxiety and mood disorders have been shown to have impaired emotion regulation (ER). For those individuals who are remitted, effective ER may reduce the risk of relapse. Theta frequency activity has been associated with ER difficulties, and as such, the ability to decrease theta connectivity could improve patients' ability to regulate their emotions and avoid relapse.
Objectives: To use brain network connectivity patterns to confirm the effectiveness of and determine an ideal method for enhancing ER with noninvasive stimulation.
Methods: Participants were 11 adults ages 18-64 (average age 32, 2 male 9 female) with a score of 23 or more on the Depression Anxiety Stress Scale (DASS-21) and no major active medical or neurologic problems. 5 participants received transcranial direct current stimulation (tDCS) while 6 received transcranial alternating current stimulation (tACS) during 2 runs of both an Emotion Regulation Task (ERT) and a resting task. We compared subject reported affect collected during the ERT and before/after stimulation using the Spielberger State-Trait Anxiety Inventory (STAI) and Beck Depression Inventory (BDI).
Results: BDI scores for both tACS and tDCS participants significantly decreased from the start of the stimulation visit to the end, while STAI scores showed no significant change. Preliminary analyses of the EEG data comparing connectome measures between sham and active tACS sessions only show a reduction connectivity between stimulation electrodes at all frequencies and in the theta frequency band during the resting task. Conversely, tDCS participants only see a reduction in edge electrode connectivity in all and theta frequencies when performing the ERT. To test overall group differences, we used a mixed model analysis with within-subject variables (sham vs active) and between-subject variables (tDCS vs tACS) and did not find a significant difference across all conditions.
Conclusions: We observed the anticipated effects of tACS reducing theta connectivity more than tDCS during resting tasks, but tDCS reduced theta connectivity more during the ERT than tACS did. These results would suggest that ER can be improved via transcranial stimulation.

Despite the need for further analyses, tCS still appears to be a promising tactic for assisting patients with mood disorders in regulating their emotions.

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Poster

593. Emotion: Neurocircuitry

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 593.05/U10

Topic: G.03. Emotion

Support: CIHR
NSERC
Ontario Graduate Scholarship

Title: The role of ventral hippocampal inputs to the anterior hypothalamus in escape behaviours and stress response

Authors: *J. BANG[1], J. K. SUNSTRUM[7], J. ZHAO[1], S. ST-CYR[2], D. GARAND[3], M. RAHMAN[9], G. M. PARFITT[4], M. A. WOODIN[1], P. O. MCGOWAN[5], W. INOUE[8], J. KIM[6]; [1]Univ. of Toronto, Toronto, ON, Canada; [2]Cell and Systems Biol., Univ. of Toronto, Scarborough, ON, Canada; [3]Cell and Systems Biol., [4]Dept. of Psychology, Univ. of Toronto, Toronto, ON, Canada; [5]Biol. Sci., Univ. of Toronto, Scarborough, ON, Canada; [6]Psychology, Univ. of Toronto, Toronto, ON, Canada; [7]Neurosci., [8]Univ. of Western Ontario, London, ON, Canada; [9]Univ. of Toronto Scarborough, Toronto, ON, Canada

Abstract: Animals rely on innate and conditioned fear responses to maximize their chance of survival. Previous studies found that an intact ventral hippocampus (vHPC) is essential for processing contextual information associated with conditioned fear as well as the expression of innate defensive behaviours such as escape from predators. Furthermore, being a major target of glucocorticoids, vHPC has also been implicated in the negative feedback control of stress-induced HPA activity. We hypothesized that the vHPC conveys contextual information to the anterior hypothalamic nucleus (AHN) to encode and retrieve memory of a predator threat. We found that a direct AHN activation is sufficient to evoke robust escape responses (running, jumping, freezing) in the absence of threat and can act as an unconditioned stimulus in the conditioned place aversion test. Rabies virus tracing and electrophysiological recordings revealed that GABAergic neurons in the AHN receive direct monosynaptic inputs from the

vHPC. Next, we optogenetically manipulated vHPC inputs to the AHN while mice are subjected to natural predator cues or physical restraint stress and then assessed its impact on escape behaviours, autonomic responses, and the formation of contextual memory. In physical restraint stress, the activation of vHPC inputs to the AHN decreased heart rates and respiration while increasing struggle movements. Our data thus far suggest that the hippocampal-hypothalamic circuit plays an important role in modulating escape and stress responses, and establish the AHN as a key hippocampal target that integrates threat signals and environmental contexts.

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Poster

593. Emotion: Neurocircuitry

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Program #/Poster #: 593.06/U11

Topic: G.03. Emotion

Support: Wellcome Trust Investigator award 108089/Z/15/Z
Medical Research Council Career Development Award RG62920

Title: A focus on primate area 25 and its regulation of reward and threat driven responses

Authors: *C. M. WOOD[1], L. ALEXANDER[1], A. M. SANTANGELO[1], L. OIKONOMIDIS[1], J. ALSIÖ[2], P. L. R. GASKIN[1], S. J. SAWIAK[3], Y. T. HONG[4], T. D. FRYER[4], A. C. ROBERTS[1]; [1]Dept. of Physiology, Develop. and Neurosci., [2]Dept. of Psychology, [3]Behavioural and Clin. Neurosci. Inst., [4]Wolfson Brain Imaging Ctr., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Heightened activity within subcallosal cingulate cortex (including area 25) has been observed in patients with depression, with successful treatment often resulting in normalisation of activity within this region. Recently, we revealed the causal involvement of area 25 activation in blunting reward-driven responses and heightening anxiety-like behaviors, by infusions of a glutamate uptake blocker into area 25 in marmoset monkeys (Alexander et al. 2019, Neuron 101(2) p307-320). Here we extend our findings to address three additional questions: 1) whether the same pattern of effects can be induced via viral-mediated overactivation of area 25 with a hM3Gq DREADD receptor? 2) Whether area 25 overactivation increases the stress hormone, cortisol since FDG activity in area 25 is associated with increased cortisol levels in the rhesus monkey (Jahn et al. 2010 Biol. Psychiatry 67(2) p175-181)? 3) Whether area 25 overactivation induces the same pattern of altered network activity under threat as it does during reward anticipation.
In addressing 1) we infused a DREADD hM3Gq viral construct into area 25 and used the

DREADD activator Clozapine-N-Oxide to show that area 25 overactivation blunts cardiovascular and behavioural arousal in anticipation of reward during appetitive Pavlovian conditioning and heightens negative reactivity to uncertain threat, similar to that seen after the blockade of glutamate uptake. Control studies with DREADD activators indicate no effects, suggesting that the cardiovascular and behavioural response are DREADD-specific. In addressing 2) we show that area 25 overactivation by blocking glutamate uptake increases salivary cortisol during recall of Pavlovian conditioned threat but not under neutral conditions. Finally, to address 3) we are using ^{18}F-FDG imaging in animals exposed to Pavlovian conditioned threat cues following overactivation of area 25.

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Poster

593. Emotion: Neurocircuitry

Location: Hall A

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Program #/Poster #: 593.07/U12

Topic: G.03. Emotion

Support: NIMH Grant 1R01MH107556-01
BBRF NARSAD Young Investigator Award

Title: Ultrasonic vocalizations as a means of inducing anxiety via potential threat exposure: Evidence from behavioral, neural, and fMRI analyses in the rat

Authors: *J. A. HONEYCUTT, L. E. GRANATA, C. DEMAESTRI, P. P. KULKARNI, C. F. FERRIS, H. C. BRENHOUSE;
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Abstract: The utilization of ultrasonic vocalizations (USVs) as a means of social communication is well established in rats, with distinct USV frequency ranges indicative of different affective states. Aversive USVs within the 22 kHz range are typically emitted by adult rats as alarm calls during situations involving anxiety or fear (e.g. predator, social defeat), whereas 55 kHz range USVs are indicative of appetitive situations (e.g. play, reward). Previous work from our group and others indicate that playback of USVs to a listening rat can induces acute changes in affective state, as evidenced by increased anxiety-like or approach behaviors following either 22 or 55 kHz USV playback (respectively). Furthermore, we present evidence suggesting that these changes in behavior following USV presentation may be associated with differential activation of key brain regions associated with anxiety. Indeed, cFos quantification following playback within the basolateral amygdala (BLA), bed nucleus of the stria terminalis (BNST), and the

nucleus accumbens suggests distinct differences in activation based on whether the rat heard an aversive or appetitive train of USVs. Additional differentiation was evident within the BNST after 22 kHz playback, with increased cFos density observed within the anterodorsal nuclei, whereas 55 kHz playback showed increased activity exclusively within the oval nucleus. In addition to these findings, we are currently employing a novel USV playback methodology within the fMRI in order to leverage the anxiety-provoking characteristics of 22 kHz playback to probe circuit-specific alterations across the rat brain. Here, we present preliminary evidence suggesting that playback of aversive USVs activates anxiety-related circuitry similar to that seen in analogous human task-based fMRI. Taken together, this work provides critical groundwork for leveraging ethologically-relevant stimuli in the rat to improve our overall understanding of anxiety-related etiology in both typical and pathological populations/models.

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Poster

593. Emotion: Neurocircuitry

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

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Topic: G.03. Emotion

Support: NSERC Grant RGPIN-2017-06131

Title: Lateral hypothalamic neural outputs drive active coping response

Authors: *E. MARTIANOVA[1,2], A. PAGEAU[3], D. LEBLANC[3], C. PROULX[1,2];
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Abstract: The lateral hypothalamus (LHA) sends neural outputs to brain regions known to control reward and motivated behaviors. However, how these distinct LHA outputs process information to control behavior is poorly known. Here, we use *in vivo* fiber photometry calcium (Ca^{2+}) imaging to characterize LHA outputs in freely moving mice. An AAV encoding the calcium indicator GCaMP6s was injected in the LHA, and optic fiber cannulas were implanted to target three majors downstream LHA targets: the lateral habenula (LHb), the ventral tegmental area (VTA), and the dorsal raphe nucleus (DRN). This allowed to record neural activity simultaneously and specifically at LHA-LHb, LHA-VTA, and LHA-DRN pathways, in mice subjected to different stimuli or placed in different contexts. Ca^{2+} signals in three LHA outputs increased when mice were presented with aversive airpuffs and decreased during rewarding sucrose consumption (SCT). From these three LHA outputs, we found a significant correlation between Ca^{2+} signals and mobility scores in mice free to explore an open field (OFT) or during

tail-suspension test (TST). The correlation was significantly higher during TST suggesting that LHA may guide motivated coping responses in stressful contexts. This assertion was supported by an increased correlation between Ca^{2+} signals and mobility scores after administration of cued foot-shocks. Cross-correlation analysis between LHA outputs showed synchronous increase of Ca^{2+} signal in all three outputs at nearly each event of mobility onset in TST and at delivery of airpuffs. To examine further the contribution LHA outputs for behavioral responses, we injected an AAV-ChR2-eYFP in the LHA and implanted cannulas with the tips above the LHb, VTA, and DRN. Optogenetic activation of individual LHA outputs caused passive avoidance in real-time preference test and increased mobility in OFT and TST. During SCT, optogenetic stimulation of the LHA-LHb at the onset of drinking events significantly reduced total sucrose consumption, stimulation of LHA-DRN only decreased drinking duration, and LHA-VTA stimulation had no impact on sucrose consumption. Combined, these results suggest that LHA outputs may encode different and complementary teaching signals to motivate active coping response in aversive contexts.

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Poster

593. Emotion: Neurocircuitry

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Title: Preferential activation for emotional music versus sounds in motor, interoceptive, and language brain areas

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Abstract: Recent meta analyses suggest that there is a common brain network involved in processing emotion in music and in sounds (Koelsch, 2014; Frühholtz, et al, 2016). However, as no studies have directly compared the neural substrates of equivalent emotional music and

emotional sound, we don't fully understand how emotional music is represented in the brain compared to other auditory emotional stimuli, or whether other brain systems, such as the motor or language networks would be more or less involved in processing music versus sounds. Using functional magnetic resonance imaging (fMRI) and a region of interest approach, we investigated whether brain activation in motor cortex, interoceptive cortex, and Broca's language area during an auditory emotional appraisal task differed as a function of whether the emotional information was communicated through music or non-linguistic sounds. Musical and non-musical stimuli were matched for both valence (positive and negative) and arousal level (Lepping, et al. 2016). Thirty-nine adults (Mean age=31.44, SD=12.52 years, 17 men, 22 women; 19 with current major depressive disorder) underwent fMRI scanning while listening to the stimuli and determining emotional valence (positive or negative). An analysis of variance revealed an interaction between stimulus type and region [F(1.18, 44.8)=9.30, p=.002]. Activation was relatively greater to music in motor and interoceptive cortex - areas associated with movement and internal physical feelings - and relatively greater to sounds in Broca's language area. No differences in activation were found based on depression status (all F's&lt2.6). We conclude that emotional sounds are appraised through verbal identification of the source, and that emotional music is appraised through evaluation of bodily feelings. The current results also indicate that at least some neural systems involved in emotional appraisal are functionally intact during a depressive episode, which may help clarify the mechanism of music therapy for depression.

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Poster

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Title: Synaptic organization of amygdala to prefrontal cortex circuits

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Abstract: Connections from basolateral amygdala (BLA) to medial prefrontal cortex (mPFC) are important for threat detection and response. Disorders involving aberrant threat processing are linked to disruptions in the normal connectivity of the BLA-mPFC circuit. Distinct classes of projection neurons in the prelimbic (PL) or infralimbic (IL) subdivision of mPFC are believed to

integrate BLA input and thereby regulate either the activation or suppression of threat-evoked behavior. Recent work suggests BLA input targets both corticoamygdalar (CA) neurons and pyramidal tract (PT) neurons in mPFC, but how this targeting differs between PL and IL, and whether this reflects distinct pathways, is unclear. Using whole-cell electrophysiology and optogenetics in acute slices, we show how distinct BLA nuclei target cells in IL and PL. Using soma-tagged optogenetics, we also examine the local circuits that link layers within and between IL and PL. Together, our results indicate that sub-divisions of the BLA target remarkably different networks of cells, which themselves make distinct connections to influence mPFC output.

Disclosures: K. Manoocheri: None. **A.G. Carter:** None.

Poster

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Support: Natural Sciences and Engineering Research Council Discovery Grant
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Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign (UIUC-BI)

Title: Spatio-temporal dynamics and individual differences linked to vlPFC's role in emotion-cognition interactions: Evidence from a simultaneous fMRI-ERP investigation

Authors: *M. MOORE[1], A. T. SHAFER[2], R. BAKHTIARI[3], A. SINGHAL[3], F. DOLCOS[1]; [1]Univ. of Illinois at Urbana-Champaign, Urbana, IL; [2]Natl. Inst. on Aging, Baltimore, MD; [3]Univ. of Alberta, Edmonton, AB, Canada

Abstract: Despite extensive evidence identifying brain regions and networks involved in emotion-cognition interactions, the link between spatial and temporal dynamics of mechanisms underlying these phenomena remains unclear. Of particular importance are brain regions that appear to be engaged during multiple processes, suggesting complex and dynamic functional heterogeneity. One such region is the ventrolateral prefrontal cortex (vlPFC), which has been implicated in processing of emotional and salient information, response inhibition, affect regulation, and coping with emotional distraction. Notably, previous evidence suggests dissociable sub-regional specificity between anterior and posterior parts of the vlPFC, with the former showing more general involvement in emotion processing, and the latter being more specifically linked to coping with emotional distraction. Capitalizing on a multimodal imaging

approach in a sample of 22 healthy young adults, we investigated the link between spatial and temporal aspects of processing in an emotional oddball task, and in relation to personality measures assessing basic affective responses and emotion control. First, fMRI captured expected overall greater vlPFC response, and ERPs showed larger late positive potentials (LPPs) to emotional distraction. Second, ERP-informed fMRI analyses showed an association between the fMRI signal in the anterior vlPFC and the LPP amplitude to emotional distraction. Third, analyses linking fMRI and personality data identified opposing relations between responses to emotional distraction and individual scores for cognitive reappraisal and self-control impulsiveness in posterior vlPFC. Namely, participants with reduced tendencies to engage reappraisal and reduced ability to control impulsive responses had increased engagement of the posterior vlPFC during emotional distraction. Together, these results provide novel evidence supporting anterior-posterior functional dissociations within the vlPFC linked to the initial impact of vs. coping with emotional distraction. Overall, these findings highlight the advantage of capitalizing on multidimensional approaches to comprehensively investigate the complex spatial-temporal dynamics of the neural mechanisms associated with emotion-cognition interactions.

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Poster

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Topic: G.03. Emotion

Support: IBS grant IBS-R001-D1

Title: Neural circuits underlying a psychotherapeutic regimen for fear disorders

Authors: *J. BAEK[1,2], S. LEE[1], T. CHO[1], S.-W. KIM[1], M. KIM[1], Y. YOON[1], K. KIM[1], J. BYUN[1], S. KIM[3], J. JEONG[2], H.-S. SHIN[1];
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Abstract: A psychotherapeutic regimen that uses alternating bilateral sensory stimulation (ABS) has been used to treat post-traumatic stress disorder in humans. However, the neural basis that underlies the long-lasting effect of this treatment—described as eye movement desensitization and reprocessing—has not been identified. Here we describe a neuronal pathway driven by non-invasive visual stimulation of the superior colliculus (SC) that mediates persistent attenuation of

fear. We successfully induced a lasting reduction in fear in mice by pairing visual ABS with conditioned stimuli during fear extinction. Among the types of visual stimulation tested, ABS provided the strongest fear-reducing effect and yielded sustained increases in the activities of the SC and mediodorsal thalamus (MD) throughout the extinction session. Optogenetic manipulation revealed that the SC-MD circuit was necessary and sufficient to prevent the return of fear. ABS suppressed the activity of fear-encoding cells and stabilized inhibitory neurotransmission in the basolateral complex of the amygdala (BLA). The direct MD-BLA projection formed a novel feedforward inhibitory circuit that was required for the observed long-lasting suppression of fear. Together, these results reveal the neural circuit that underlies an effective strategy for sustainably attenuating traumatic memories.

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Poster

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Title: Regulation of prefrontal cortex by two opposing hippocampal pathways

Authors: *C. SANCHEZ BELLOT, A. F. MACASKILL;
Univ. Col. London, London, United Kingdom

Abstract: The subiculum is the main output region of the hippocampus. Despite targeting multiple downstream regions, its efferents are thought to be organised as parallel projections, with any one neuron targeting only one downstream region. Here, we focus on the projection from the ventral subiculum to the prefrontal cortex (PFC). The ventral hippocampal-prefrontal pathway is involved in the production of a range of behaviours including working memory, aversive learning and anxiety, and its dysfunction is linked to key aspects of several psychiatric disorders. Through anatomical, electrophysiological and morphological investigation of the ventral hippocampal-prefrontal pathway, we show that PFC projecting neurons are formed of two distinct populations. These populations are differentially controlled by upstream structures and have unique connectivity within downstream PFC. Finally, these two populations show distinct contributions during different aspects of behaviour.

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Poster

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Topic: G.03. Emotion

Support: Wellcome Trust
University College London

Title: Input-output mapping of ventral hippocampal circuits

Authors: *R. W. S. WEE, A. MACASKILL;
Univ. Col. London, London, United Kingdom

Abstract: The ventral hippocampal output region in CA1 and subiculum (vH) is comprised of multiple non-overlapping populations of projection neurons that send output to different regions, including prefrontal cortex, nucleus accumbens and ventromedial hypothalamus. These projection-defined populations are involved in many related but distinct aspects of behaviour, suggesting that they integrate different inputs. To investigate the input connectivity of projection-defined vH neurons, we combined anatomical and rabies-based trans-synaptic tracing. We observed that diverse cortical, subcortical and thalamic sources of input provide selective innervation to vH projection-defined neurons. Using regression models, we also probed the relative influence of spatial topology and output region on input source. Finally, we employed channelrhodopsin-2 (ChR2)-assisted circuit mapping to functionally validate newly identified inputs. Together, our findings indicate anatomical segregation of inputs to projection-specific vH neurons, providing a basis for selective control of individual projections during behaviour.

Disclosures: R.W.S. Wee: None. **A. Macaskill:** None.

Poster

593. Emotion: Neurocircuitry

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Topic: G.02. Motivation

Support: Intramural research program at NIDA/NIH

Title: Ventral tegmental area glutamatergic neurons differentially express calcium-binding proteins

Authors: *S. MONGIA, T. YAMAGUCHI, H. WANG, B. LIU, M. MORALES;
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Abstract: The ventral tegmental area (VTA) has three major subclasses of neurons: dopaminergic (expressing the rate-limiting enzyme for dopamine production, tyrosine hydroxylase; TH), GABAergic (expressing vesicular GABA transporter; VGaT) and glutamatergic (expressing vesicular glutamate transporter 2; VGluT2). However, recent evidence has shown that in addition to DA, GABA and glutamate neurons, the VTA contains combinatorial neurons that co-release glutamate and GABA or glutamate and dopamine. While VTA dopaminergic and GABAergic neurons have been further characterized based on their expression of calcium-binding proteins (calbindin, CB; calretinin, CR or parvalbumin, PV), it is unclear whether these calcium binding proteins are expressed in VTA glutamatergic neurons. Here, by a combination of *in situ* hybridization (for detection of VGluT2 mRNA) and immunohistochemistry (for detection of CB, CR or PV), we found expression of CB, CR or PV in some VGluT2 neurons, which were concentrated in the medial nuclei of the VTA. We determined that among the total population of VTA VGluT2 neurons and depending on the VTA rostro-caudal level, 30% co-expressed CB, 3% co-expressed PV and less than 1% co-expressed CR. Given that some VGluT2 neurons co-express VGaT or TH, we examined whether these neurons co-expressed CB. By a combination of RNAscope (for co-detection of VGluT2 and VGaT mRNAs) and immunohistochemistry (for detection of CB and TH), we found that within the total population of VGluT2-CB neurons, 13% co-expressed VGaT mRNA, 19% co-expressed TH and 6% co-expressed VGaT mRNA and TH. These findings show that (a) while CR and PV are infrequently present in VTA VGluT2 neurons, CB is present in almost one-third of the entire population of VTA VGluT2 neurons; (b) within the total population of VTA VGluT2-CB neurons, one-third have the capability to co-release dopamine or GABA; and (c) a small subpopulation of VTA VGluT2-CB neurons has the capability to co-release both GABA and dopamine. These findings further provide evidence for molecular diversity among VTA VGluT2 neurons, neurons that may play a role in specific circuitry and behaviors.

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Poster

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Topic: G.02. Motivation

Support: The Intramural Research Program of the National Institute on Drug Abuse (NIDA/NIH) supported this work.

Title: Cytoarchitectural characterization of zona incerta doapmine neurons

Authors: *Z. D. BRODNIK[1], M. F. MORALES[2];
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Abstract: A population of tyrosine hydroxylase expressing (TH^+) neurons in the zona incerta has been identified for several decades, and it has generally been assumed that these neurons are functional dopamine neurons. Nevertheless, recent work has shown that the expression of TH does not necessarily identify a neuron as capable of producing and releasing dopamine. Specifically, some TH^+ neurons do not co-express other proteins that are required for the synthesis (AADC) or packaging (VMAT) of dopamine and are thus unlikely to release dopamine as a neurotransmitter. Additionally, it has been found that some TH^+ neurons are capable of releasing glutamate or GABA. The TH^+ neurons of the zona incerta have not been characterized with such rigor, and thus the neurochemical identity of zona incerta TH^+ neurons remains unclear. We used a combination of immunohistochemistry and in-situ hybridization with radiolabeled probes to identify the proportion of zona incerta neurons that co-express TH and AADC or VMAT as well as the proteins required for the packaging of glutamate (VGluT2) or GABA (VGaT). We found that the majority of TH^+ neurons in the zona incerta express AADC (95%) or VMAT (63%). Additionally, we found that a negligible proportion of TH^+ neurons express VGluT2 (2%), but that a substantial proportion express VGaT (75%). Together, our studies identify that the majority of zona incerta TH^+ neurons express the genes necessary for DA neurotransmission and suggest that many DA neurons in the zona incerta may co-release GABA but not glutamate.

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Poster

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Topic: G.02. Motivation

Support: NIDA-IRP

Title: VTA glutamate neurons establish excitatory synapses on mPFC parvalbumin neurons

Authors: *S. ZHANG[1], H. WANG[2], M. F. MORALES[2];
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BALTIMORE, MD; [2]Integrative Neurosci. Res. Br., Natl. Inst. of Health, Natl. Inst. on Drug Abuse, IRP, Baltimore, MD

Abstract: Dopamine inputs from the ventral tegmental area (VTA) to the medial prefrontal cortex (mPFC) have been implicated in neuropsychiatric pathologies for decades. Recent findings indicate that the mPFC is also innervated by VTA neurons expressing the vesicular glutamate type 2 (VGluT2). We found that the mesocortical pathway was originated from three major subpopulations of VTA neurons: VGluT2-only, TH-only and dual VGluT2-TH neurons. These subpopulations of VTA neurons innervated with higher frequency the infralimbic (IL) than the prelimbic (PrL) cortex (Dr. Wang's SfN 2019 abstract). Here, we analyzed mPFC sections from those brains in which VTA VGluT2 neurons were tagged with ChR2-eYFP or ChR2-mCherry. By confocal microscopy, we found that fibers expressing eYFP were predominantly localized in the deep layers of the IL and dorsal peduncular (DP) cortex. By immunoelectron microscopy, we detected within the IL and DP cortex mCherry (from infected VTA-VGluT2 neurons) restricted to axons and axon terminals, and determined that mCherry terminals co-expressed VGluT2 and established asymmetric (excitatory-type) synapses on IL and DP cortical dendrites. By ex vivo electrophysiological and optogenetic approaches, we found that mPFC photoactivation of fibers from VTA VGluT2 neurons evoked monosynaptic firing of local parvalbumin (PV)-GABAergic neurons, and polysynaptic inhibition of pyramidal neurons. By three-dimensional reconstruction of confocal data analysis and immunoelectron microscopy, we confirmed that dual mCherry-VGluT2 terminals formed asymmetric synapses with cortical PV-dendrites, and with dendritic spines. These findings indicate that VTA VGluT2-mesocortical-fibers establish monosynaptic excitatory synapses with PV-GABAergic neurons and pyramidal neurons. By in vivo mPFC photostimulation of fibers from VTA VGluT2 neurons, we found that this stimulation induced conditioned place aversion, which depended on activation of both glutamate and GABA receptors (Dr. Wang's SfN 2019 abstract). These findings indicate that the VTA provides a glutamatergic excitatory input to a subpopulation of IL cortical PV-GABAergic neurons, and that activation of these PV neurons inhibits neighboring pyramidal neurons, promoting aversive behavior.

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Poster

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Support: NIDA-IRP.

Title: VTA glutamate neurons promote aversion by activation of mPFC parvalbumin neurons

Authors: *H.-L. WANG[1], H. WANG[2], M. F. BARBANO[3], A. N. FIGUEROA GONZÁLEZ[2], M. AKBARI[2], M. F. MORALES[4];
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Abstract: Dopamine inputs from the ventral tegmental area (VTA) to the medial prefrontal cortex (mPFC) have been implicated in neuropsychiatric pathologies for decades. Recent findings indicate that the mPFC is also innervated by VTA neurons expressing the vesicular glutamate type 2 (VGluT2). However, it is unclear the extent to which the subdivisions of the mPFC are targeted by the different subclasses of VTA VGluT2 neurons. In this study, we injected the retrograde track tracer fluorogold (FG) in either the prelimbic (PrL) or infralimbic (IL) cortex of wild type rats, and phenotyped the VTA FG-positive (mesocortical) neurons by a combination of *in situ* hybridization (to detect VGluT2 mRNA or glutamate acid decarboxylase, GAD mRNA) and immunohistochemistry (to detect both FG and tyrosine hydroxylase [TH]). For the mouse analysis of mesocortical VGluT2 neurons, we injected the AAV-DIO-eYFP viral vector into the VTA of VGluT2::Cre transgenic mice. In these mice, we also injected FG into the PrL or IL cortex, and evaluated VTA co-expression of FG and eYFP neurons. In rats and mice, we found that (1) both IL and PrL cortex received inputs from VTA neurons, but these VTA neurons provided 4.4 times more inputs to the IL than PrL cortex. (2) Four classes of VTA neurons innervated the mPFC: TH-only, VGluT2-only, dual VGluT2-TH, and GABA-only. (3) The VTA inputs to mPFC were mostly from VGluT2-only, TH-only and dual VGlu2-TH neurons, and less frequently from dual VGluT2-GABA or GABA-only neurons. By photoactivation of mPFC VGluT2 inputs from VTA neurons, we found that this mesocortical VGluT2 pathway induced conditioned place aversion, which depended on activation of both glutamate and GABA receptors. Next, we determined the type of IL neurons activated by the mesocortical VGluT2 pathway and found that this pathway induced c-Fos expression in parvalbumin (PV) GABA interneurons. By electrophysiological and ultrastructural analysis, we found that PV neurons of the IL cortex were the major target of VTA VGluT2 terminals (Dr. Zhang's abstract). Our findings indicate that the VTA provides a glutamatergic excitatory input to a subpopulation of IL cortical PV-GABAergic neurons, and that activation of these PV neurons inhibits neighboring pyramidal neurons, promoting aversive behavior.

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Poster

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Topic: G.02. Motivation

Support: NIDA IRP program

Title: Electrophysiological properties of ventral tegmental area combinatorial glutamate-GABA neurons

Authors: *J. A. MIRANDA-BARRIENTOS[1], I. CHAMBERS[1], D. H. ROOT[2], H.-L. WANG[3], G. MATEO-SEMIDEY[1], B. LIU[1], M. F. MORALES[4];
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Abstract: The ventral tegmental area (VTA) is a midbrain structure that contains dopamine neurons involved in diverse aspects of motivated behavior. In addition to dopamine neurons, the VTA contains glutamate neurons expressing the vesicular glutamate transporter 2 (VGluT2) and GABA neurons expressing vesicular GABA transporter (VGAT). We have recently shown that the VTA contains combinatorial neurons that co-express VGluT2 and VGAT and co-release glutamate and GABA. In this study, we determined the electrophysiological properties of VTA combinatorial VGluT2-VGAT neurons and compared these properties with those found in VGluT2-only or VGAT-only neurons. To selectively tag each class of VTA neurons, we crossed VGluT2::Cre mice with VGaT::FlpO mice and in the VTA of these dual transgenic mice injected intersectional and subtractive viral vectors that express enhanced yellow fluorescent reporter protein. By combination of immunohistochemistry (for detection of eYFP), *in situ* hybridization (for detection of endogenous VGluT2 or VGAT transcripts), we confirmed the specific expression of the reporter protein in the targeted combinatorial VGluT2-VGAT, VGluT2-only or VGAT-only neurons, and prepared VTA slices to determine their electrophysiological properties by *in vitro* patch clamp electrophysiology. Based on electrophysiological passive properties, we found that combinatorial VGluT2-VGAT neurons had hyperpolarized resting membrane potentials, indicating that these neurons require strong excitatory inputs to fire. By comparing combinatorial VGluT2-VGAT neurons with VGAT-only neurons, we found that VGluT2-VGAT neurons had lower excitability and lower basal firing frequency than VGAT-only neurons, indicating that the firing of VGluT2-VGAT neurons requires stronger excitatory inputs than those required by VGAT-only neurons. By comparing combinatorial VGluT2-VGAT neurons with VGluT2-only neurons, we found that some combinatorial VGluT2-VGAT and some VGluT2-only neurons had Ih currents, though the Ih current amplitude was lower in VGluT2-VGAT neurons. Based on the firing properties, we found two major categories of combinatorial VGluT2-VGAT neurons: those with rapid onset firing (located through the medial VTA), and those with delayed onset firing (located in the dorsomedial part of the VTA), indicating different ion channel configurations in spatially distributed VGluT2-VGAT neurons. In summary, we determined that combinatorial VTA VGluT2-VGAT neurons are diverse in their electrophysiological properties, and depending on their distribution within the VTA they may have rapid or delayed onset firing.

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Poster

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Title: VTA glutamatergic, but not GABAergic, neurons play a role in innate defensive behavior

Authors: *M. F. BARBANO, H.-L. WANG, B. LIU, A. FIGUEROA-GONZÁLEZ, M. MORALES;
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Abstract: Defensive behavior is characterized by different responses, such as freezing, fighting or escape. The brain circuits underlying freezing and fighting behaviors have been extensively studied but those underlying escape are not well understood. Recent studies suggested that dopamine neurons from the ventral tegmental area (VTA) play a role in escape behavior. However, the VTA comprises other type of neurons besides dopamine, such as glutamatergic and GABAergic neurons. We have started to characterize an escape response resulting from the activation of glutamatergic neurons of the VTA by optical stimulation of lateral hypothalamic glutamatergic inputs. However, it is unclear if GABAergic VTA neurons also play a role in this escape behavior. To further characterize the behavioral role of LH glutamate neurotransmission to VTA, we injected Cre-dependent viral vectors encoding ChR2 tethered to eYFP in the LH of VGluT2-Cre mice to tag LH axons expressing the vesicular glutamate transporter 2 (VGluT2). Stimulation of VTA inputs from LH glutamatergic neurons resulted in a specific increase of cFos in VGluT2-positive neurons. Then, we conducted looming tests with or without VTA optical stimulation of LH VGluT2 inputs. The looming stimulus induced escape in both eYFP and ChR2-eYFP mice without stimulation, but only ChR2-eYFP mice showed a significant increase in escape during VTA optical stimulation. By chemogenetics, we found that blockade of VTA VGluT2 neurons resulted in a decreased escape latency when mice were presented with threatening stimuli such as cat or fox urine odor. Next, to evaluate the behavioral consequences of ablating VTA VGluT2- or VGaT-expressing neurons (VGaT, vesicular GABA transporter), we injected Cre-dependent viral vectors encoding caspase and we repeated our odor and looming tasks in VGluT2-Cre or VGaT-Cre mice. We found that the ablation of VTA glutamatergic neurons decreased the latency to escape from predator odor, as well as the escape responses to a looming stimulus, while the ablation of VTA GABAergic neurons was without consequences. From these behavioral findings and cFos data, we conclude that VTA glutamatergic, but not

GABAergic, neurons play a role in innate defensive behaviors; and that one pathway conveying relevant information to this neuronal subpopulation arises from LH glutamatergic neurons.

Disclosures: **M.F. Barbano:** None. **H. Wang:** None. **B. Liu:** None. **A. Figueroa-González:** None. **M. Morales:** None.

Poster

593. Emotion: Neurocircuitry

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 593.21/U26

Topic: G.03. Emotion

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Cornell Presidential Life Sciences Fellowship
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NARSAD Young Investigator Award

Title: The prefrontal cortex-ventral tegmental area projection signals movement but not reward in positive and negative environments

Authors: *R. J. POST[1], B. J. SLEEZER[1], V. LEE[1], K. PELLEGRINO[4], N. W. RINGELBERG[5], B. A. MONCRIEFFE[2], M. R. WARDEN[1,3];
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Abstract: Major depressive disorder manifests as combinations of symptoms, and may include fatigue or decreased energy, decreased interest in things that were once considered pleasurable (anhedonia), psychomotor agitation or retardation, weight loss or weight gain, and many others. Recent research has begun to unravel distinct neural correlates for these behaviors. The medial prefrontal cortex (mPFC) and its projections to downstream brain regions such as the dorsal raphe nucleus has been shown to influence mobility in high-threat environments like the forced swim test, and ventral tegmental area (VTA) dopamine (DA) neuron stimulation has been shown to reverse both stress-induced immobility in high-threat environments and anhedonia; however, the role of the mPFC-VTA projection in these behaviors remains unclear. To interrogate the contribution of the mPFC-VTA projection to depression-related behaviors, male mice were injected in the mPFC with either AAV-CaMKIIα-ChR2-eYFP or a fluorophore-only control, and a fiber optic was implanted over the VTA. In comparison to fluorophore-only controls, optogenetic stimulation of mPFC axons in the VTA significantly increased struggling behavior

in the tail suspension test (n=21, $p<0.01$), mobility in the forced swim test (n=20, $p<0.05$), locomotion in a brightly lit, novel open field (n=22, $p<0.01$), and locomotion in a dark, familiar open field with home cage bedding (n=13, $p<0.01$), but did not affect the consumption or preference of freely available sucrose or water (n=22). Unlike the stimulation of VTA DA neurons (n=12, $p<0.01$), stimulation of the mPFC-VTA projection did not support place preference (n=13). To measure endogenous mPFC-VTA activity in behaving mice, an AAVretro vector expressing the calcium indicator GCaMP6s was injected in the VTA, and a fiber optic was implanted over the mPFC. mPFC-VTA calcium activity was positively correlated with locomotion in the open field and in an operant task in which mice worked for water, but did not reflect reward delivery or reward prediction error (n=10). These results highlight a selective role for the mPFC-VTA projection in movement.

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Poster

593. Emotion: Neurocircuitry

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Support: K01MH105731
BBRF NARSAD Young Investigator Award
John P. McNulty Scholars Program
Undergraduate Research Fellowship
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BP Endure

Title: Infralimbic projections to the basal forebrain regulate fear extinction recall

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Abstract: Cross-species research shows that projections between the medial prefrontal cortex (mPFC) and the basolateral amygdala (BLA) contribute to extinction learning, although the circuit-level mechanisms of mPFC-mediated regulation of the BLA in extinction remain elusive. One region that may be regulating the mPFC-BLA dialogue during fear extinction is the basal forebrain (BF), a downstream target of the mPFC that also sends cholinergic and GABAergic

projections to the BLA. To probe this circuit, we first studied the anatomical connectivity between the Infralimbic (IL)/Prelimbic (PL) regions of the mPFC with BLA projecting neurons in the BF. We injected the retrograde tracer cholera toxin B (CTB) in the BLA, and the anterograde tracer synaptophysin-mCherry in the IL or PL. We then examined the overlap between tracers in the BF while counterstaining for cholinergic cells (choline acetyl transferase, ChAT+), and GABAergic neurons that express parvalbumin (PV+), and somatostatin (SOM+). We found that ChAT+ and PV+ (but not SOM+) cells project from the BF to the BLA. Further, the PL projects more to ChAT+ BLA projectors, whereas the IL preferentially targets PV+ BLA projectors. We then tested whether ChAT+ and PV+ BF cells are differentially recruited during fear or extinction recall. We injected CTB in the BLA and exposed mice to fear conditioning (4kHz tones) followed by either extinction training or white noise presentations. We then tested extinction or fear recall 24h later, and used cFos as a marker to look at neural activity in the BF. We found that PV+ and ChAT+ BLA projectors are more active during extinction and fear recall, respectively. We then used optogenetic manipulation of IL terminals in the BF to identify whether this circuit contributes to IL driven changes in extinction. Mice received injections of either the inhibitory opsin archaerhodopsin (eArch3.0/eYFP) or the excitatory opsin rhodopsin (ChR2/mCherry) in the IL, and optrodes were implanted in the BF. After fear conditioning, groups of mice underwent extinction training where tones coincided with inhibition (eArch/eYFP, 35s, 9mW) or excitation (ChR2, 35s, 7 or 20Hz, 9mW) of IL terminals in the BF. Extinction recall was tested 24h later. Animals that received inhibition of IL input to the BF during extinction training showed significantly impaired extinction recall, with a concomitant decrease in BF low gamma power. Conversely, animals that received excitation of IL terminals in the BF during extinction training showed enhanced fear extinction recall. Overall, our findings suggest that IL inputs to the BF modulate consolidation of fear extinction learning, likely by strengthening BF PV+ activity.

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Poster

593. Emotion: Neurocircuitry

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Topic: G.03. Emotion

Support: NIH BP Endure

Title: Auditory safety training improves novel auditory discrimination learning and sensory discrimination curves

Authors: *I. NAHMOUD[1], J. G. VASQUEZ[2], H. CHO[3,4], T. DENNIS-TIWARY[3,4], E. LIKHTIK[1,4];
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Abstract: Overgeneralized fear (OF), or indiscriminate fear responses to threat and non-threat, is a core feature of anxiety. While research has focused on maladaptive fear learning in the emergence of OF, recent evidence suggests that maladaptive Safety Learning may play a unique role in OF. Yet, the independent influence of Safety conditioning on OF is not understood. To address this question, we tested how three different Safety Conditioning protocols with varied levels of uncertainty compared to classic Fear Conditioning as to how they impact behavior on subsequent tests of innate anxiety and differential fear learning of new aversive and neutral cues. Using a high anxiety strain of mice (129SvEv, Taconic), we show that animals undergoing Fear Conditioning (n=12) using 5 pairings of a tone (4kHz, 30sec,80dB) with a shock (0.5mA, 1 sec) show little exploration of the anxiogenic center of an Open Field 24 hours later, and poor discrimination during new differential conditioning 7 days later. Three groups of mice underwent Safety Conditioning, where (A) the safety tone was unpaired with a shock (n=12), (B) the safety tone was unpaired with the shock and co-terminated with a 1 sec house light signaling the end of the cue (n=12), and (C) the safety tone was unpaired with the shock and co-started with a 1 sec house light that signaled the beginning of the cue (n=12). All tones were 4kHz, 30sec,80dB, and shocks 0.5mA, 1 sec long. Mice from all Safety training groups (A-C) showed better discrimination on the new differential fear conditioning task than those from the Fear Conditioning group, with the group that underwent Safety Training C showing the strongest discrimination on new learning. We then tested whether Fear and Safety Conditioning differentially affect auditory discrimination curves. To this end, we first Fear or Safety Conditioned mice using paradigm C (beginning of tone co-occurs with a 1s light). Next, we exposed mice to a series of tones in the training context and compared freezing behavior to the target training cue (4 kHz) with a series of tones that were -2 to +2 octaves away from the training cue (1,2,4,8,16kHz). Mice that were Fear conditioned showed freezing to all the presented tones, whereas mice that were Safety Conditioned showed a selective decrease in freezing to the trained target tone (4kHz). These data suggest that Safety Conditioning sharpens auditory discrimination. We are currently investigating how Fear or Safety conditioning affects auditory discrimination during novel learning, and the physiology of auditory cortex, prefrontal cortex, and the amygdala communication that accompany Safety Conditioning.

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Poster

593. Emotion: Neurocircuitry

Location: Hall A

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Program #/Poster #: 593.24/U29

Topic: H.01. Animal Cognition and Behavior

Title: Nucleus accumbens neurons exhibit cell-type specific coupling to hippocampal inputs

Authors: *E. F. OLIVEIRA[1], L. L. SJULSON[2];
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Abstract: The Nucleus Accumbens (NAc) is a key brain area involved in reward-guided behavior and drug addiction. Besides its many inputs from critical areas responsible for cognitive functions (including prefrontal cortex, amygdala, and thalamus), one of prime interest is hippocampus (HPC). The HPC plays a key role in memory formation and generation of sequences representing environmental variables. The HPC-NAc pathway has the potential to be involved in reinforcing representations developed in the HPC, as presented in previous work. However, little is known about how HPC representations are transformed in the NAc and how the NAc performs computations on HPC inputs. Here, we investigated how NAc units respond to network activity form HPC, such as theta oscillations and sharp-wave ripples. We split the NAc units into putative cell types (medium spiny neurons (MSN) expressing D1 and D2, tonically active neurons (TAN) and fast spiking interneurons (FSI)) and looked at their firing behavior with respect to HPC activity. Our preliminary results show that these cell types respond differentially to theta oscillations and SWRs. Surprisingly, the same cells are not generally modulated by both. Our results also point that cells theta or SWR responsive are usually spatially segregated in the dorsal-ventral and medial-lateral axis of NAc. These results suggest that cells in different regions of NAc are performing different computations with HPC inputs, and that these computations performed by sub-regions of NAc are brain state dependent.

Disclosures: E.F. Oliveira: None. **L.L. Sjulson:** None.

Poster

594. Emotion: Fear, Anxiety, and Pain II

Location: Hall A

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Topic: G.03. Emotion

Support: NIH Grant EY026100
NIH Grant EY027713

Title: Parsing the neural circuits for visually-evoked emotional contagion

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Abstract: The ability to assess and perceive the behavior and internal state of others is an essential trait of social animals. This process, termed emotional contagion, enables organisms to adapt to their environment with reduced risk as well as promoting social bonds. Failures of emotional contagion are also implicated in developmental cognitive disorders, such as autism spectrum disorder. Despite the considerable study of the neural correlates of emotional contagion in humans and non-human primates, we know very little about the underlying cell types, circuit architectures, and computations that drive this crucial phenomenon.
We have developed a behavioral paradigm that allows precise measurement of the robust behavioral responses triggered in mice ("observer") while viewing innate defensive behaviors of conspecifics ("demonstrator") exposed to visual threat 'looming stimuli'. Using this "visually-evoked emotional contagion (VEEC)" assay, we asked:
1) Do mice visually determine and adopt the internal state of their conspecifics?
2) What behavioral repertoires do the observer mice perform?
3) Which regions in the brain are necessary for visually-evoked emotional contagion?
We found that freezing is the major responsive behavior of the observer mice to an observational threat. Autonomic responses of the observer mice revealed that this is defensive freezing indicating the observer's response is caused by changes in internal state, not by the pure mimicry of the demonstrators' behavior. Circuit mapping revealed increased neuronal activity in the claustrum of the observer mice that experienced observational threat. Chemogenetic inhibition of claustrum neurons impairs defensive freezing in observer mice during VEEC assay while activation of those induces defensive freezing. Interestingly, when mice are directly under looming stimuli, a threat with a higher risk than an observational threat, activation of claustrum neurons promotes arousal-enhanced responses to threat such as confrontational behavior (tail rattling), whereas inhibition of claustrum neurons promotes arousal-reduced responses such as freezing. Moreover, activation of claustrum neuronal activity increases autonomic arousal. These findings reveal that emotional contagion generated by vicarious visual threat exists in rodents and suggest that claustrum plays an important role by gating the saliency level during visual threat perception.

Disclosures: H. Jung: None. **A.D. Huberman:** None.

Poster

594. Emotion: Fear, Anxiety, and Pain II

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Support: JSPS KAKENHI 17K10290
NIH grant P50MH100023
Public Health Research Foundation

Title: Pair bonding attenuates fear memory acquisition through oxytocin receptor signaling in monogamous prairie voles

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Abstract: Social bonds can ease the distress of experiencing of life-threatening events, such as disasters. We have used monogamous prairie voles to explore the relationship between pair bonds and response to stressful events. Previously we found that the single prolonged stress (SPS) paradigm enhances fear memory in a contextual fear conditioning paradigm in non-bonded, but not in pair bonded males. Here, we confirmed the pair bond-dependent attenuation of fear memory using another fear memory paradigm, a passive avoidance test. Adult male voles were cohabited with an unrelated female prairie vole (pair bond group; N = 17) or with a male (cagemate group; N = 16) for 4 days. Pair bonding was confirmed by a partner preference test. The next day subjects were allowed to freely investigate a passive avoidance apparatus. The next day subjects were placed in the light chamber and the latency to enter the dark chamber was recorded. When subjects entered the dark chamber a 2 sec electric shock was delivered twice with 1min interval (conditioning). Subjects were again placed in the light chamber 24 h after conditioning, and latency to enter the dark chamber was recorded (memory test). The pair bond group showed shorter latency compared to the cagemate group in the memory test ($p < 0.001$). Further, the cagemate group delayed the latency in the memory test compared to at conditioning ($p < 0.0001$), while the pair bond group did not ($p > 0.05$). There were no group differences in fear extinction in the absence of shock. We hypothesized that oxytocin (OT) may mediate this phenomenon. OT receptor antagonist (OTA) or vehicle was administrated i.c.v. in pair bonded male subjects 30 min prior to testing. The OTA group showed longer latency to enter the dark chamber than the vehicle group ($p < 0.008$) and OTA delayed the latency to enter the dark chamber in the memory test compared to that at the conditioning ($p < 0.0001$). In contrast, the latency between the memory test and conditioning was not different in the vehicle group ($p >$

0.05). These results suggest that pair bonding attenuates fear memory acquisition probably through central oxytocin receptor signaling.

Disclosures: **Y. Hirota:** None. **L.J. Young:** None. **S. Mitsui:** None.

Poster

594. Emotion: Fear, Anxiety, and Pain II

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Topic: G.03. Emotion

Support: UIC Graduate College Provost Graduate Research Award

Title: Central oxytocin is anxiolytic and anti-depressive in B6 mice

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Abstract: There is accumulating evidence that the induction of endogenous oxytocin release or exogenous administration facilitates social preference and social bonding. This may result from oxytocin supporting reward in social contexts. Alternatively, oxytocin may be anxiolytic in social contexts or oxytocin may have both rewarding and anxiolytic effects. Other findings suggest that oxytocin also affects reward outside a social context, as oxytocin can modify the rewarding effects of drugs of abuse. The present experiment investigated whether a central infusion of oxytocin, alone, can affect reward and/or anxiety. Because oxytocin has been suggested to be a possible anti-depressive treatment, this study further explored whether an oxytocin infusion affects performance in the tail suspension task (TST). To carry out these experiments, a guide cannula was first unilaterally implanted into the lateral ventricle of C57Bl/6J (B6J) mice. Subsequently, mice received an intracerebroventricular (ICV) infusion of vehicle or one of three doses of oxytocin (100, 200 or 500 ng) and tested on the conditioned place preference (CPP), elevated zero maze (EZM) or TST. In the CPP test, B6J mice received ICV injections of oxytocin during the conditioning phase. Initial findings indicate that oxytocin at 200ng, but not 100ng or 500ng increases time spent in the open zones of the EZM. Correspondingly, ICV infusion of oxytocin dose dependently reduces immobility duration in the TST. In contrast, preliminary results indicate that ICV injection of oxytocin, across all doses, during the conditioning phase of the CPP did not lead to a CPP. Taken together, these preliminary results suggest that central infusions of oxytocin may have an anxiolytic and anti-depressive effect, but does not lead to reward. In an ongoing study, the effects of oxytocin infused directly into the nucleus accumbens core on these various behavioral measures are being explored.

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Poster

594. Emotion: Fear, Anxiety, and Pain II

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Topic: G.03. Emotion

Support: R15MH102717
R25NS080685

Title: Social buffering in a novel social fear conditioning procedure in male and female rats

Authors: *L. M. DAWUD[1], E. C. LOETZ[2], A. L. HAAS[1], S. TRAN[1], J. WISEMAN[2], I. MAMAYAN[1], B. N. GREENWOOD[2], S. T. BLAND[2];
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Abstract: Social fear is a learned behavior that may contribute to stress-related disorders such as Post-Traumatic Stress Disorder (PTSD) and Social Anxiety Disorder (SAD). We have developed an innovative animal model of conditioned social fear in which footshock unconditioned stimuli are paired with social cue conditioned stimuli (CS rats). Here we assess social buffering in our paradigm. Social buffering is a phenomenon observed in social animals, in which an animal better recovers from a stressor if another animal of the same species (conspecific) is present. We have previously observed social buffering in female rats that were exposed to a paired footshock and CS rats in which they had reduced freezing behavior when compared to the footshock only controls following re-exposure to the conditioning apparatus. To further investigate social buffering, we exposed male and female Sprague-Dawley rats to a same-sex conspecific social stimulus during fear conditioning using a two-by-two design. All experimental rats received 4 footshocks (0.8 mA, 1.0 sec) with 1 min interstimulus intervals on Day 1, either with or without a social stimulus and were re-exposed to the conditioning chambers on Day 2, either with or without a CS rat. CS rats did not receive footshocks as they were contained in a special insert. This special insert was built with a Plexiglas platform protecting the CS rat from footshocks and a wire mesh that separates experimental rats from the CS rats. This wire mesh allows for the experimental rats to see and smell the CS rats. Experimental rats were thus assigned to one of four groups: the conditioned social fear (CSF) group that received a social stimulus on Day 1 but not Day 2, the CSF group that received a social stimulus on Day 2 but not Day 1, a social stimulus only group, and a footshock only group. Freezing behavior was the dependent variable analyzed during Day 1 (during each interstimulus interval) and Day 2 for the 8-minute re-exposure. Experimental rats that received foot shocks with a CS rat had decreases in freezing behavior compared to rats that got footshocks with no CS rat. These results suggest that both male and female rats display social buffering of fear conditioning using our procedure.

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Poster

594. Emotion: Fear, Anxiety, and Pain II

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Support: JSPS KAKENHI Grant Number 1 5 K 1 6 3 7 6

Title: Visual recognition of mirror, video-recorded, and still images in rats

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Abstract: Several recent studies have claimed that rodents have high visual recognition abilities. However, extent to which rats can recognize the other rats and distinguish between males and females using visual information alone remains unclear. In the present study, we investigated the ability of rats to visually recognize mirror, video-recorded, and still images and to discriminate between images of males and females. Rat was examined in a place preference apparatus with a mirror, a video recording of a rat, or a still image of a rat at one end. Male and female rats spent significantly more time in the mirror chamber and the video recording chamber than in their respective blank chambers ($P < 0.05$), and male rats also spent more time in the chamber containing a still image. Furthermore, it was found that both male and female rats exhibited significantly more sniffing behavior around the mirror than in the blank chamber ($P < 0.05$), whereas there were no significant differences in the sniffing behaviors in the moving or still image experiments ($P > 0.05$). Identical results were obtained regardless of whether the rat in the image was the same or opposite sex. These results indicate that rats can process the differences in mirror, video-recorded, and still images as visual information, but are unable to use this information to distinguish between the sexes.

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Poster

594. Emotion: Fear, Anxiety, and Pain II

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Support: 2R01 MH099073

Title: An ecologically-relevant paradigm to study fear and foraging strategies in mice

Authors: *P. R. ZAMBETTI[1], B. P. SCHUESSLER[1], J. J. KIM[2];
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Abstract: Laboratory models used to investigate fear have consistently relied upon Pavlovian fear conditioning (pairing a neutral cue with an aversive stimulus, and later measuring the fear response to the cue) to understand the neural mechanisms underlying adaptive and maladaptive fear behavior. However, in nature, it is disputed that Pavlovian fear conditioning is the primary mechanism by which animals come to fear stimuli; animals' are typically not afforded multiple conditioning trials to learn that a particular stimulus (e.g., a predator) is dangerous and therefore should be avoided. In contrast, ecological studies from multiple labs investigating innate, unlearned fear responses to artificial predator stimuli have shown that rodents display reliable fear and avoidance behaviors to such stimuli with no prior experiences necessary. Our lab has previously developed a naturalistic, "approach-food avoid-predator" paradigm in rats used to study innate fear and risky-decision making behaviors and their underlying neurocircuitry (Choi and Kim, 2010). Briefly, hungry animals foraging for food pellets encounter a robotic "terrestrial predator", which is programmed to surge at the animal as it approaches a food pellet. Fear responses are measured over multiple predator testing days. In light of the rapidly increasing use of mice in neuroscience research—largely due to the availability and feasibility of transgenic animals—we have adapted our approach-food-avoid-predator paradigm for use in mice. Additionally, we made the predator stimulus more realistic than our rat version by replacing the robotic threat with a taxidermy weasel. We demonstrate that mice naturally forage for food pellets in an open arena as well as flee from a surging predator. Likewise, mice required multiple days of predator testing for fear responses to habituate to the consistent looming threat, as seen in rats. Finally, we show that the presence of stationary but realistic predator does not deter mice from attempting to procure food, suggesting that the looming motion is evolutionarily reliable signal of danger. This paradigm would be useful for researchers seeking to harness the powerful capabilities of transgenic animals to study naturalistic fear behavior and neurocircuitry.

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Poster

594. Emotion: Fear, Anxiety, and Pain II

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Topic: G.03. Emotion

Support: Supported by R01 MH099073 (J.J.K.)

Title: The effects of lateral habenula lesions on foraging and avoidance behavior in rats living in a naturalistic, risky foraging environment

Authors: *B. P. SCHUESSLER[1], J. J. KIM[2];
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Abstract: The lateral habenula has long been implicated in associative fear learning, particularly instrumental avoidance and to a lesser extent Pavlovian (classical) fear conditioning. These findings have been predicated on rodent studies using paradigms that implement discrete cues predicting aversive outcome, such as active avoidance or standard tone-shock fear conditioning tasks. These tasks are brief in duration and measure a limited set of behaviors. Additionally, not much is known on how the lateral habenula participates in risky decision-making. To further probe the lateral habenula's contributions to fear-and-anxiety related behavior and decision-making processes, the current study employed a longitudinal, "closed economy" risky foraging paradigm. In this paradigm, animals live continuously and largely undisturbed in modified operant chambers partitioned into a safe nest area and risky foraging area. Animals must acquire all their food and water in the foraging area, which contains a steel rod floor, operant levers and a water port. After a baseline foraging assessment, animals received bilateral electrolytic lesions (or sham lesions; electrodes lowered but no current passed) of the lateral habenula, which was followed by a post-surgery baseline foraging assessment. After the post-surgery baseline assessment, pseudo-random, unsignaled foot shock was introduced in the foraging area. Finally, shocks were terminated to examine extinction behavior. Lateral habenula lesions greatly altered baseline feeding patterns, which persisted throughout the remaining phases of the experiment. However, the introduction of unpredictable foot shocks in the foraging area led to similar compensatory changes in feeding behavior to that of sham lesion animals. Lesioned animals spent more time in the risky foraging zone during the shock period, and consequently received more shocks than sham lesion animals. Lesions also blunted shock-induced drinking suppression, and lesioned animals were quicker to return to baseline water consumption levels during extinction. These results highlight the role of the lateral habenula in regulating both appetitive and defensive behavior.

Disclosures: B.P. Schuessler: None. **J.J. Kim:** None.

Poster

594. Emotion: Fear, Anxiety, and Pain II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 594.08/U37

Topic: G.03. Emotion

Support: KAKENHI 24240060

Title: Potent and quick responses to conspecific faces and snakes in the anterior cingulate cortex of monkeys

Authors: *N. KONOIKE, H. IWAOKI, K. NAKAMURA;
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Abstract: Appropriate processing of others' facial emotion is a fundamental ability of primates in social situations. Several mood and anxiety disorders such as depression cause a negative bias in the perception of facial emotions. Depressive patients show a decrease of activation in the perigenual portion of the anterior cingulate cortex (ACC) and an increase of activation in the amygdala. However, it is not known whether neurons in the ACC have a function in the processing of facial emotions. Furthermore, the existence of predators in their vicinity is life-and-death information for monkeys. In the present study, two adult rhesus monkeys (*Macaca mulatta*) were used (monkey C: 8 kg, male; monkey P: 7 kg, female). We recorded the activity of single neurons from the monkey ACC and examined the responsiveness of the ACC neurons to various visual stimuli including monkey faces, snakes, foods, and artificial objects. About one fourth of the recorded neurons showed a significant change in activity in response to the stimuli. The ACC neurons exhibited very high selectivity to certain stimuli, and more neurons exhibited the maximal response to monkey faces and snakes than to foods and objects. The responses to monkey faces and snakes were faster and stronger compared to those to foods and objects. Many ACC neurons preferred scream, a negative facial emotion. The response characteristics of the ACC neurons were similar to those of the amygdala neurons. Most of the responsive neurons were located just above or anterior to the genu of the corpus callosum, that is, the perigenual portion of the ACC, which has a strong mutual connection with the amygdala. These results suggest that the perigenual portion of the ACC collaborating with the amygdala forms the neural network underlying emotional information processing, especially for negative life-and-death information such as screaming faces and snakes.

Disclosures: **N. Konoike:** None. **H. Iwaoki:** None. **K. Nakamura:** None.

Poster

594. Emotion: Fear, Anxiety, and Pain II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 594.09/U38

Topic: G.03. Emotion

Support: MR/M023990/1

Title: Opposing contributions of subregions of the primate orbitofrontal cortex to the regulation of threat in the common marmoset

Authors: *Z. M. STAWICKA, R. MASSOUDI, L. OIKONOMIDIS, N. K. HORST, A. C. ROBERTS;
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Abstract: Structural and functional abnormalities of the orbitofrontal cortex (OFC) have been implicated in affective disorders such as anxiety and depression. However, the primate OFC is composed of a number of distinct subregions including areas 14, 11, and 13 in the medial, anterior and posterior OFC, respectively. Aside from differences in cytoarchitecture and connectivity, these regions have been shown to contribute to different aspects of the signaling of reward value, but their potentially separable roles in the processing of threat and anxiety remain unclear. To address this issue, the current study compares the effects of inactivation and in some cases overactivation of areas 11, 13 and more caudal area 14 in marmoset monkeys on tests of uncertainty and conditioned threat. Temporary inactivation was induced by infusing GABA A/B agonists (muscimol and baclofen, respectively) into the target regions through implanted cannulae. Overactivation was induced by infusing an inhibitor of the GLT-1 glutamate transporter, dihydrokainic acid, to increase synaptic glutamate. We used the human intruder test, a paradigm used commonly in primates, to examine the natural display of behaviours towards uncertain threat in order to study anxiety. The test revealed differing effects following manipulations of area 11 and 13, compared to caudal area 14. Anxiety was heightened, and avoidance of the human intruder enhanced following temporary inactivation of area 11 or 13, although detailed comparison revealed differences in the specific behavioural repertoire displayed. Conversely, a similar heightening of anxiety was seen following overactivation, rather than inactivation, of medial area 14. Consistent with an increase in threat-driven responses following area 14 activation, inactivation was shown in a subsequent Pavlovian conditioning paradigm to reduce the acquisition and expression of conditioned cardiovascular and behavioural arousal to threat, in which a rubber snake acted as an ethologically relevant unconditioned stimulus. Distinct roles of the medial (area 14) and central (areas 11 and 13) OFC have previously been described in terms of reward value processing and decision-making. However, our findings imply that these theories require further refinement to incorporate the roles of these

subregions in response to threat. Our observations suggest that temporarily altered activity in both the caudal medial and central regions can impact on the expression of fear and anxiety-like behaviours but do so in an opponent fashion. Future studies will be required to tease out the unique functions of these three regions in the regulation of threat driven responses.

Disclosures: Z.M. Stawicka: None. **R. Massoudi:** None. **L. Oikonomidis:** None. **N.K. Horst:** None. **A.C. Roberts:** None.

Poster

594. Emotion: Fear, Anxiety, and Pain II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 594.10/U39

Topic: G.03. Emotion

Title: Differentiation between physical and emotional response patterns with the application of electrophysiological sensors in a VR environment

Authors: *J. KRITIKOS[1], **M. DOULOUDI**[2];
[1]Electrical and Computer Engin., Natl. Tech. Univ. of Athens, Athens, Greece; [2]Biol., Natl. Kapodistrian Univ. of Athens, Athens, Greece

Abstract: Motion artifact is considered as a serious blockade in electrophysiological measurements, since it leads to ambiguous and less accurate results, making both the recording and data interpretation process more challenging and time-consuming. As a result, instructions concerning the appropriate usage of electrophysiological sensors restricts any possible movement during measurements by urging the patients to remain calm and motionless. However, the expansion of virtual reality systems as an immersive and interactive tool to efficiently provoke specific and actual emotions with the introduction of stronger and more realistic stimuli, necessitates the presence of physical movements during the simulations, making the appearance of motion artifact unavoidable. On the other hand, denoising approaches cannot stand as reliable methods to extract wholly the artifact, considering the risk of fatigue phenomenon that arises in a physical effort - dependent way. In our study, by employing a Virtual Reality (VR) environment, we aim to decipher distinct emotional patterns, adequate enough to distinguish fatigue conditions from non-fatigue ones and also to propose a denoising system, capable to predict and remove motion artifact based on these patterns. For the purpose of our study, we collected ten healthy subjects, six males and five females, all belonging in the same age group (22-30 years old) and with an average physical condition. All volunteers were divided into two different groups of five people and appropriate physiological responses (electrodermal activity and heart rate) where measured by applying the corresponding sensors, while being exposed to the same horror video in the VR. In the first group, we measured the electrophysiological signals of fully rested for a considerable amount of time users, whereas in the second group we measured

electrophysiological signals while users were susceptible to fatigue, which was introduced with a set of specific training exercises prior to the VR session. We deciphered two distinct characteristics in our measurements, each corresponding to our selected sensors. We concluded that these specific motives are consistent with potential fatigue signals and thus we attempted to predict and establish a non-fatigue framework by removing the noise derived from physical exercise.

Disclosures: **J. Kritikos:** None. **M. Douloudi:** None.

Poster

594. Emotion: Fear, Anxiety, and Pain II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 594.11/U40

Topic: G.03. Emotion

Support: Daniel M. Soref Charitable Trust at the Medical College of Wisconsin

Title: Resting state functional connectivity of the human periaqueductal grey using 7-Tesla MRI

Authors: ***C. N. WEIS**, A. A. HUGGINS, K. P. BENNETT, E. A. PARISI, C. L. LARSON; Univ. of Wisconsin Milwaukee, Milwaukee, WI

Abstract: The periaqueductal grey (PAG) is a region of the midbrain that has been implicated in a variety of complex behaviors including defensive responses to threat. Functional differences in the longitudinal columns of the PAG in animal models have been well established. The dorsal columns have been implicated in active-coping defensive strategies such as fear, panic, and fleeing behaviors, while the ventral columns appear to facilitate passive-coping strategies such as freezing or quiescence behaviors. Thus, misevaluation or appraisal of threat stemming from aberrant PAG activity may be a potential neural mechanism of human psychopathological disorders such as anxiety and posttraumatic stress disorder. The distinct functional roles of the PAG columns are well-maintained across species including humans; although, most functional connectivity work of the human PAG has examined task-based effects that elicit the distinct behavioral outcomes of PAG columns. Therefore, the current study utilized high resolution 7-Tesla MRI to characterize the functional connectivity of the PAG *at rest*. A sample of 57 neurologically healthy undergraduate participants (M_{age}=22.2, SD_{age}=3.62) underwent structural and resting state functional MRI scans. Whole brain voxel-wise analyses show the PAG is functionally connected to occipital cortices, thalamus, medial prefrontal cortex, pons, superior/inferior colliculi, caudate, and insula. These results support previous work showing the resting connectivity of PAG to emotion regulation and fear networks. Interestingly, comparison of functional connectivity of the dorsal and ventral PAG columns did not reveal any significant

differences. These results may suggest functional distinctions of the columns only emerge when presented with threat directly whereas at rest these regions are functionally indistinguishable.

Disclosures: C.N. Weis: None. **A.A. Huggins:** None. **K.P. Bennett:** None. **E.A. Parisi:** None. **C.L. Larson:** None.

Poster

594. Emotion: Fear, Anxiety, and Pain II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 594.12/V1

Topic: G.03. Emotion

Title: Brain responses elicited by recollecting a break-up event of oneself

Authors: *L.-Y. CHIEN, W.-J. KUO;
Yangming Univ., Taipei, Taiwan

Abstract: We humans are social animals. Social rejection or exclusion will induce negative emotions and cause psychological feelings of pain. Driven by social attachment, the ancient pain system may have provided neural bases for responding to events of social rejection or exclusion. There is evidence indicating that the neural networks of social pain and physical pain matrix overlapped. However, in studies of social rejection, they mostly included only two conditions, one for social rejection and one neutral control. In this study, in order to have a more comprehensive emotion spectrum to profile the neural bases of social rejection, we included one more condition which could help to induce positive emotions from the same participant for comparison. We recruiting female participants who had just experienced a romantic relationship break-up (being dumped by their ex-partner) within one year. The major task was arranged as follows. By cuing with presenting photos of their ex-partner, their good friend, and an acquaintance, the participants were instructed to recollect their common life event in the past and try to re-experience it. We believed, compared to previous studies, current arrangement of the good-friend condition could serve as a better checking point for brain activities among conditions. For the task, several mental processes were expected to take place, including recollecting autobiographical memories, eliciting corresponding emotions, self-evaluation processing, and emotional regulation. The subjective rating scores indicated that the participants seemed to feel sadder over the ex-partner trials than over the friend and neutral trials. The fMRI results showed that the brain areas activated by the ex-partner condition overlapped with the pain processing network, for example the thalamus, anterior insula, and dorsal ACC. We also found that the mPFC was significantly activated in both the ex-partner and good-friend conditions. It positively correlated with emotional arousal. On the other hand, higher activities in the ventrolateral PFC were only observed in the ex-partner condition. Therefore, we supposed the processes of valuation and emotion regulation were significantly involved. Taken together, we

replicated the findings that the psychological pains will recruit physical pain network for responses. More important is the finding that the valuation and regulation processes were involved as well. It might justify that why some can get rid of grief from the social rejection event and some cannot.

Disclosures: L. Chien: None. **W. Kuo:** A. Employment/Salary (full or part-time):; YangMing University.

Poster

594. Emotion: Fear, Anxiety, and Pain II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 594.13/V2

Topic: G.03. Emotion

Support: IMSD

Title: Multimodal affect recognition: Deep learning analysis of physiological, environmental, facial expression, and mobile sensor data for emotion detection in chronic pain patients

Authors: *L. P. WHEELER[1], P. NEJEDLY[2], V. KREMEN, JR[3], B. BRINKMANN[2], G. A. WORRELL[2];
[1]Mayo Clin. Grad. Sch. of Biomed. Sci., Rochester, MN; [3]Neurol., [2]Mayo Clin., Rochester, MN

Abstract: Background: Of the 1 in 6 people worldwide with primary neurological disorders, approximately 40-60% present with chronic pain and affective disorders as frequent comorbidities. The relationship between chronic pain and mood disorders is bidirectional, and neither can be effectively treated until all sensory, affective, psychological, and emotional aspects of both conditions are addressed. The unclear association in which increases in symptom recurrence, severity, and morbidity as well as accurate pain and emotional assessments have limited effective integration of the affective dimension of pain into guiding treatment modalities. The growing popularity of sensors and low power integrated circuits, along with the increasing use of wireless networks have led to the development of affordable, robust, and efficient wearable devices which can capture and transmit data in real time. These data sources provide a unique opportunity for innovative ways in recognizing affect and pain levels through human physiological sensing while also taking into account environmental factors, activity levels, motion patterns, and cognitive function from mobile sensing. Here, we present a novel, multimodal hierarchical fusion strategy which uses a deep learning approach on raw mobile and sensor data to achieve real time, state-of-the art results on emotion recognition.
Methods: We collected raw sensor data including blood volume pulse, electrocardiogram, skin conductance level, respiration rate, mobile key-strokes, electroencephalogram, video, and patient ratings of pain intensity, emotion, and mood from a subset of chronic pain patients. We also

integrated data from databases including DEAP, CK DFAT, and UNBC-McMaster Shoulder Pain Database. Our model learns the spatio-temporal hierarchical features from sensors through a multiple-fusion-layer based ensemble classifier using Deep Neuroevolution optimization of a combination of Convolution Neural Network and Long Short-term Memory Recurrent Neural Network. For the dynamic facial action unit coding system, we extracted textural and geometric features through Gabor wavelet and Procrustes analysis, and then trained Gentle Adaboost classifiers.
Results: Here, we present a state-of-the-art method for physiological affect detection and automated facial action coding for neuropsychiatric research. Using a hybrid deep learning model and multiple sensor modalities, we were able to achieve an objective and quantitative evaluation of affect, valence, arousal, and pain intensity with an %5.2 improved affect recognition accuracy rate over the best emotion recognition algorithms in existing literature.

Disclosures: L.P. Wheeler: None. **P. Nejedly:** None. **V. Kremen:** None. **B. Brinkmann:** None. **G.A. Worrell:** None.

Poster

594. Emotion: Fear, Anxiety, and Pain II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 594.14/V3

Topic: G.03. Emotion

Support: Manchester-Weizmann collaborative program

Title: When and why two emotional experiences are similar to each other

Authors: *M. RIBERTO[1,2], M. C. IORDAN[3], R. PAZ[4], G. POBRIC[2], D. TALMI[5];
[1]Weizmann Inst. of Sci., Rehovot, Israel; [2]The Univ. of Manchester, Manchester, United Kingdom; [3]Princeton Univ., Princeton, NJ; [4]Neurobiology, Weizmann Institue of Sci., Rehovot, Israel; [5]Sch. of Psychological Sciences, Univ. of Manchester, Manchester, United Kingdom

Abstract: Rationale. Emotional similarity refers to the tendency to group stimuli together because they evoke the same feelings. The study of emotional similarity may impact research about the over-generalization bias in anxiety disorders. No previous studies have investigated the relationship between similarity judgments and anxiety, nor the differences in similarity judgments between neutral and emotional stimuli. Mixed results have been reported about the neural correlates of emotionally similar stimuli. We hypothesized a positive correlation between similarity judgments and anxiety, and higher similarity within emotional than neutral stimuli. We also predicted higher activation in high-order visual areas, as well as in brain regions involved in emotional processing. **Methods.** We selected 72 complex pictures from freely-available sources, and divided them into 4 categories, 2 neutral (i.e., people doing laundry, people on the phone)

and 2 negative emotional (i.e., poverty scenes, car accidents). All categories differed in valence and arousal, and were balanced for visual properties. Before functional magnetic resonance imaging (fMRI), 8 participants filled the State-Trait Anxiety Inventory (STAI). During the scan, participants rated the visual complexity of the pictures. After the scan, the participants judged the similarity of these pictures by using the multi-arrangement method. We analysed the similarity judgments by using Representation Similarity Analysis (RSA). **Results.** We found that participants with the higher STAI scores perceived the pictures within each emotional category to be more similar to each other ($r= 0.72$, $p=0.02$). Second, the emotional pictures within the 'car accidents' category were judged as more similar to each other than neutral stimuli ($p<0.001$). Finally, we observed higher activation for the emotional pictures than neutral pictures in the bilateral Middle Occipital Gyrus (left: $T= 10.26$, $pFDR<0.001$; right: $T= 9.48$, $pFDR<0.001$) and in the right Insula ($T=7.76$, $pFDR=0.02$). We also found that the emotional pictures were associated with lower activation in the right Ventromedial Prefrontal Cortex (VMPFC) than the neutral stimuli ($T= 8.81$, $pFDR=0.02$). **Conclusion.** These preliminary results suggest that anxiety might increase the similarity among emotional stimuli. In line with previous findings, negative and arousing stimuli are perceived as highly similar. This might be related to the higher activation in the Insula, which in turn amplifies the activation in high-order Occipital areas, and leads to a lower recruitment of the VMPFC compared to neutral stimuli.

Disclosures: **M. Riberto:** None. **M.C. Iordan:** None. **R. Paz:** None. **G. Pobric:** None. **D. Talmi:** None.

Poster

594. Emotion: Fear, Anxiety, and Pain II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 594.15/V4

Topic: G.03. Emotion

Support: NARSAD Grant 27094
Forsknings-ALF Grant LIO-692621

Title: Prospectively assessed childhood trauma is associated with dysregulation of emotion processing in adulthood

Authors: *L. M. MAYO, Y. CHO, D. MIRO, P. GUSTAFSSON, M. HEILIG;
Linköping Univ., Linköping, Sweden

Abstract: Exposure to trauma in childhood or adolescence is associated with an increased susceptibility to the development of psychiatric disorders in adulthood. One potential contributing factor is disruption of the endocannabinoid (eCB) system, a neuromodulatory system involved in stress and emotion processing. The eCB system undergoes extensive

reorganization during adolescence, and perturbations of this process, such as exposure to trauma, can last into adulthood. Thus, childhood trauma may produce dysregulation of the eCB system, producing deficits in stress and emotion processing that contribute to the development of psychiatric disease in adulthood.
Recently, we have shown (Mayo et al., 2018; Mayo et al., in prep) that potentiated eCB signaling produces beneficial emotion regulation capabilities in healthy adults, including enhanced fear extinction and attenuated stress-induced negative affect. Here, we aimed to determine if childhood trauma is associated with deficits that mirror the beneficial effects produced by enhancing eCB signaling.
We recruited patients (ages 22-36) with prospectively assessed childhood trauma (expected N = 40; current N = 31) and matched non-trauma exposed controls (expected N = 40; current N = 34). Trauma-exposed patients were recruited from a specialized trauma unit of Child & Adolescent Psychiatry at the Linköping University Hospital that has been operating since the mid-1990's. Participants completed a laboratory session assessing fear learning, emotion processing, and stress reactivity using facial electromyography (EMG). We assessed baseline EMG responses to emotional images, reactivity to a standardized laboratory stressor, and stress-induced changes in emotional reactivity. In addition, participants underwent a fear conditioning and extinction using fear potentiated startle.
We find that patients exposed to trauma in childhood show attenuated emotional reactivity at baseline, perhaps reflective of "emotional numbing"; a core feature of PTSD. However, after stress, trauma-exposed patients demonstrate greater negative emotionality. Current analyses are underway to examine the acquisition and extinction of conditioned fear. Together, our preliminary analyses suggest that the deficits in emotion processing and regulation evident in trauma-exposed patients closely mirror the beneficial effects we see find following elevation of the eCB anandamide in healthy adults. Thus, the eCB system may represent a novel target to ameliorate stress- and emotion-related deficits following childhood trauma exposure.

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Poster

594. Emotion: Fear, Anxiety, and Pain II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 594.16/V5

Topic: G.03. Emotion

Support: CIHR 275228
CIHR 106445

Title: Exploration of the long-term anxiogenic effects of vicarious juvenile stressor experience

Authors: *E. F. ALI[1,3], P. KENT[3], J. S. JAMES[3], C. CAYER[4], A. ABIZAID[2], Z. MERALI[3]; [2]Neurosci., [1]Carleton Univ., Ottawa, ON, Canada; [3]The Royal's Inst. of Mental Hlth. Res., Ottawa, ON, Canada; [4]Psychology/Biology, Univ. of Ottawa, Ottawa, ON, Canada

Abstract: The experience of stress is diverse as it can be directly experienced or be vicariously transmitted by witnessing a traumatic event. Stress during childhood can lead to negative long-term mental health effects; vicarious stress in the form of witnessing violence can lead to symptomology of mental illnesses. The behavioural effects of vicarious stress are largely unexplored and therefore crucial to investigate further using animal models. The juvenile period is sensitive as the hypothalamic-pituitary-adrenal axis is hyper-responsive to stress. There is a lack of evidence if vicarious stress can be induced during juvenility and whether there are long-term effects. The objective of this study was to explore if vicarious juvenile stress could elicit a potent stressor response leading to anxiogenic behavioural effects in adulthood. Modifying a juvenile stressor procedure to include a witness, male rats were subjected to six days of stress during postnatal days (PD) 27-32. Groups (n=10) included witnesses that observed their cage mate (demonstrator) endure a 10 minute session of the following: 10x1mA 1s footshocks (PD27 and 32), an inescapable swim stress (PD28 and 30), and restraint stress (PD29 and 31). Control rats remained in their home cage throughout the study and the witness-control group only observed their cage mate undergo no stress in the same contextual stress conditions. Corticosterone response was measured on PD27 and PD32 after the footshock and after a mild stressor in adulthood. Fear expression during the juvenile stressor was observed in the witness and witness-controls. In adulthood, fear expression and elevated plus maze (EPM) was conducted. On the first and last day of the juvenile stressor, corticosterone levels were elevated in all groups when compared to the home cage controls, and were particularly higher in the demonstrators and witnesses. Also, witnesses and witness-controls did not differ in fear expression during the stressor procedure. In adulthood, demonstrators exhibited greater fear expression, when placed back into the footshock context, than witnesses and witness-controls. There were no differences in elevations of corticosterone between the groups after a mild stressor. In the EPM, only stressed demonstrators showed anxiogenic behaviour. In sum, this model of juvenile stressor exposure can elicit a stressor response yet the long-term anxiogenic effects were not robust in the witnesses. It is possible that vicarious stress using this paradigm requires prior direct stress. Also, different central mechanisms could be at play that may explain the differences between direct and vicarious stress during the juvenile period.

Disclosures: E.F. Ali: None. **P. Kent:** None. **J.S. James:** A. Employment/Salary (full or part-time):; The Royal's Institute of Mental Health Research. **C. Cayer:** None. **A. Abizaid:** None. **Z. Merali:** None.

Poster

594. Emotion: Fear, Anxiety, and Pain II

Location: Hall A

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Program #/Poster #: 594.17/V6

Topic: G.03. Emotion

Support: NIMH-F32MH112232
NIH-R37HD083217
Gålös-stiftelsen
NIAAA-R01AA023181

Title: Abusive caregivers are not a secure base for their infant: Understand the neurobiology using a rodent model

Authors: *A. I. BLOMKVIST[1], M. OPENDAK[2], D. A. WILSON[3], R. M. SULLIVAN[4]; [1]Stockholm Univ., Stockholm, Sweden; [2]Child and Adolescent Psychiatry, New York Univ., New York, NY; [3]Child and Adolescent Psychiatry, New York Univ. Sch. of Med., New York, NY; [4]Emotional Brain Inst., NKI & NYU Sch. of Med., New York, NY

Abstract: The human attachment literature highlights the quality of the infants attachment relationship to the caregiver as predictive of later life outcomes. Yet, we understand little of the neurobiology of this relationship. While the attachment literature highlights the infant's proximity seeking of the caregiver, it also highlights the attachment figure's role as a safe haven and secure base. The safe haven characteristic of the attachment figure provides comfort and relief under threat but also provides the infant with a safe base to explore the environment, which significantly impacts the infant's exposure to novel objects and social partners. The goal of the present research is to better understand the neural and behavioral features and balance between two infant behaviors: proximity seeking of the attachment figure vs. exploration of a novel social figure of an unrelated mother. Ten to 13-day old infant rats, with either a typical or atypical attachment to their caregiver, had their neurobehavioral response to simultaneous presentation of their own mother and an novel mother (maternal odor distinct from their own mother). All of pups' behaviors to the two anesthetized mother were recorded during measurement of cortical local field potential (LFP) oscillations. Results suggest that typical attached pups show both proximity seeking of the mother and the stranger, while atypically attached pup remained with the mother. LFP recordings show divergent LFP responses to the mother and stranger based on attachment quality. These results suggest that the neural processing of the mother in atypical attachment diverges from infants with typical attachment.

Disclosures: A.I. Blomkvist: None. **M. Opendak:** None. **D.A. Wilson:** None. **R.M. Sullivan:** None.

Poster

594. Emotion: Fear, Anxiety, and Pain II

Location: Hall A

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Program #/Poster #: 594.18/V7

Topic: G.03. Emotion

Support: NIH F32MH112232
NIH T32MH019524
NIH R37HD083217
Gålös-stiftelsen
NYU undergraduate DURF award
Fulbright Fellowship

Title: Maternal suppression of learned fear and developmental transitions in prefrontal activity

Authors: *P. A. ROBINSON-DRUMMER[1], M. OPENDAK[1], A. BLOMKVIST[1,2], R. SULLIVAN[1];
[1]Emotional Brain Inst., NKI & NYU Sch. of Med., New York, NY; [2]Univ. of Stockholm, Stockholm, Sweden

Abstract: Within the infant-caregiver attachment system, the primary caregiver acquires regulatory control over the developing emotion circuits and can modulate infant physiological and behavioral responses. A less well-understood feature of the attachment system is the caregiver's ability to reduce fear, commonly associated with the notion of a 'safe haven' in the developmental literature. In adult animals, the social support system that attenuates fear is associated with the prefrontal cortex (PFC). Evidence suggests that this system may overlap with the developing infant systems to produce the modulatory effects of maternal presence during fear learning. Here, using odor-shock conditioning in young rodents, we questioned when the infant system transitions to the adult-like system and whether the late-developing PFC is involved in the caregivers' reduction of infant fear. Rat pups were odor-shock conditioned (0.6mA) at either postnatal day (PN)18 or 28 with either the mother present or absent, with PFC assessment during acquisition followed 24hr later by cue testing. Since the human literature suggests poor attachment attenuates the mother's ability to socially buffer the infant, half of the pups at each age were reared with an abusive mother from PN8-12. Results showed that for typical control rearing, the mother attenuated fear in both PN18 and PN28 pups, although the PFC was only engaged at PN28 (infralimbic, ventral prelimbic). Abuse-rearing completely disrupted maternal social buffering at PN18. At PN28, pups showed that while the mother modulated learning in both control and abuse-reared pups, the behavioral and PFC effects were attenuated after maltreatment. Our data suggests that pups transition to the adult-like PFC social support circuit after independence from the mother (PN28), and this circuit remains functional after early life

trauma, although its effectiveness appears reduced. This is in sharp contrast to the effects of early life trauma during infancy, where maternal regulation of the infant, such as fear suppression, is more robustly impacted.

Disclosures: P.A. Robinson-Drummer: None. **M. Opendak:** None. **A. Blomkvist:** None. **R. Sullivan:** None.

Poster

594. Emotion: Fear, Anxiety, and Pain II

Location: Hall A

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Program #/Poster #: 594.19/V8

Topic: G.03. Emotion

Support: Battaglia Endowed Chair in Pediatric Pain Management (GAB)
NIMH-F32MH112232 (MO),
BBRF NARSAD Young Investigator Award (MO),
NIH-R37HD083217 (RMS)

Title: Maternal social buffering reduces infant pain: Understanding the supporting neural circuitry

Authors: *G. A. BARR[1], M. OPENDAK[2], R. PERRY[2], R. M. SULLIVAN[3];
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Abstract: Infants and children have the brain circuitry required to perceive pain and also the brain circuitry to have that pain attenuated by a significant social partner such as an attachment figure. This latter mitigating effect is termed “social buffering”. For example, a child’s normal infrequent pains, such as falling while learning to walk, can be comforted by the caregiver as evidenced by reduced crying and reduced stress hormone levels. Similarly, basic science research finds that social buffering reduces the behavioral and neural response to pain, including the alteration of amygdala function. Over the past decade, social buffering has been introduced into medical settings where it has been useful in dampening frequent procedural pain, reducing the need for opioids for pain relief. However we know little about the neural circuitry supporting social buffering, nor about the long-term impacts of this form of pain relief. Recent animal research indicates that social buffering, *if used frequently*, initiates unique developmental trajectory that disrupts the normal development of the amygdala and alters adult pain processes and emotionality. Here we interrogate if and how infant and adult behaviors, and concomitant amygdala activation, are modified by experiencing infant pain vs. infant pain with social buffering. We tested these hypotheses by using rodent models of pain (foot stick or mild tail

shock) with or without social buffering produced by maternal presence during the age range of the sensitive period of pain programming and infant attachment learning to the mother. Our results show that maternal social buffering, when the infant is in pain, reduces activity and ultrasonic vocalizations, induces coherent changes in GPCR gene expression, and reduces Fos expression in several pain and attachment network brain regions to control levels after one day, although this effect was significantly diminished after 5 days of treatment. Adult assessment showed a slight hypoalgesia to heat but no injury induced hyperalgesia in any treatment group. Disruption of adult social behavior was seen when infant pain was socially buffered, although pain with and without social buffering both impacted threat responding. These studies aid in our understanding of the neural basis of social buffering and suggest it protects against some enduring effects of infant pain, though it worsens others.

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Poster

594. Emotion: Fear, Anxiety, and Pain II

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Topic: G.03. Emotion

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Title: Developmental transitions in amygdala PKC isoforms and AMPA receptor expression associated with threat memory in infant rats

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Abstract: Although infants learn and remember, they rapidly forget, a phenomenon known as infantile amnesia. While myriad mechanisms impact this rapid forgetting, the molecular events supporting memory maintenance have yet to be explored. To explore memory mechanisms across development, we used amygdala-dependent odor-shock conditioning and focused on mechanisms important in adult memory, the AMPA receptor subunits GluA1/2 and upstream protein kinases important for trafficking AMPAR, protein kinase M zeta (PKMζ) and iota/lambda (PKCι/λ). We use odor-shock conditioning in infant rats because it is late-

developing (postnatal day, PN10) and can be modulated by corticosterone during a sensitive period in early life. Our results show that memory-related molecules did not change in pups too young to learn threat (PN8) but were activated in pups old enough to learn (PN12), with increased PKMζ-PKCι/λ and GluA2 similar to that observed in adult memory, but with an uncharacteristic decrease in GluA1. This molecular signature and behavioral avoidance of the conditioned odor was
recapitulated in PN8 pups injected with CORT before conditioning to precociously induce learning. Blocking learning via CORT inhibition in older pups (PN12) blocked the expression of these molecules. PN16 pups showed a more adult-like molecular cascade of increased PKMζ-PKCι/λ and GluA1–2. Finally, at all ages, zeta inhibitory peptide (ZIP) infusions into the amygdala 24hr after conditioning blocked memory. Together, these results identify unique features of memory processes across early development: AMPAR subunits GluA1/2 and PKC isoform expression are differentially used, which may contribute to mechanisms of early life forgetting.

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Poster

594. Emotion: Fear, Anxiety, and Pain II

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Title: Infant neurobehavioral processing of the caregiver: Translating across species during typical and maltreatment rearing

Authors: *M. OPENDAK[1], E. THEISEN[2], A. I. BLOMKVIST[3], T. LIND[4], E. C. SARRO[5], M. DOZIER[6], R. M. SULLIVAN[7], D. A. WILSON[8];
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Abstract: Infants rely on the mother to provide them with the sensory stimulation needed for normal brain development. Altered maternal care, such as maltreatment, initiates a pathway to pathology, much of which remains dormant until later life when mental health is compromised. However, immediate effects can be detected in the maltreated infant by using the Strange Situation Procedure (SSP), which progressively stresses the child to uncover atypical responses to the caregiver (Ainsworth, 1969). Here we adapted this test for use in rat pups to aid in identifying the pups' atypical neurobehavioral features within a maltreatment-associated dyad. Using the Scarcity-Adversity Model of maltreatment induced by low bedding (SAM-LB) for nest building from postnatal days (PN)8-12, we compared SSP performance in maltreated rodents (PN13-14) and children; both exhibited behavioral features of disordered attachment in the SST. In pups, recording of cortical oscillations using local field potentials (LFP) showed that the mother had reduced ability to modulate the infant's rhythmic brain activity during SSP, compared to pups with no maltreatment experience. Next, we considered the progression of pups' atypical behavior and cortical oscillations by recording LFP in both pup and mother during brief periods of SAM (between PN10-17). Neocortical telemetry LFP elctrodes were implanted in PN10 pups and mothers and LFP recorded during 1 hr periods of SAM (maltreatment) or typical rearing in the same animal. Mother-infant interactions were recorded and then scored for behavior and LFP power was decomposed into delta (0-5Hz), theta (5-15Hz), beta (15-35Hz), and gamma (35-80Hz) frequency bands. During the early days of SAM treatment, maltreatment had produced the largest observable effects on both LFP and behavior. The dynamic range of LFP induced by mother-pup interactions decreased, with both pup and mother showing impaired LFP responses to specific interactions, such as milk ejection and grooming. Blocking stress hormone synthesis via metyrapone during maltreatment and the SSP restored pup behavior, maternal regulation of LFP power, and cross-frequency coupling patterns to control levels. These results suggest that when a mother is stressed, she has impaired ability to modulate both her own and pups' neural function. Considering the critical role of brain oscillations in brain functioning and its critical role programming brain development, these maltreatment-related impairments are likely contribution to the pathological developmental pathway induced by maltreatment in early life.

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Poster

594. Emotion: Fear, Anxiety, and Pain II

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Title: What happens to the infant during maltreatment? Stress targets hippocampus but stress with mother targets amygdala and social behavior

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Abstract: Animal models designed to simulate early-life abuse have provided insight into the role of parental care in determining the trajectory of the child's neurobehavioral development. However, the inherent complexity of maternal abuse has prevented understanding of the mechanisms during the abuse that initiate the pathway to pathology and later-life outcome. Here, we deconstruct the abusive experience to identify which components of trauma are most salient and deleterious in initiating pathology in the developing infant. To this end, we began with a naturalistic manipulation in Experiment 1 and then deconstructed this experience by manipulating stress hormones and maternal behavior and presence in Experiment 2. All treatment occurred between postnatal days (PN)8 to 12. Testing occurred at PN13 using social interaction with an anesthetized mother to facilitate identification of pup behaviors. Experiment 1 used a naturalistic early-life abusive rearing (Scarcity-Adversity Model of Low Bedding) vs. control rearing (PN8-12). Maltreatment pups exhibited elevated levels of the stress hormone corticosterone (CORT), impairments in infant social behavior, and alterations in amygdala structure and function, including elevated c-Fos, volumetric changes, modified neurogenesis and changes in local field potentials (LFP). These pups also showed morphological changes in the hippocampus, including neurogenesis and volume. In Experiment 2, we deconstructed the complex maltreatment paradigm in the following conditions to identify specific links between pups' experiences and outcome. In each condition, pups received either a CORT or vehicle injection paired with opportunities to interact with an awake mom, an anesthetized mom or a polyethylene tube. In all conditions, CORT injections recapitulated the hippocampal deficits produced by maltreatment. However, the amygdala and social behavior deficits were only produced in the pups receiving CORT injections in the presence of awake and anesthetized mothers. The results indicate that increased stress hormone impacted hippocampal development regardless of the type of stimulus present during treatment, but amygdala structure and function were only disrupted if stress hormone increases occurred within a social context with the mother, including an anesthetized mother. The critical role of the amygdala in producing abnormal infant social behavior was verified by temporary amygdala suppression, which eliminated pups' disrupted social behavior. Taken together, these results highlight the critical role of trauma context in initiating distinct outcomes for brain development and social behavior.

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Poster

594. Emotion: Fear, Anxiety, and Pain II

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Title: The fluctuation of anxiety behavior dependent on female estrous cycle

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Abstract: The prevalence of stress- and fear-related disorders, such as major depressive disorder, anxiety disorder and post-traumatic stress disorder, has been known to be higher in women than men. Although it is supposed that these phenomena may be caused by sex differences in biological and pharmacological factors, most researches investigating neural mechanisms of mental disorders has been limited to the use of male rodent models due to variance in female hormone levels. To elucidate the neurobiological mechanisms of anxiety disorders in consideration of sex difference, we focused on female estrous cycle, recurring physiological changes that are induced by reproductive hormones, by using naive female mice. We observed that anxiogenic behavior of female mice was fluctuated dependent on female estrous cycle stages. Therefore, we investigated the molecular mechanism by which female sex hormones, such as estrogen and progesterone, modulate to anxiety behavior.

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Poster

594. Emotion: Fear, Anxiety, and Pain II

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MINECO SAF2016-76565-R
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Title: Sex differences in macrocircuitry and microcircuitry of the Tac2 pathway in fear conditioning

Authors: *A. FLORIDO[1], E. R. VELASCO GARCIA[1], J. A. GONZÁLEZ-PARRA[1], A. GOMEZ-GOMEZ[2], Ó. J. POZO[2], R. ANDERO GALI[1];
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Abstract: Fear-based disorders are highly disabling conditions and current treatments are not successful in many cases. Women endure almost three times more life prevalence of these disorders than men. Recent research has shown that centromedial amygdala (CeM) tachykinin 2 (Tac2) neurons are crucial for the regulation of fear conditioning (FC) in male mice. Here, we have found that systemic administration of a Tac2 antagonist after cued-fear acquisition altered memory consolidation in a sex-opposite manner. Further, this pharmacological manipulation altered the normal rise in testosterone to FC in male mice. Interestingly, females only exhibited memory consolidation alterations when the drug was given in the proestrus stage of the estrous cycle (high estradiol and progesterone). Concordantly, chemogenetic silencing of CeM-Tac2 neurons after FC mimicked the memory consolidation alterations observed after systemic drug administration. CeM-Tac2 anterograde transynaptic neuronal tracing showed differential density of projections to limbic areas in males when compared to females. The current experiments using *in vivo* calcium imaging in freely moving mice (Miniscopes) in this FC paradigm may reveal different neuronal activation patterns in both males and females. Altogether, these data uncover differences in the neurobiology of fear memory consolidation between males and females by aiming research towards sex-specific treatments for fear-related disorders.

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Poster

594. Emotion: Fear, Anxiety, and Pain II

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NARSAD 22434

Title: PACAP-PAC1R system in females: Contributions to fear learning and adaptations to stressors

Authors: *E. R. VELASCO GARCIA[1], A. FLORIDO[1], Á. FLORES[1], E. SENABRE[2], A. TORRES[3], A. ROCA[3], L. GARCIA-ESTEVE[3], R. ANDERO GALI[1];
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Abstract: Anxiety and fear-based disorders are conditions that are twice as prevalent in women compared to men. In the case of Posttraumatic stress disorder (PTSD), the experiencing or witnessing of a highly stressful event triggers neuronal changes that result maladaptive for a subset of people. The Pituitary adenylate cyclase-activating peptide (PACAP) and its main receptor, the type1 receptor (PAC1R), are implicated in neuroendocrine stress responses and neuronal survival. Previous studies have shown that dysregulations of the PACAP-PAC1R system can result in abnormal stress responses in women with PTSD, but not men. Also pointing at an estrogen-dependent regulation of this system. For this, we aim to study the contribution of the PACAP-PAC1R system to the processing of fear memories in naturally cycling women and female mice, also identifying stress responsive circuits modulated by PACAP. Here we describe convergent evidence from rodents and humans regarding the impact of the estrous/ menstrual cycle phase during trauma. In a cohort of women victims of sexual assault, we observe no influence of the phase of menstrual cycle at the time of trauma for the subsequent development of posttraumatic symptoms. Likewise, female mice undergoing acute immobilization stress show further impairments in cued- fear extinction regardless of the estrous cycle phase. However, immobilized female mice had upregulation of PACAP and PAC1R mRNA in the amygdala and hypothalamus after a fear extinction session. Additionally, immunohistochemistry studies reveal that immobilization stress increases PACAPergic neuronal activation in stress responsive areas and decreases their activity in medial prefrontal structures. Ongoing tracing studies from the BNST and prelimbic cortex are being used to identify the PACAPergic afferent and efferent circuits driving these behavioral adaptations, which will further undergo chemogenetics manipulation. In sum, this study provides circuit mechanisms for the PACAP-PAC1R system adaptation to stressors that may be useful for PTSD or fear-related disorders.

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Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.01/V15

Topic: G.05. Anxiety Disorders

Support: DFG SFB/TRR 58

Title: TGFB-inducible early growth response protein 2 (TIEG2) gene: Impact of genetic variation on anxiety-related traits in healthy individuals

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Abstract: The most frequent mental disorders are anxiety disorders (AD) with a life-time prevalence of 21.0% in the US. Twin studies suggested a moderate genetic component with a heritability of up to 48%. A functionally relevant variable number tandem repeat (VNTR) in the monoamine oxidase A (*MAOA*) gene promoter region has repeatedly been found to be associated with AD, particularly in female patients. The TGFB-Inducible Early Growth Response Protein 2 (*TIEG2*) is an activating transcription factor and binds to Sp1 binding sites in the *MAOA* gene promoter. Genetic variation in the *TIEG2* gene could therefore be a new potential risk factor for anxiety disorders such as panic disorder.

In this study, 3,156 healthy probands (w=1,733; age=25.26±5.644) recruited within the CRC-TRR58, subproject Z02, from 2008 through 2016 were genotyped for six tagSNPs [rs4669519 (A/G), rs4669520 (G/A), rs35927125 (G/A), rs4444493 (A/C), rs4669522 (C/T), and rs7632 (T/C)] by competitive allele-specific polymerase chain reaction (KASP). Furthermore, anxiety-related traits were assessed by several psychometric instruments, e.g. the State-Trait-Anxiety-Inventory, Trait version (STAI-T) (not available for all probands). Linear regression analyses controlled for age and gender revealed the following associations: First, the minor A allele of tagSNP rs4669519 was shown to be associated with an increase in STAI-T scores (N=2,927, b=0.5373, p=0.026). Second, the minor C allele of tagSNP rs7632 was shown to be associated with a decrease in STAI-T value (N=2,937, b=-0.4419, p=0.024). With regard to other investigated tagSNPs as well as all remaining psychometric instruments, no significant associations could be detected (all ps>0.05).

The current study partly confirms the hypothesized association between genetic variations in the *TIEG2* gene and anxiety-related traits in healthy probands. Both associated SNPs are predicted to be functionally relevant, with rs4669519 altering a transcription binding site in the *TIEG2* promoter region and rs7632 being located in a microRNA binding site in the 3'-UTR region of the gene. However, this predicted functionality on gene expression remains to be validated experimentally (e.g. by quantitative PCR analysis). Furthermore, given the observed opposite associations of two minor tagSNP alleles, *TIEG2* gene variation might differentially influence anxiety risk and resilience and thus constitute a 'plasticity' rather than a 'risk' gene for anxiety. However, the failure to discern association of the remaining tagSNPs with any anxiety score

points towards a generally rather weak impact of the *TIEG2* gene on anxiety-related traits in healthy individuals.

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Poster

595. Human Studies: Fear and Anxiety

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Support: German Research Foundation (DFG SFB-TRR 58 Fear, Anxiety, Anxiety Disorders); Project C09

Title: Exposure treatment in spider phobia: Associations between resting state connectivity, symptom severity and within-session extinction

Authors: *F. R. SEEGER[1], H. SCHWARZMEIER[1], N. SIMINSKI[1], B. GATHMANN[2], T. STRAUBE[2,3], J. REPPLE[4], J. BOEHNLEIN[4], E. J. LEEHR[4], U. DANNLOWSKI[4], K. ROESMANN[5,3], M. JUNGHOEFER[5,3], M. J. HERRMANN[1];
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Abstract: Objective. Even though specific phobia is a frequent anxiety disorder, it is largely unknown how state and trait symptom severity and within-session extinction (WS-ext) during exposure treatment are associated with pre-treatment resting state connectivity. Gathering information about potential associations between those variables might aid in selecting appropriate neurobiological predictors for machine-learning or the establishment of Research Domain Criteria. Therefore, the aim of the present analysis was to identify resting state signatures linked to state and trait pretreatment symptom severity and WS-ext in spider phobia patients. **Methods.** 72 patients (female n = 63) underwent an 8 min resting-state measurement within a 3T fMRI scanner prior to behavioral exposure. ROI-to-ROI connectivity measures were computed with *CONN*. Trait symptom severity was assessed using the Spider Phobia Questionnaire (SPQ). State symptom severity was assessed via a behavioral avoidance task with a living bird spider. All patients received a one-session exposure-based cognitive behavioral

therapy treatment in virtual reality. Self-reported anxiety ratings during exposure were used to compute WS-ext values. Patients were divided into subgroups of high and low symptom severity and WS-ext via a median split. Regression analyses and group comparisons were performed in *CONN*. **Results.** Trait anxiety was negatively associated with connectivity between anterior cingulate cortex (ACC) and rostral prefrontal cortex (rPFC) in the high SPQ group. WS-ext was negatively associated with connectivity between hippocampus (HC) and medial PFC (mPFC). Group comparisons revealed significantly stronger negative connectivity between amygdala and ACC as well as rPFC within the group of high WS-ext patients. Similarly, negative connectivity between the insula and rPFC was stronger in the high WS-ext group. Furthermore, significantly stronger positive connectivity was found between amygdala and HC among high WS-ext patients. **Discussion.** Findings highlight the relevance of inhibitory functional connectivity between frontal and defensive system structures in phobic patients. In line with our hypothesis, enhanced extinction learning was associated with stronger inhibitory mPFC-HC connectivity and ACC/rPFC-amygdala connectivity as well as positive connectivity between the amygdala and HC. Findings underline the relevance of those neural networks conferring emotion regulation and context conditioning involved in behavioral exposure. As there are no comparable studies addressing connectivity in specific phobia our results are preliminary and need replication.

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Poster

595. Human Studies: Fear and Anxiety

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Program #/Poster #: 595.03/V17

Topic: G.05. Anxiety Disorders

Title: Mindfulness meditation alters neurophysiological symptoms of anxiety in preadolescents

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Abstract: Mindfulness meditation interventions (MMI) are formal training programs which utilize mindfulness techniques to improve attentional control and reduce stress and anxiety. During individual sessions of training, mindfulness-elicited electrophysiological changes have been reported including increased alpha and theta waves; a pattern reflecting a mental state of “relaxed alertness”. Prior investigations have shown that mindfulness-based interventions are effective in improving symptoms of anxiety and depression in both adolescents and adults, making this a promising natural approach to treating mood disorders. However, the lasting

resting-state electrophysiological effects of mindfulness training programs are less well-understood. The primary aim of this study was to expand on prior research by examining the effects of a 10-week MMI on resting-state electroencephalogram (EEG) measures relating to anxiety and negative affect. These measures included frontal alpha asymmetry, intrahemispheric alpha coherence, and cortical-wide power values for theta, alpha, and beta bands. The novel contributions of this project were the wide array of resting-state EEG measures and the relatively unexplored age-range (7- to -10-year-olds) in the mindfulness literature. Participants trained with MMI demonstrated significant increases in intrahemispheric alpha coherence from pre- to -post, F (9, 585) = 4.46, p = .008, as well as increased theta, alpha, and beta power particularly in frontal and central areas; reflecting a lower neurological risk for anxiety development during the adolescent years (all p's < .05). The precise changes in EEG power from pre- to -post can be seen in the table below. However, two common measures linked to anxiety, frontal and posterior alpha asymmetry remained largely unchanged following the training period. None of these results were altered with gender and ethnicity entered as covariates. These preliminary results exemplify the utility of MMI for preadolescents as an alternative method for mitigating electrophysiological symptoms of anxiety. Future studies should expand on these findings given that this age-range has traditionally shown poorer responses to medication and cognitive behavioral therapy than adults.

Frequency Band	Mean pre-training	Mean post-training	T-statistic	P-value
F3Theta	3.62 (.50)	3.73 (.47)	-2.21	.032**
F4Theta	3.69 (.46)	3.75 (.46)	-1.38	0.173
F7Theta	3.97 (.47)	4.04 (.43)	-1.36	0.183
F8Theta	3.98 (.45)	4.07 (.45)	-1.83	0.072
C3Theta	2.82 (.41)	3.10 (.92)	-2.62	.011**
C4Theta	2.96 (.55)	3.14 (.76)	-1.58	0.11
F3Alpha	3.33 (.63)	3.37 (.49)	-0.71	0.48
F4Alpha	3.42 (.62)	3.43 (.62)	-0.221	0.837
F7Alpha	3.64 (.82)	3.69 (.82)	-0.74	0.463
F8Alpha	3.71 (.86)	3.72 (.96)	-0.092	0.932
C3Alpha	2.98 (.80)	3.14 (.65)	-2.19	.043**
C4Alpha	3.09 (.61)	3.34 (.82)	-1.68	.005**
F3Beta	2.33 (.51)	2.52 (.56)	-2.92	.005**
F4Beta	2.46 (.44)	2.60 (.44)	-3.08	.003**
F7Beta	2.70 (.50)	2.81 (.50)	-1.96	0.055
F8Beta	2.81 (.47)	2.85 (.47)	-2.73	.007**
C3Beta	1.42 (.84)	1.92 (.67)	-3.35	.001**
C4Beta	1.77 (.67)	2.01 (.67)	-2.26	.027**

Disclosures: **N.A. Shanok:** None. **C. Reive:** None. **K.D. Mize:** None. **K. Cobty:** None. **I. Bakir:** None. **N.A. Jones:** None.

Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.04/V18

Topic: G.05. Anxiety Disorders

Support: German Research Foundation: SFB-TRR 58 C06

Title: Temporal unpredictability modulates brain activity in threat confrontation

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Abstract: Objective. Brain networks recruited during threat anticipation and threat confrontation differ widely and depend on stimulus predictability. Paralleling findings from animal electrophysiology, human functional magnetic resonance imaging (fMRI) suggests that an initial, phasic response in Amygdala can be distinguished from a sustained response in the Bed Nucleus of the Stria Terminalis (BNST). Moreover, these effects seem to be gated by stimulus predictability. However, given the importance of predictability for learning and conditioning there is a surprising lack of neuroscientific studies in humans investigating the modulatory role of predictability on confrontation with a threatening stimulus in Amygdala and BNST. **Methods**. During fMRI, 109 healthy individuals (37 male, age = 27.1 ± 6.3 years) anticipated either a negative or a neutral stimulus. An additional cue either predicted the exact moment of the impending confrontation with these stimuli or it signaled that the moment was temporally unpredictable. Mean estimated parameter values of these four conditions were extracted from Amygdala, BNST and Insula and analyzed in a repeated-measures analyses of variance using Brain Voyager 20.6.
Results. Brain activation to confrontation with threat revealed significant main effects of predictability and valence in Amygdala and BNST. These regions showed higher activation during confrontation with threat as well as during confrontation with unpredictable threat. Furthermore, Insula showed higher activation during unpredictable compared to predicted confrontation. No interactions were found. **Discussion.** Higher activation of BNST and Insula during confrontation with unpredictable stimuli supports theories suggesting an important role of unpredictability for neural brain activity related to anxiety. However, higher Amygdala activation during confrontation with unpredictable stimuli questions the separation of fear and anxiety. Therefore, future studies should use this study design in clinical anxiety groups to

further evaluate modulation effects of temporal predictability in fear- and anxiety- related brain activity.

Disclosures: **N. Siminski:** None. **S. Boehme:** None. **J. Zeller:** None. **M.P.I. Becker:** None. **A. Muehlberger:** None. **T. Straube:** None. **M.J. Herrmann:** None.

Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

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Program #/Poster #: 595.05/V19

Topic: G.05. Anxiety Disorders

Support: German Research Foundation (DFG SFB-TRR58 Fear, Anxiety, Anxiety Disorders); Project C09

Title: Spider phobia and brain morphometry: Brain-structural predictors of within-session extinction during behavioral exposure

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Abstract: Objective. Behavioral exposure, a first-line treatment for spider phobia (SP), is conceptionally based on fear-inhibitory learning during fear extinction. Although showing large effect sizes, a significant proportion of patients does not benefit sufficiently. Identifying potential predictors of treatment response and (neural) mechanisms that are instrumental for fear inhibition may help in personalizing treatments. The present study aimed at identifying brain-structural markers of within-session extinction during behavioral exposure in SP.
Methods. From 75 recruited patients, quality-controlled T1-weighted magnetic resonance imaging (MRI) was obtained before exposure therapy from 69 SP patients (n= 60 female, mean age = 28.3 yrs) at two different time points, separated by one week, to assess test-retest-reliability. Voxel-based morphometry (VBM) analysis was carried out using the CAT12 toolbox and SPM12. Multiple regressions were performed on grey matter density (GMD) across the brain (p=0.001, uncorrected, cluster-level extent threshold k_E = 50) and trait spider anxiety (Spider Phobia Questionnaire; SPQ), state spider anxiety (behavioral-avoidance-test; BAT) and the

magnitude of fear reduction within the exposure-based therapy session. Total intracranial volumes (TIV), age and gender were entered as variables of no interest into the statistic model. **Results**. GMD in the visual cortex, encompassing, among others, bilateral calcarine sulcus and bilateral lingual gyrus prior to exposure correlated reliably in both MRI sessions with a significantly higher within-session fear reduction. No correlations were observed with trait or state spider anxiety.
Discussion. Structural alterations in basic visual processing areas in SP mirror previous functional findings on the involvement of visual cortices in specific phobia in general. Findings may reflect abnormalities in the visual network in SP possibly resulting from excessive vigilance as an early cortical marker underlying increased defensive reactivity as a function of psychopathology. A higher within-session extinction may be mediated by enhanced situational monitoring or by intensified visual processing of the feared stimulus during exposure as conferred by greater visual cortex GMD. Since activity in the visual cortex immediately after therapy predicted long-term therapeutic outcome in a functional MRI study on SP (cf. Hauner et al.,2012), future studies are needed to clarify the relationship between brain morphometry and long-term outcome in SP.

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Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.06/V20

Topic: G.05. Anxiety Disorders

Title: Effects of a smartphone-based virtual reality exposure app to treat fear of heights, a randomized-controlled trial

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Abstract: Fear of heights is a common problem with a lifetime prevalence of around 20% and with 2-5% of the general population meeting diagnostic criteria for specific phobia (natural-environmental type: heights). Despite the plethora of research supporting exposure as treatment of choice with high success rates, its translation into clinical practice is still limited. Low

threshold treatment options are therefore needed. The rapid development of virtual reality (VR) technologies and the use of VR via smartphones is facilitating new treatment avenues. We developed a stand-alone VR heights-exposure app for smartphones in which sufferers from fear of heights are exposed to heights situations in a gradual manner. The course of exposure is adapted to subjective fear levels using a gaze selection-based visual analog scale. To test for immediate effects of our VR heights-exposure app (study phase 1), we randomized 70 participants with a fear of heights (42 fulfilling DSM-V criteria for specific phobia) to either one exposure session (3x20min units) with our VR heights-exposure app (experimental condition) or one session (3x20min units) with a Google Street View VR app (control condition). To test for delayed effects of repeated administration of our VR heights-exposure app (study phase 2), participants of the experimental condition of study phase 1 were offered to take part in an additional 2-week home-training (6x30min units) with the VR heights-exposure app, whereas participants of the control condition received no further treatment. Strength of fear of heights was measured with a real-life behavioral avoidance test (BAT) on a lookout tower, and with questionnaires specific to the fear of heights (timepoints at study phase 1: before and after using the VR app and at study phase 2: 3-5 weeks after the end of home-training). During the BAT, participants were instructed to climb the tower as far as their current fear allows; subjective fear on the reached platform (1-14) was prompted on a scale of 0-10 (0=no fear, 10=maximal fear). The results will be presented at the conference. An amelioration of fear of heights after repeated use would recommend the app as a low-threshold treatment option for fear of heights. Short-term effects after a single exposure session with our VR heights-exposure app would most likely promote the acceptability of the app and might lead to less attrition under real-life conditions.

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Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.07/V21

Topic: G.05. Anxiety Disorders

Title: Therapeutic effects of ketamine on treatment refractory generalized anxiety and social anxiety disorders are unrelated to plasma levels: A double blind active controlled study

Authors: *S. M. SHADLI[1], P. GLUE[2], N. MCNAUGHTON[1], N. MEDLICOTT,[3];
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Abstract: Ketamine acts swiftly in a range of neurotic disorders even in patients resistant to conventional antidepressant and anxiolytic drugs. We recently reported effects of ketamine on frontal EEG in patients with treatment-resistant (TR) generalised anxiety (GAD) and social anxiety (SAD) disorders. Ketamine increase high frequency EEG power, and decreased low frequency power. Interestingly, only the decrease in "theta" power at the right frontal site F4 significantly correlated with changes in Fear Questionnaire (FQ) scores. Here we report blood levels of ketamine, norketamine and BDNF in the same patients. Three ascending ketamine dose levels (0.25, 0.5 and 1 mg/kg) and midazolam (0.01 mg/kg), were given double blind at 1-week intervals to each patient, with the midazolam counterbalanced in dosing position across patients. Twelve patients with DSM-IV TR-GAD and/or TR-SAD provided blood samples pre-dose and at 15, 30, 60 and 120min post-dose. Plasma concentrations of R- and S-ketamine and norketamine were measured using a chiral mass spectroscopy assay and plasma BDNF concentrations using an ELISA, validated for human plasma. Other assessments included ratings of anxiety and dissociation, safety and tolerability. A dose-response profile was noted for anxiolytic effects, dissociative side effects, and changes in blood pressure and heart rate after ketamine dosing. Midazolam had minor brief effects on anxiety ratings. Ketamine produced dose-related decreases in FQ and HAM-A scores. ANOVA by ranks showed a significant effect of FQ vs dose (differences of ranks 342.5, $q=20.2$, $p<0.001$), FQ vs time (differences of ranks 187.0, $q=11.0$, $p<0.001$), and time vs dose (differences of ranks 155.5, $q=9.2$, $p<0.001$). Ketamine was safe and well tolerated, with dissociation ratings correlated with pharmacokinetics. Plasma BDNF was not changed and neither ketamine or norketamine concentrations related to anxiety ratings. In sum, we replicated ketamine's therapeutic effect in TR GAD/SAD but this did not related to plasma levels of the compounds we measured. Ketamine may be an important therapeutic alternative for neurotic disorders with high rates of treatment resistance and few alternative treatment options but its mechanism of action remains obscure.

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Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.08/V22

Topic: G.05. Anxiety Disorders

Support: German Research Foundation (DFG SFB-TRR58 Fear, Anxiety, Anxiety Disorders); Project Z02

Title: The role of anxiety sensitivity in overgeneralization of conditioned fear

Authors: *M. S. VIETZ[1,2], T. B. LONSDORF[3], P. ZWANZGER[4,5,6], A. REIF[7], J. DECKERT[1,2], P. PAULI[8,2], K. DOMSCHKE[9], M. A. SCHIELE[9];
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Abstract: Anxiety sensitivity (AS), the tendency to interpret bodily symptoms as dangerous, is a modifiable risk marker of anxiety disorders (AD). Recently, overgeneralization of conditioned fear has been proposed as a learning mechanism involved in AD development and maintenance. Here, we present preliminary data on the role of AS in the modulation of fear generalization in healthy adults.
N=1,082 (f=646, age= 25.43 ± 5.73 yrs) healthy probands underwent a fear conditioning and generalization (GEN) task. Two neutral faces served as conditioned stimuli (CS), one was paired with an aversive scream (CS+), while the other was not (CS-). During GEN, four gradual morphs of CS+ and CS- were presented. Subjective ratings of arousal and valence were recorded after the 1st and 2nd half of acquisition and GEN phases. Probands were assessed for AS (Anxiety Sensitivity Index-3; ASI-3) and grouped according to AS (high, ASI-3 ≥ 17 vs. low, ASI-3 < 17). Differences in subjective ratings were tested via repeated measures ANOVA with AS group as between-subject factor.
No group differences were found prior to conditioning (ps≤.193), despite overall higher arousal ratings in the high AS group (p=.014). After conditioning, the CS+ was rated as most arousing/least pleasant and vice versa for the CS- (p<.001). As indicated by a significant interaction stimulus x phase (p≤.003), CS- was rated less arousing/more pleasant than CS+ in the

2nd phase. The high AS group displayed overall higher arousal (p=.001) to all stimuli, which was further qualified by a significant interaction phase x AS (p=.026): the low AS group showed a higher decrease in arousal in the 2nd phase whereas arousal remained high in the high AS group. During GEN, a decrease in arousal/increase in valence ratings was observed with decreasing similarity to the CS+ (p<.001), again with overall higher arousal in the high AS group (p<.001). As indicated by a significant interaction stimulus x phase (p<.001) and a significant three-way interaction stimulus x phase x AS (p=.038), overgeneralization of conditioned fear as indexed by arousal ratings remained higher in the high AS group in phase 2, whereas no stimulus overgeneralization was observed in the low AS group in the 2nd compared to the 1st phase, indicating better discrimination learning and/or facilitated habituation in the low AS group. The present results indicate that fear GEN may be modulated by AS. Probands with high AS displayed less stimulus discrimination and less habituation of conditioned fear, which may contribute to an elevated risk for the development and maintenance of AD and could serve as a starting point for preventive measures for AD, e.g. in form of a discrimination training.

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Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.09/V23

Topic: G.05. Anxiety Disorders

Title: Dissociation between striatal volume and risky decision-making in OCD

Authors: P. S. MOREIRA[1], P. MARQUES[1], A. COELHO[1], P. COSTA[1], J. MACOVEANU[2], H. R. SIEBNER[3], N. SOUSA[1], ***P. MORGADO**[1];
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[3]Copenhagen Univ. Hosp. Hvidovre, Hvidovre, Denmark

Abstract: Background: Impaired decision-making has been proposed as one of the core behavioral manifestations of the Obsessive-Compulsive Disorder (OCD). Here, we explored the association between structural brain patterns and risky decision-making in OCD. **Methods:** Eighty individuals (40 OCD patients and 40 matched healthy controls) underwent were assessed with structural Magnetic Resonance Imaging. Risk-taking attitude was assessed during a risky decision-making task. The study was approved by ethical committee and informed consent was obtained from all participants. **Results:** Healthy controls displayed a positive association between the volume of striatal regions and risk taking, whereas this pattern was absent in OCD patients. **Conclusions:** The lack of a normal structure-behavior relationship between striatal

volume and risky choices in OCD patients may be a structural marker of aberrant basal ganglia function in this psychiatric condition.

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Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.10/V24

Topic: G.05. Anxiety Disorders

Title: Effects of phychological and physical stress on intestinal microbiota, generalized anxiety and depressive disorders and serum levels of kynurenine metabolites

Authors: G. S. AZPILCUETA-MORALES[1], B. PALACIOS-GONZALEZ[2], V. PEREZ-DE LA CRUZ[3], L. RAMOS-CHAVEZ[3], ***L. SANCHEZ-CHAPUL**[4], E. ESTRADA-CAMARENA[1]; [1]Neuropsicofarmacologia, Inst. Nacional de Psiquiatria "Manuel de La Fuente", Ciudad de Mexico, Mexico; [2]Vinculacion Cientifica, Inst. Nacional De Ciencias Genomicas, Ciudad de Mexico, Mexico; [3]Neuroquimica, Inst. Nacional de Neurologia Y Neurocirugia "Ramon de La Fuente", Ciudad de Mexico, Mexico; [4]Div. de Neurociencas, Inst. Nacional De Rehabilitacion, Ciudad de Mexico, Mexico

Abstract: High psychological stress increases the risk of developing anxiety, depression, changes in the proportions of the intestinal microbiota, particularly in the bacterial phylum *Firmicutes / Bacteroidetes* and in levels of circulating kynurenine metabolites. Kynurenine metabolites in a state of peripheral inflammation can accumulate in the brain and has been associated with depression; however, this accumulation can be suppressed by activating kynurenine clearance in exercised skeletal muscle. The practice of regular exercise is associated with the decrease of continuous psychological stress and an improvement of microbiota balance. However, the effect of high intensity physical exercise is unknown. Thus, our aim was to describe the effect of continuous psychological stress and high intensity physical exercise on the proportions of Bacteroidetes and Firmicutes of the gut microbiota, and relate them to the stress perception, generalized anxiety, major depressive disorder and serum levels of kinurenine metabolites.
A quasi-experimental, prospective and longitudinal study of two measurements was made. We obtained blood and fecal samples from 49 individuals (18 to 35 years, 38 male) who performed high intensity exercise (5-6 hours / day, 6 times a week) for a month following a standardized diet. Biological samples were taken in two times: at the beginning of the high intensity exercise (basal) and 1 month later. The change in the proportions of the bacterial phylum was evaluated, as well as the anxiety, depression and perceived stress scales. Serum levels of Trp, kynurenine

(Kyn), kynurenic acid (KYNA), QUIN and 3-hydroykynurenine (3-HK) were measured. Results showed that the prevalence of depression, anxiety and stress increased compared to the basal measurement ($p < 0.05$). The Firmicutes / Bacteroidetes ratio ranged from 1: 1 at the beginning of the study to 4:1 ($p < 0.001$) after 1 month. The serum levels of Trp ($p<0.0001$), KYNA ($p < 0.0280$), QUIN ($p < 0.0006$) and 3-HK ($p < 0.0001$) diminished after 1 month, not those of Kyn that increased ($p < 0.0001$) after 1 month. Also serum ratios of Kyn/Trp ($p<0.0362$), KYNA/Trp ($p<0.0037$) increased while 3-HK/Trp ($p<0.0003$) decreased one month after training. Then, the effect of psychological stress in combination with high intensity exercise increases the perception of stress, anxiety and depression, as well as the Firmicutes / Bacteroidetes ratio. Results suggested that implementation of high intense exercise increased psychological stress perception reducing the advantages of making exercise.

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Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.11/V25

Topic: G.05. Anxiety Disorders

Support: NIMH Grant R15MH110951

Title: The interplay between neural and cognitive risk factors in individuals with high trait anxiety: A network analysis

Authors: *L. FANG[1], J. A. ANDRZEJEWSKI[1], T. SUSA[2], H. GILBERTSON[1], J. M. CARLSON[3];
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Abstract: Individuals with high levels of trait anxiety demonstrate hyperactive attention bias to threat and this hyperactivity is associated with the development of anxiety disorders. Previous research has shown elevated attentional bias toward threat and conflict monitoring among high anxious individuals. Moreover, dysfunction within resting state networks has been associated with trait anxiety. However, how hyperactive attention bias and conflict monitoring interact with resting state network dysfunction remains unknown. This study explored the interplay between neural and cognitive risk factors in individuals with high levels of self-reported trait anxiety. Attention bias to threat was measured with the dot-probe task, and conflict-monitoring levels were assessed by the flanker task. The resting state fMRI data was collected via a 1.5T scanner, and functional connectivity in the fronto-parietal and salience networks was examined as

potential neural risk factors in the network analysis. We tested different network models to gain a more comprehensive understanding of how neural and cognitive factors relate to levels of trait anxiety. The results suggest that the reduced functional connectivity in regions of the fronto-parietal network could be a central hub in the concentration network, as it was consistently associated with attentional bias to threat, trait anxiety level, conflict monitoring, and functional connectivity in the salience network. In addition, after considering the effects of all the other variables, the functional connectivity in the salience network still showed a relatively strong association with conflict monitoring. Therefore, our findings suggest that the fronto-parietal network may play an important role in the interactions between impaired cognitive control and dysfunction in resting state networks associated with trait anxiety.

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Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.12/V26

Topic: G.05. Anxiety Disorders

Title: Alterations in resting-state functional connectivity following mindfulness training in adolescents with attentional and emotional disturbances: A pilot investigation

Authors: *S. JUN[1], A. T. SHAFER[2], Y. HU[1], A. D. IORDAN[3], S. DOLCOS[1], A. SINGHAL[4], S. VOHRA[5], F. DOLCOS[1];
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Abstract: Research on mindfulness has provided strong support for its benefits in a multitude of aspects related to well-being, in both healthy functioning and psychopathology. However, few studies have examined mindfulness-induced changes in the neural mechanisms associated with spontaneous thoughts, as measured by resting-state functional connectivity (RSFC). This is an important limitation in the literature, given that many psychopathologies emerge during this developmental period marked by important neural and psychological changes. Also, maladaptive alterations in the RSFC of specific brain regions have been associated with clinical conditions. Hence, the present study aimed to clarify adaptive changes in the RSFC associated with behavioral and psychological benefits following meditation-based stress reduction (MBSR) training in adolescents with attentional and affective disorders. The main focus was on two brain regions associated with emotion processing that have been identified by previous research as sensitive to meditation training in young adults: the amygdala (AMY) and the insula (INS).

Twenty-six adolescents were recruited from a residential mental-health treatment facility and randomly assigned to either receive only a typical socio-emotional treatment (Control Group) or to also receive a supplemental MBSR training (MBSR Group). All participants underwent resting-state fMRI recordings before and after an eight-week treatment/training period. RSFC results showed decreased RSFC of both AMY and INS with brain regions associated with top-down emotion control (medial orbitofrontal cortex), possibly reflecting changes in valuation processes of emotional and interoceptive information, as a result of present-centered, non-judgmental mindfulness training. Moreover, functional decoupling between the AMY and the DLPFC, and between the INS and the left IFC, may reflect reduced bottom-up emotion signaling as a result of mindfulness training. Taken together, these results suggest that MBSR training in adolescents with psychopathology alters the spontaneous brain activities at rest, reflected in functional decoupling between regions signaling bottom-up salience (AMY, INS) and regions of higher-level integration and top-down control (OFC, dlPFC).

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Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.13/V27

Topic: G.07. Other Psychiatric Disorders

Support: Intramural Research Program, National Institute of Mental Health

Title: Suicidal ideation and the salience network: Modeling connectivity with MEG and dynamic causal modeling

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Abstract: Defining the neurobiological underpinnings of suicidal ideation (SI) is crucial to improving our understanding of risk for suicide. This study used magnetoencephalographic (MEG) changes in gamma power as a surrogate marker for population-level excitation/inhibition balance and synaptic potentiation in order to explore the underlying neurobiology of SI and depression. In addition, effects of pharmacological intervention with the glutamatergic modulator ketamine, which has been shown to rapidly reduce SI and depression, were also assessed. Data were obtained from 29 drug-free patients with major depressive disorder and corresponding SI who participated in a double-blind, crossover, placebo-controlled experiment comparing an

intravenous subanesthetic dose of ketamine to a placebo-saline infusion. MEG recordings were collected prior to the first infusion and six to nine hours after both ketamine and placebo infusions. During scanning, patients rested with their eyes closed. SI and depression were assessed across timepoints using several clinical measures, and a linear mixed-effects model was used to identify brain regions showing associations between gamma power and SI and depression. Two regions of the salience network, the anterior insula and anterior cingulate cortex, were then probed using dynamic causal modeling to test for ketamine effects on modeled parameter estimates.
Clinically, patients showed significantly reduced SI and depression following ketamine administration. In addition, distinct regions in anterior insula were found to be associated with SI compared with depression. When modeling anterior insula to anterior cingulate connectivity, ketamine was found to lower the membrane capacitance for superficial pyramidal cells, which are thought to be the primary generators of the MEG signal. Finally, AMPA-mediated connectivity between anterior insula and anterior cingulate was associated with improvements in depression symptoms, but not SI.
These findings suggest that the anterior insula plays a key role in SI, perhaps via its role in salience detection. In addition, these findings suggest that transient changes in superficial pyramidal cell membrane capacitance and subsequent increases in cortical excitability might be one mechanism via which ketamine improves SI.

Disclosures: J.R. Gilbert: None. **E. Ballard:** None. **C.S. Galiano:** None. **A. Nugent:** None. **C.A. Zarate:** None.

Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.14/V28

Topic: G.07. Other Psychiatric Disorders

Title: Reduced habituation of the amygdala in women with borderline personality disorder when experiencing shame and guilt

Authors: *M. GÖTTLICH[1], A. L. WESTERMAIR[2], F. BEYER[4], M. L. BUßMANN[2], U. SCHWEIGER[2], U. M. KRÄMER[1,3];
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Abstract: Borderline Personality Disorder (BPD) is characterized by instability of affect, emotion dysregulation and interpersonal dysfunction. Especially shame and guilt, so-called self-conscious emotions, are of central relevance in BPD. To date, there is however only little experimental work on the experience of shame or guilt in BPD and none on its neurobiological

underpinnings. Furthermore, the involvement of the amygdala in BPD is still unclear as previous neuroimaging studies showed inconsistent results. In the present functional magnetic resonance imaging study, we took a scenario-based approach to experimentally induce feelings of shame, guilt and disgust. Scenarios with neutral content were used as control condition. With this approach, we set out to investigate the higher shame proneness in persons with BPD and its neural basis. We included 19 women with BPD (age 26.4±5.8 years; DSM IV diagnosed; medicated) and 22 healthy female control subjects (age 26.4±4.6 years) in the study. Compared to controls, women with BPD reported more intense feelings when being confronted with affective scenarios, especially higher levels of shame, guilt and fear. In terms of imaging results, we found increased amygdala reactivity in BPD to shame and guilt relative to disgust scenarios (p=0.05 FWE corrected at the cluster level; p<0.0001 cluster defining threshold) caused by a diminished habituation in women with BPD relative to control participants. This effect was specific to guilt and shame scenarios whereas both groups showed habituation of amygdala activity to disgust scenarios. Our work thus shows that dysregulated levels of self-conscious emotions can be experimentally induced in BPD and that this is associated with reduced habituation of amygdala activity. These findings might help to clarify inconsistencies in previous imaging work regarding the involvement of the amygdala in BPD. Our results suggest that persons with BPD might not present generally increased amygdala activation but aberrant habituation to self-conscious emotions.

Disclosures: M. Göttlich: None. **A.L. Westermair:** None. **F. Beyer:** None. **M.L. Bußmann:** None. **U. Schweiger:** None. **U.M. Krämer:** None.

Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.15/V29

Topic: G.07. Other Psychiatric Disorders

Support: The Naito Foundation

Title: Neurocircuitry disfunction in anorexia nervosa identified by neuropathological analysis

Authors: *I. KAWAKAMI[1,2,3], K. UMEDA[2], Z. TANEI[1], M. HASEGAWA[3], S. MURAYAMA[1], S. IRITANI[4];
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Abstract: Background—Anorexia nervosa (AN) is a serious eating disorder characterized by self-starvation and extreme weight loss, with the highest mortality ratio among all psychiatric disorders. Recent functional/structural neuroimaging research indicates that impaired cognitive-behavioral flexibility is associated with an intact functioning of cortico-striatal loop systems, including the caudate, pallidum, the nucleus accumbens, and anterior/posterior cingulate. However, the pathophysiology in AN remains unknown, with many interacting developmental, genetic, environmental, and neurobiological factors. **Objective**—To clarify the pathophysiology in AN, by investigating the neuropathology of the patients' brains. **Materials and Methods**—We investigated the neuropathology of 3 AN patients by some antibodies, such as tyrosine hydroxylase (TH), a faithful marker of dopaminergic neurons, and glia cell markers in serially-cut paraffin sections. Ethical issues were carefully considered in this study. **Results**—Macroscopically, they show the slight frontal atrophy with enlargement of lateral ventricles. Histologically, neuronal loss and gliosis were seen in the frontal cortex and cingulate. In the nucleus accumbens, comparison of the adjacent sections stained for TH and GFAP indicates that gliosis preferentially occurs in areas where the fine, mesh-like TH staining is relatively light. **Conclusion**—The results indicate that impaired functional connectivity in a reward-related network may induce neuro-psychiatric conditions in AN. The findings should be helpful in developing more effective treatments in AN.

Disclosures: I. Kawakami: None. **K. Umeda:** None. **Z. Tanei:** None. **M. Hasegawa:** None. **S. Murayama:** None. **S. Iritani:** None.

Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.16/V30

Topic: G.07. Other Psychiatric Disorders

Support: Wellcome Trust RNAG/472
Bernard Wolfe Health Neuroscience Fund
NIH Oxford-Cambridge Scholars Program

Title: Stress responses, inhibitory control and food intake in women with eating disorders

Authors: *M. L. WESTWATER[1], H. ZIAUDDEEN[1], A. X. GORKA[3], F. MANCINI[1], C. GRILLON[4], M. ERNST[3], P. C. FLETCHER[2];
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Abstract: Stress profoundly affects eating behavior, inducing both increases and decreases in food intake and body weight across individuals. Notably, among patients with eating disorders,

stress has been shown to precede episodic binge eating; however, the neural mechanisms underpinning this relationship remain poorly understood. One model suggests that binge-eating emerges when stress attenuates prefrontally mediated inhibitory mechanisms, leading to impulsive behavior and ensuing loss-of-control eating. The present study explored this model by characterising the effect of stress on inhibitory control and food intake in women suffering with binge-eating disorders. We recruited eighty-five women (three matched groups: anorexia nervosa, binge-purge subtype = 22, bulimia nervosa = 33, healthy controls = 30) for two functional MRI scanning sessions on consecutive days. One scan involved an acute stress induction and the other a neutral condition, and conditions were counterbalanced across individuals. Immediately pre- and post-induction, participants performed the stop-signal anticipation task (SSAT) as a measure of proactive (anticipation of stopping) and reactive (outright stopping) inhibitory control. Our analyses related SSAT performance and neural correlates to subsequent energy intake at a free-choice meal that followed each MRI scan. Preliminary results suggest an effect of inhibitory control, indexed as stop-signal reaction time, on food consumption, and this association was modulated by stress. Results further characterize the effect of eating disorder status on neural responses in the inferior frontal cortex, striatum and posterior parietal cortex during successful and failed inhibitory control, as well as anticipation of stopping a motor response. Moreover, using linear mixed-effects modeling, findings will provide novel insight into how the interaction of stress and eating disorder status modulate neural and behavioral responses to the SSAT, relating these responses to food intake within each participant. Our results are the first to characterize the impact of acute stress on impulsivity and eating behavior in women with severe eating disorders.

Disclosures: M.L. Westwater: None. **H. Ziauddeen:** None. **A.X. Gorka:** None. **F. Mancini:** None. **C. Grillon:** None. **M. Ernst:** None. **P.C. Fletcher:** None.

Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.17/V31

Topic: G.07. Other Psychiatric Disorders

Support: Herman Dana Foundation

Title: Prospective six months follow up study of salivary DHEA-S levels and treatment response among adolescents with eating disorders

Authors: *T. GOLTSER[1,2], R. GIESSER[2], A. SHALEV[2], A. MELTZER[2], R. MASARWA[2], D. PEVZNER[1,2], L. CANNETI[1], E. GALILI-WEISSTUB[2], R. SEGMAN[1];
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Psychiatry, Dept. of Psychiatry, Hadassah - Hebrew Univ. Med. Center; Jerusalem Israel, Jerusalem, Israel

Abstract: Background: The aim of the current study is to prospectively characterize neuroendocrine reactivity among adolescent ED patients and correlate them with treatment response.
Methods: ED patients referred to the ambulatory clinic, day care facility and in patient unit of the Herman Dana Child Psychiatry Center were assessed using a structured clinical interview with repeated psychological and physical assessments. Hormonal assays were sampled at baseline and following treatment, correlated with treatment response measures, and compared with healthy age matched adolescents.
Results: Analysis of ED patients revealed at 6 months of treatment a significant prospective increase in BMI compared with baseline, and improvement in pathological eating attitudes. Findings replicate previously described hypercortisolism among ED, partly adaptive to energy conservation during chronic malnourishment and that be informative regarding long term weight restoration. Additional hormonal reactivity including cortisol, and testosterone has been similarly analyzed and will be described.
Significance: Reprograming of neuroendocrine function may be partly adaptive to energy conservation during chronic malnourishment and may be informative regarding long term weight restoration.
This work was supported by the Herman Dana Foundation.

Disclosures: T. Goltser: A. Employment/Salary (full or part-time):; The Herman-Danna Division of Pediatric Psychiatry, Department of Psychiatry, Hadassah - Hebrew University Medical Center; Jerusalem Israel, Molecular Psychiatry Laboratory - Department of Psychiatry, Hadassah - Hebrew University Medical center, Jerusalem, Israel.. **R. Giesser:** None. **A. Shalev:** None. **A. Meltzer:** None. **R. Masarwa:** None. **D. Pevzner:** None. **L. Canneti:** None. **E. Galili-Weisstub:** None. **R. Segman:** None.

Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.18/V32

Topic: G.07. Other Psychiatric Disorders

Support: Oberlin College Grant-in-Aid

Title: Effects of juvenile stress on social behavior and impulsivity: Relationship to changes in dopamine-related proteins

Authors: *T. A. PAINE, C. TANNOUS-TAYLOR, S. BRAINARD, E. HARDEBECK, I. SCHWOB, S. CHANG;
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Abstract: Early adverse experiences are associated with a number of adult health consequences, including an increased risk of developing a substance use disorder. A majority of the research investigating early adverse experiences has focussed on the early post-natal period with relatively fewer experiments focussing on stress exposure during the juvenile period. Moreover, many studies examine the effects of early adverse experiences on male, but not female, rats. The goal of the current experiment was to investigate the effects of juvenile (post-natal days (PND) 25-29) stress exposure on behaviors associated with an increased risk of developing a substance use disorder, including social behavior and impulse control. Litters were culled to 8 (4 males and 4 females) pups at PND 10 and rats were weaned at PND 21. At weaning rats were pair housed with a same sex rat from a different litter. At PND 25 rats in the "stress" condition began the stress exposure protocol in which they were singly housed and underwent 10-min forced swim, 30-min restraint *or* 10-min intermittent foot shock once a day for 5 days. At the end of the stress exposure protocol, the rats were re-paired with their previous cage mate. Control rats were weighed daily but were otherwise undisturbed from PND 25-29. At PND 55, rats underwent a social interaction test, a sucrose intake test and then were trained on the 5-choice serial reaction time task (5CSRTT). At the end of the experiment, rats were sacrificed, their brains rapidly extracted and the expression of dopamine transporter (DAT) protein, tyrosine hydroxylase (TH) and dopamine D2 receptors (DRD2) were quantified using Western blots. Male rats exposed to the stress exhibited a reduction in the amount of time they spent interacting with a novel rat during the social interaction test; they did not exhibit any changes in behavior in the 5CSRTT. Female rats exposed to stress did not exhibit changes in social behavior but exhibited increased cocaine-induced impulsivity in the 5CSRTT. Expression of DRD2 in the caudate-putamen was increased in female rats that had been exposed to stress. These data point to a sex difference in the behavioral response to early adverse experiences. Future research will investigate whether DRD2 contribute to the increased cocaine-induced impulsivity in female rats.

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Poster

595. Human Studies: Fear and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 595.19/V33

Topic: G.07. Other Psychiatric Disorders

Support: National Institute of Mental Health (MH059299)

Title: OCD symptom dimensions predict the degree of dorsal anterior cingulate cortex network dysfunction in obsessive-compulsive disorder

Authors: *T. D. MERAM[1], T. J. ATTISHA[2], A. Z. CHOWDURY[3], P. EASTER[5], G. HANNA[6], P. ARNOLD[7], D. R. ROSENBERG[4], V. A. DIWADKAR[8];
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Abstract: Introduction: Obsessive-Compulsive Disorder (OCD) is characterized by intrusive thoughts/urges (obsessions), and repetitive behaviors (compulsions) (Rosenberg et al., 2004). Interest in OCD's pathology has focused on brain network profiles of the dorsal Anterior Cingulate Cortex (dACC) given the dACC's role as a principal control region (Paus 2001). Both motor control (Diwadkar et al., 2015) and memory (Friedman et al., 2017) induce dysfunctional dACC profiles in OCD. Here, we investigated the relationship between OCD symptom dimensions (obsessions, compulsions) measured using the Y-BOCS (Scahil et al., 1997), and the degree of dysfunctional modulation by the dACC.
Methods: fMRI data were collected for 28 OCD subjects (10 males, mean age = 16.35 years, right handed) (Siemens Verio 3T) during motor control and working memory. The motor task required participants to tap their right forefinger in response to a flashing white probe; the memory task was a standard 2-back. fMRI data were processed using the unified segmentation method (Ashburner & Friston, 2005) in SPM12. Psychophysiological Interactions (PPI), a model of directed functional connectivity, were employed with a dACC seed. The 1st level PPI maps for each subject (Motor, Working Memory) were submitted to separate regression analyses using Obsession and Compulsion scores as covariates of interest (COIs). Both positive and negative relationships were assessed ($p<0.05$, cluster level).
Results: For the motor task, an increase in obsessive symptoms strongly predicted increased dACC modulation of areas including the Postcentral, Middle frontal, and Supramarginal gyri. By comparison, for the memory task, an increase in compulsive symptoms strongly predicted increased dACC modulation of areas including the Superior occipital lobule, Precentral and Postcentral gyri. Conversely, during memory, increases in obsession symptoms associated with decreased dACC modulation, observed in the Insula and Superior frontal gyrus. Under the motor task, decreased dACC modulation tracked with increases in obsession symptoms in the Inferior frontal operculum and Angular gyrus, and with increases in compulsion symptoms in the Rolandic operculum and Supramarginal gyrus.
Conclusions: The dACC is ideally positioned to translate intentions to actions, placing heavy emphasis on the link between cognition and motor responses (Paus, 2001). Here, we link the dimensions of OCD—obsessions and compulsions—to the pathology of the dACC in OCD. Our findings demonstrate that OCD symptom dimensions can predict distinctive dysfunction in motor and memory tasks, and that different dimensions are associated with each task.

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Poster

596. Stress and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 596.01/V34

Topic: G.05. Anxiety Disorders

Support: NIH R01MH104261
ONR N00014-12-1-0366
NIDA U01DA043098
Hope for Depression Research Foundation
Pritzker Neuropsychiatric Research Consortium

Title: Adolescent environmental enrichment prior to social stress induces resilience in a novel rodent model of vulnerability

Authors: *A. M. O'CONNOR, E. K. HEBDA-BAUER, S. J. WATSON, Jr., H. AKIL; Univ. of Michigan, Ann Arbor, MI

Abstract: Selectively bred High Responder (bHR) and Low Responder (bLR) rats are a novel rodent model of mood disorders. bHRs emulate externalizing mood disorders and are resilient to stressors, while bLRs emulate internalizing mood disorders and are vulnerable to stressors. Adult environmental enrichment (EE) decreases anxiety-like behavior of bLRs and alters social behavior of bHRs. Adolescence is a critical period for emotional circuitry and a time of increased vulnerability to environmental influences and stressors. bHR and bLR rats show differing phenotypes by adolescence, suggesting that they may respond differently to EE and stressors during this time. This study examines the impact of adolescent EE on anxiety-like behavior of bHR and bLR animals experiencing a social stressor. Male animals from generations F49, F53 and F56 of the bHR/bLR colony were placed in EE for 1 hour/day/5 days a week starting at 35 days postnatal (P35) and ending at P60. Control animals were standard housed with no handling. Half of all animals underwent social defeat (SD) from P61-P64. All animals underwent behavioral testing consisting of open field on P65, social interaction on P66 and elevated plus maze (EPM) on P67. All animals were sacrificed on P68 and brains and plasma collected. Plasma hormone levels were assessed using ELISA kits for testosterone and corticosterone. Social defeat increased bLR freezing, and bHR exploration, within the open field; EE increased exploratory behavior on the EPM in bHRs but not bLRs. Adolescent EE prior to SD decreased social anxiety in bLRs, with EE + SD animals showing decreased social avoidance, increased social interaction and altered ultrasonic vocalizations (USV) compared to standard housed bLR rats experiencing SD. Social interaction behavior was similarly changed in bHRs, without the

concomitant changes in USVs. Thus, bLR EE + SD animals behaved similarly to bHR EE + SD animals during social interaction testing, and were more sociable than baseline bHRs. Adolescent EE decreased bLR plasma testosterone and there was no impact of either EE or SD on plasma corticosterone levels. This data shows that bLR animals that experienced EE prior to SD showed bHR-like patterns of social interaction behavior, with greater changes in USV production and social engagement than bHRs. Adolescent EE flips the bLR social behavior phenotype after social stress, providing evidence that genotype-environment interactions can induce resilience in a usually vulnerable line. This behavioral change does not appear to be mediated by circulating testosterone or corticosterone; work is underway to determine the neural underpinnings of this adolescent reprogramming.

Disclosures: A.M. O'Connor: None. **E.K. Hebda-Bauer:** None. **S.J. Watson:** None. **H. Akil:** None.

Poster

596. Stress and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 596.02/V35

Topic: G.05. Anxiety Disorders

Title: Effect of chlordiazepoxide on cardiovascular and behavioral measures in a rat model of panic

Authors: *S. LOIODICE[1], E. C. O'CONNOR[2], S. NOURRY[1], G. VIARDOT[3], E. P. PRINSSEN[2], C. L. DRIEU LA ROCHELLE[1];
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Abstract: Panic is characterized by a sudden onset of intense distress, anxiety and a strong desire to escape the situation. These emotions are coupled to heightened autonomic responses, including stimulation of the cardiovascular system. From a drug discovery perspective, physiological responses to panic measured in rodents may offer objective and translational efficacy biomarkers that are not so readily obtained from solely behavioral-based measures. Here we sought to establish a rodent model of panic, namely ultrasound-induced defensive behavior in Lister-Hooded rats, and to evaluate the effects of a reference panicolytic drug on behavioral and cardiovascular endpoints. Rats were operated for electrocardiogram (EGC) and electromyogram (EMG) telemetry recording. To establish the panicogenic effect of ultrasound, ECG and EMG were first recorded for 3 hours during 3 consecutive, once daily sham sessions (no ultrasound) followed by 1 session with ultrasound stimulation (1 min, 93 dB, 22 kHz). Thereafter the effect of chlordiazepoxide (10 mg/kg, po) or vehicle was evaluated on 1 sham session and 1 ultrasound session using a crossover study design. Ultrasound presentation led to a strong increase in heart

rate (~20%) and EMG power (~600%) compared to baseline, indicative of defensive escape behavior. Confirming its panicolytic properties, chlordiazepoxide reversed the ultrasound-triggered heart rate response, without affecting heart rate during the sham session. Chlordiazepoxide decreased EMG power following ultrasound presentation, but also during sham sessions. Taken together, these data illustrate the value of the ultrasound-induced cardiovascular and behavior test for drug discovery in panic disorder.

Disclosures: S. Loiodice: None. **E.C. O'Connor:** A. Employment/Salary (full or part-time):; Roche. **S. Nourry:** None. **G. Viardot:** None. **E.P. Prinssen:** A. Employment/Salary (full or part-time):; Roche. **C.L. Drieu La Rochelle:** None.

Poster

596. Stress and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 596.03/V36

Topic: G.05. Anxiety Disorders

Support: JSPS KAKENHI Grant Number JP16K10183

Title: SSRI exerts anxiolytic action via 5-HT1A and 5-HT2A receptors in the amygdala

Authors: *T. IZUMI[1], K. KONNO[2], M. WATANABE[2], K. TANAKA[4], T. YOSHIDA[3], H. SHIKANAI[1], M. YOSHIOKA[3];
[1]Dept. of Pharmacol., Pharmaceut. Sciences, Hlth. Sci. Univ. of Hokkaido, Ishikari-Tobetsu, Japan; [2]Dept. of Anat., [3]Dept. of Neuropharm., Hokkaido Univ. Grad. Sch. of Med., Sapporo, Japan; [4]Dept. of Neuropsychiatry, Keio Univ. Sch. of Med., Sapporo, Japan

Abstract: SSRIs are widely used as anxiolytics. Previously, we demonstrated that local injection of an SSRI into the basolateral nucleus of the amygdala (BLA) had anxiolytic effect in rats. In the present study, we investigated the effect of local co-administration of an SSRI and 5-HT_{1A} or 5-HT_{2A} antagonists into the BLA on conditioned fear in Wistar/ST rats, and indicated the expression of 5-HT_{1A} and 5-HT_{2A} receptor mRNAs in the BLA by *in situ* hybridization in C57BL/6 mice. All protocols complied with the guidelines of the Animal Research Committee of the Hokkaido University. Local injection of citalopram (SSRI) into the BLA attenuated conditioned freezing, and this effect was blocked by local co-administration of WAY100635 (5-HT_{1A} antagonist) or MDL11939 (5-HT_{2A} antagonist). In *in situ* hybridization, 5-HT_{1A} mRNA was mainly expressed in GABAergic interneurons expressing somatostatin (SOM) mRNA, and 5-HT_{2A} mRNA was in those expressing parvalbumin (PV) or SOM mRNA. From these results, it is speculated that SSRIs exert anxiolytic effect via 5-HT_{1A} and 5-HT_{2A} receptors in the BLA. Because PV- and SOM-positive GABAergic interneurons are known to form local neural circuits

with glutamatergic pyramidal neurons, the anxiolytic action of SSRIs is likely to be mediated by serotonergic modulation of pyramidal neurons via these interneuron subclasses.

Disclosures: **T. Izumi:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Mochida Pharmaceutical, Asahi Kasei Pharma, Yoshitomiyakuhin Corporation. **K. Konno:** None. **M. Watanabe:** None. **K. Tanaka:** None. **T. Yoshida:** None. **H. Shikanai:** None. **M. Yoshioka:** None.

Poster

596. Stress and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 596.04/V37

Topic: G.05. Anxiety Disorders

Title: Prefrontal excitatory and inhibitory balance in stress-induced anxiety: Evidence for over-inhibition

Authors: *C. PAGE[1], L. COUTELLIER[2];
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Abstract: Chronic stress-induced emotional disorders like anxiety and depression involve imbalances between the excitatory glutamatergic system and the inhibitory GABAergic system in the prefrontal cortex (PFC). However, the precise nature and trajectory of excitatory/inhibitory (E/I) imbalances in these conditions is not clear, with the literature reporting glutamatergic and GABAergic findings that are at times contradictory and inconclusive. We have previously found that chronic stress increases the activity of prefrontal parvalbumin (PV)-expressing neurons in both sexes, and chemogenetic activation of this cell population increases anxiety-related behaviors in female mice only. These findings support the idea that chronic stress could lead to emotional dysfunction due to increased activity of the inhibitory GABAergic system, thereby inducing hypoactivity of the PFC. Here, we wanted to investigate further this idea by enhancing pharmacologically the activity of the GABAergic system during exposure to chronic stress. To this end, we exposed female mice to 4 weeks of chronic stress and administered the GABA agonist lorazepam (or vehicle) during the first 2 weeks of chronic stress exposure. We find that GABA agonism during the first 2 weeks of a 4-week chronic stress exposure exacerbates anxiety-like behaviors. In addition, the lorazepam-treated stress group showed elevated mRNA expression of prefrontal *GAD1*, the gene for the GABA-synthesizing enzyme GAD67, indicative of increased pre-synaptic inhibition. Increased *GAD1* expression in the PFC significantly correlates with increased anxiety-like behavior. These findings suggest that increased GABAergic system activity in the PFC during chronic stress plays a role in anxiety. Our combined chemogenetics and pharmacological findings lend support for an overly inhibited PFC in chronic stress-induced emotional dysregulations. We are continuing to investigate possible

mechanisms underlying the effects of chronic stress combined with chronic lorazepam administration on anxiety-like behavior, and will discuss implications for the treatment of stress-induced anxiety disorders.

Disclosures: C. Page: None. **L. Coutellier:** None.

Poster

596. Stress and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 596.05/V38

Topic: G.05. Anxiety Disorders

Support: NIAAA Grant R03AA024890
NIAAA Grant P50AA017823
Binghamton University Center for Development and Behavioral Neuroscience

Title: Moderate prenatal alcohol exposure on gestational day 12 alters social behavior and prelimbic cortex glutamate transmission in adult rats

Authors: *K. R. PRZYBYSZ, J. M. JOHNSON, E. I. VARLINSKAYA, M. R. DIAZ; Psychology - Behavioral Neurosci., Binghamton Univ., Binghamton, NY

Abstract: Prenatal alcohol exposure (PAE) is associated with a variety of cognitive and behavioral deficits collectively termed Fetal Alcohol Spectrum Disorders (FASDs). The most common behavioral dysfunction associated with FASD is social impairment. Animal models investigating binge-level PAE have identified gestational day (G) 12 as a critical period for increasing anxiety-like states, including social anxiety in exposed offspring. However, low-moderate PAE is more common than binge-level PAE, and we have shown that moderate PAE is capable of producing increases anxiety-like behaviors. Whether moderate PAE on G12 also produces social impairment is currently unknown. Additionally, the neural disruptions related to social deficits caused by PAE are poorly understood. One brain area that is critical for modulating social behavior is the medial prefrontal cortex, and the prelimbic subdivision (PL) of the medial prefrontal cortex has been shown to regulate negative social interactions. However, whether PAE alters PL function to produce the social deficits characteristic of FASD has not been investigated. Therefore, the current study was designed to determine whether moderate PAE on G12 is capable of producing alterations to 1) social behavior and 2) PL physiology in adult animals. Pregnant Sprague-Dawley rats were exposed to ethanol vapor or air for 6 hours on G12 (blood ethanol concentration ≈ 60-90 mg/dl), and their male and female offspring were group-housed with same-sex littermates until adulthood. Animals were either behaviorally tested (postnatal day (P) 77) using a modified social interaction paradigm, or were sacrificed for whole-cell patch-clamp electrophysiology (P100+). Behaviorally, PAE males and females exhibited

decreased social investigation relative to their air-exposed counterparts. Additionally, a trend toward a reduction in social preference was evident in PAE males, but not females, indicating a potential sex-dependent effect in PAE-induced social anxiety-like alterations. For physiological experiments, PL-containing brain slices from adult males and females were made and spontaneous excitatory postsynaptic currents (EPSCs) and miniature EPSCs were recorded from layer 2/3 pyramidal cells. PAE resulted in reduced spontaneous EPSCs in males, while females were unaffected. These sex-dependent physiological results may contribute to reduced social preference in male PAE offspring. Overall, this work lends support to the importance of investigating moderate PAE in both sexes and provides further evidence that G12 is a key developmental point for moderate PAE-induced behavioral deficits.

Disclosures: K.R. Przybysz: None. **J.M. Johnson:** None. **E.I. Varlinskaya:** None. **M.R. Diaz:** None.

Poster

596. Stress and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 596.06/V39

Topic: G.05. Anxiety Disorders

Support: Stress and Motivated Behavior Institute, RJS, Director

Title: Localization of brain regions with enhanced synaptic plasticity associated with avoidance learning in Wistar-Kiyoto rats

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Abstract: Behavioral inhibition is a personality temperament characterized by a tendency to avoid novel stimuli. Behaviorally inhibited people show increased vulnerability to anxiety and stress disorders. *Wister-Kiyoto* (WKY) rats display behavioral inhibition, attain signaled lever press avoidance at a higher rate, and are more resistant to extinction than control, Sprague Dawley (SD) rats. Thus, we have proposed that WKY rats are a model for anxiety and stress research. In previous research, we trained WKY and SD rats on either 100% tone-shock pairing or 50% tone-shock pairing in a signaled lever-press avoidance task. WKY rats in both the 100% and 50% contingency displayed the highest rate of avoidance learning, while SD rats in the 50% contingency failed to acquire avoidance learning. WKY rats appear to acquire avoidance based on the expectation of shock, whereas SD rats appear to acquire avoidance based on the presence

of shock reinforcement. In the present study, we sought to determine areas of the brain that are associated with enhanced avoidance acquisition in behavioral inhibition by staining for Zif using immunohistochemistry. Zif is an immediate early gene that is correlated with synaptic plasticity of neurons. WKY and SD rats were run in either 50% or 100% tone-shock pairings for 3 days, and then stained for Zif activation. We examined the habenula, periaqueductal gray, cingulate cortex, and the amygdala as our regions of interest. The habenula is correlated with motivational behavior. The periaqueductal gray is associated with the sensation of pain, corresponding with the delivery of shocks. The cingulate cortex receives input from the limbic system which processes emotion, learning, and memory. The amygdala is associated with fear and fear learning. Future studies will examine these areas linked with behavioral inhibition to assess the cellular and molecular changes that occur with avoidance learning. Knowing how these areas are associated with avoidance acquisition in behavioral inhibition may shed light on the acquisition of symptomology in anxiety and stress vulnerable individuals and suggest areas for treatment.

Disclosures: **N.A. McCarthy:** None. **R.C. Peterson:** None. **D.R. Cook-Snyder:** None. **D.P. Miller:** None. **R.J. Servatius:** None.

Poster

596. Stress and Anxiety

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Program #/Poster #: 596.07/V40

Topic: G.05. Anxiety Disorders

Support: CONACyT 226454/256448
INP17073.0
Fellowship CONACyT No. 27720

Title: Neuropharmacological profile of the bertholletia excelsa seeds and its influence on the metabolism of lipids in mice

Authors: *O. FRAUSTO-GONZÁLEZ[1,2,3], **M. E. GONZÁLEZ-TRUJANO**[1], C. J. BAUTISTA[3];
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Abstract: Overweight and obesity are part of the main health problems in the world. Limited efficacy and adverse effects of the current pharmacological treatment makes that population do not follow it adequately and seeks alternatives to decrease their body mass and reduce comorbidity, such as those affecting the central nervous and reproductive systems. *Bertholletia*

excelsa (Brazil seed) is a natural alternative used by population. People say that it is useful to control body weight and it also reduces anxiety or the desire to eat impulsively. However, there is not enough preclinical and/or clinical research to support its efficacy and safety. From the above, it is of interest for this project to obtain pharmacological evidence of the anxiolytic activity of an hexanic extract of *B. excelsa* (SBHX) and its effects on body weight, influence on the male reproductive system (epididymis and testicle), and in the metabolism of lipids in mice. The experimental design consisted of 5 groups (n&gt=5) of SW mice (25-30 g b.w) fed with a standard diet (Purina 5001) and water rich in carbohydrates (34% sucrose) as a high caloric diet. Groups consisted in vehicle, reference drug and different doses of SBHX (30-300 mg/Kg, i.p). The initial administration was acute and 30 min later, the neuropharmacological profile was evaluated using the open field, hole-board and plus-maze tests; as well as the sodium pentobarbital-induced potentiation of the hypnotic-like effects, nociceptive behavior induced with 1% formalin and in the PTZ-induced tonic-clonic seizures. Subsequently, a chronic administration was continued using the same doses to determine the weight, as well as the intake of water and food, every 5 days for 40 days. Finally, the tissues of the testis, epididymis and liver were extracted for the determination of weight and fat content, triglycerides and cholesterol, as well as the histological analysis. The results indicate that SBHX produces anxiolytic, sedative and analgesic effects. It significantly decreases the weight of the mice at doses of 100 and 300 mg/Kg, i.p. without altering the consumption of water and food. The tissues evaluated maintain their morphological integrity. The exploration of acute toxicity allowed the calculation of the mean lethal dose>2000 mg/kg, placing it in the minimum toxicity classification. Therefore, it is concluded that constituents of a non-polar nature of the *B. excelsa* seed produce a decrease in body weight and anxiolytic effects, giving evidence of the properties attributed to this natural product that is currently commercially available as a natural alternative to this global health problem, without any acute or chronic effects in a preclinical study.

Disclosures: O. Frausto-González: None. **M.E. González-Trujano:** None. **C.J. Bautista:** None.

Poster

596. Stress and Anxiety

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Program #/Poster #: 596.08/V41

Topic: G.05. Anxiety Disorders

Support: CONACyT CB 241247

Title: Aqueous extract of pomegranate prevents anxiety-like behavior and metabolic changes induced by cafeteria diet in an animal model of menopause: Possible participation of PPARgamma and MAS receptor

Authors: *E. M. ESTRADA-CAMARENA[1], N. M. VEGA-RIVERA[2], N. CERVANTES-ANAYA[2], D. ISLAS-PRECIADO[2,6], D. PULIDO[2], G. AZPUILCUETA MORALES[2], G. RAMÍREZ-RODRIGUEZ[3], A. GRANADOS JUÁREZ[3], P. GORTARI[4], C. LÓPEZ-RUBALCAVA[7], S. TREVIÑO[8], I. GALLARDO-ORTÍZ[9], E. GONZALEZ TRUJANO[5];
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Abstract: Women are more vulnerable than men to present psychiatry and metabolic disorders; thus therapies that contribute to treat both pathological conditions are warranted. Pomegranate (*Punica granatum*) has been proposed as hypoglycemic, lipid-lowering and antidepressant treatment; therefore, it is feasible that it could be useful to regulate glucose, lipids profile and anxiety-like behavior in an animal model of menopause subjected to a cafeteria diet The present study aimed to explore whether the Aqueous extract of *Punica granatum* (AE-PG) prevents the anxiety-like behavior, body weight, glucose and lipids increases induced by a cafeteria diet in middle-aged ovariectomized Wistar rats. Also, we evaluated the effect of AE-PG on the expression of RNAm PPARα and PPAR -γ in liver and protein of AT1, MAS and PPAR -γ, p-PPAR -γ and the ratio pPPAR-γ/PPARγ receptors in hippocampus and amygdala. Results showed that cafeteria diet-induced anxiety-like behavior and augmented cholesterol, triglycerids, glucose and insulin serum concentrations. This diet also increased body weight, promotes insulin resistance and decreased mRNA of PPARγ in the liver in comparison to control diet ($p<0.001$). AE-PG prevents anxiety, and reduce insulin resistance in rats under the cafeteria diet ($p<0.001$) which was associated with an increase of PPARγ in the liver ($p<0.001$). In the brain, cafeteria diet increased the expression in AT1 and MAS receptor only in the ventral hippocampus; this increase was prevented by AG-PG ($p<0.001$). In the amygdala, the protein expression of both receptors was reduced by AG-PG independently of diet. The expression of ratio pPPAR-γ/PPARγ suggest that a different regulation is depending on diet and the brain area evaluated, whereas in the dorsal hippocampus the AE-PG induced an increase of phosphorylation state of the receptor in control rats; this effect was canceled by a cafeteria diet. In contrast, in the ventral portion of the hippocampus, the cafeteria diet decrease phosphorylation of PPARγ and this effect is prevented by AE-PG. Finally, in the amygdala, the increase of phosphorylation induced by AE-PG in control rats was prevented by the cafeteria diet. Further, in this area, a decrease of the phosphorylation by the cafeteria diet was evident. Data suggest that AE-PG prevent anxiogenic effect induced by cafeteria diet and reduce the insulin resistance. Both effects could involve the modulation of PPARγ in the brain and hepatic levels.

Disclosures: E.M. Estrada-Camarena: None. **N.M. Vega-Rivera:** None. **N. Cervantes-Anaya:** None. **D. Islas-Preciado:** None. **D. Pulido:** None. **G. Azpuilcueta Morales:** None. **G. Ramírez-Rodriguez:** None. **A. Granados Juárez:** None. **P. Gortari:** None. **C. López-Rubalcava:** None. **S. Treviño:** None. **I. Gallardo-Ortíz:** None. **E. Gonzalez Trujano:** None.

Poster

596. Stress and Anxiety

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Topic: G.05. Anxiety Disorders

Support: NIH Grant R01MH104261
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NIDA Grant U01DA043098
Pritzker Neuropsychiatric Research Consortium
Hope for Depression Research Foundation

Title: Differences in the morphology of microglia cells in the hippocampus of selectively bred high- and low-responder rats: Implications for emotional temperament

Authors: *P. M. MARAS, E. HEBDA-BAUER, H. AKIL, S. WATSON;
Univ. of Michigan, Ann Arbor, MI

Abstract: Mood regulation is a complex process, influenced by both genetic and environmental factors, and reflecting underlying differences in emotional vulnerability. Individual differences in affective temperament clearly play an important role in mood disorders, yet their neural mechanisms remain unclear. Our laboratory uses a selective breeding technique, which has generated rats with contrasting emotional temperaments, to study the neurobiology of mood disorders. Specifically, rats bred for high locomotor responses when placed in a novel environment (bHRs) exhibit low anxiety and are resilient to depression, whereas rats bred for low locomotion in a novel environment (bLRs) are highly anxious and vulnerable to depression. Among the possible factors underlying the bHR/bLR phenotype, recent mRNA expression studies suggest that bLRs have elevated expression of key microglia-specific genes within their hippocampus compared to bHRs. Although intriguing, and consistent with a role for microglia in mood regulation, these expression data do not reveal the anatomical details of the microglia population, or distinguish between variations in the total number of microglia vs. their state of activation. The goal of the current set of experiments was therefore to fully characterize the number and morphology of microglia cells within the hippocampus of bHRs and bLRs under basal (non-stimulated) conditions. To this end, coronal brain sections from adult male bHRs and bLRs were labeled for the microglia marker Iba-1 using immunohistochemistry. Unbiased stereological procedures were used to estimate the total number of Iba-1-positive cells within the dorsal hippocampus. Further morphological analysis was accomplished using Neurolucida software to create detailed 3-D reconstructions of a subset of microglia cells. Although bHRs and bLRs did not differ in their total numbers of microglia cells, reconstruction analysis revealed interesting differences in the morphology of microglia, particularly within the resting state.

These results provide a comprehensive comparison of the microglia population between rats bred for vulnerable or resilient phenotypes, and suggest that variability in microglia morphology may have functional consequences for emotional regulation and the development of mood disorders.

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Poster

596. Stress and Anxiety

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Program #/Poster #: 596.10/V43

Topic: G.05. Anxiety Disorders

Support: Office of the Vice President of Research

Title: Importance of optimization and pharmacological validation of behavioral assays in a rodent behavioral core

Authors: *M. C. TSUDA[1], T.-Y. J. WU[2], I. LUCKI[3];
[1]HJF/Uniformed Services Univ., Bethesda, MD; [2]Uniformed Services Univ., Bethesda, MD; [3]Dept. of Pharmacol. and Mol. Therapeut., Uniformed Services Univ. of the Hlth. Scienc, Bethesda, MD

Abstract: Behavioral core facilities are important research resources that become a hub for innovation at an institution by connecting investigators with tools and expertise that help to advance research projects to the next level. At the Uniformed Services University (USU) Rat Behavior Core (RBC), we provide the necessary tools and expertise to assess the functional consequences of military relevant psychiatric and neurodegenerative disorders. In our RBC, we believe it essential to optimize procedures and establish baselines for each behavior test to ensure ability, reliability, and sensitivity of the assays. Upon establishing optimal test conditions, pharmacological validation of the assays is critical to demonstrate that under the conditions being tested, a positive control can produce the expected results. In the absence of this, understanding whether the experimental variable failed to produce an effect in the assay or whether there was a fault with the testing environment becomes challenging to interpret. The present study optimized and pharmacologically validated in-demand anxiety and cognitive behavior tests that are highly sensitive to environmental factors: open field (OFT), light-dark transition (LDT), elevated zero maze (EZM), novel object recognition (NOR), and object location (OL) tests. Adult female and male Sprague Dawley rats were used to optimize testing conditions in these tests. In the OFT, LDT, and EZM anxiety tests, we determined optimal lighting intensity, light vs. dark phase testing, and start position within the maze. In NOR and OL test, we evaluated the best object types (size, shape, material), object placement, and apparatus size. Using optimal testing conditions, we then pharmacologically validated each assay. In the

OFT, LDT, and EZM tests, administration of chlordiazepoxide, an anxiolytic benzodiazepine, 30 min prior to testing increased the time spent in the anxiogenic region of the test compared to saline administered control rats, demonstrating reduced anxiety levels. In the NOR and OL tests, administration of scopolamine, a nonselective muscarinic acetylcholine antagonist, 20 min before the acquisition trial impaired discrimination between a novel and familiar object (NOR) or impaired recognition when an object has been relocated (OL) during the retention trial, demonstrating recognition or spatial memory deficits. Both the optimization of testing conditions and successful pharmacological validation of these assays will guide the establishment of standard operating procedures for the RBC, which in turn enables USU investigators to conduct reliable and reproducible research.

Disclosures: M.C. Tsuda: None. **I. Lucki:** None. **T.J. Wu:** None.

Poster

596. Stress and Anxiety

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Program #/Poster #: 596.11/V44

Topic: G.05. Anxiety Disorders

Support: NSFC Grant 81771458
Shandong Key R&D Program 2018GSF118181

Title: Identification of neuronal circuits underlying leptin actions on anxiety

Authors: *M. GUO[1], H. YANG[1], D. ZHAO[1], J. WANG[1], X.-Y. LU[2];
[1]Inst. for Metabolic and Neuropsychiatric Disorders, Binzhou Med. Univ. Hosp., Shandong, China; [2]Med. Col. of Georgia At Augusta Univ., Augusta, GA

Abstract: Our previous studies have shown that leptin receptor LepRb signaling in ventral tegmental area (VTA) dopamine neurons regulates anxiety-related behaviors (Liu et al., 2011, 2015). While intra-VTA infusion of leptin elicits anxiolytic effects, deletion of LepRb in the VTA or specifically in dopamine neurons causes anxiogenic behavior. The objective of this study was to identify neuronal circuits underlying the actions of leptin/LepRb signaling in VTA dopamine neurons on anxiety. LepRb-expressing neurons in the VTA were labeled in Lepr-Cre mice with intra-VTA AAV-DIO-mCherry, and their projections of VTA LepRb neurons to the amygdala and the bed nucleus of the stria terminalis (BNST), two brain regions implicated in anxiety, were examined. We found that dense axonal terminals of VTA LepRb neurons were concentrated in the central nucleus of the amygdala (CeA) and the oval nucleus of BNST (ovBNST). DREADD inhibition of LepRb neurons in VTA induced anxiolytic effects as indicated by increased open-arm time in the elevated plus-maze test, whereas DREADD stimulation of these neurons showed no effects on anxiety. The role of LepRb/VTA-CeA and

LepRb/VTA-ovBNST projections in mediating the effects of VTA LepRb neurons on anxiety is currently under investigation.

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Poster

596. Stress and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 596.12/V45

Topic: G.05. Anxiety Disorders

Title: Evaluation of the Rhizoma anemarrhena herb for potential to reduce reactive oxidative species

Authors: S. SOWA, *N. SWALVE;
Alma Col., Alma, MI

Abstract: Neurological disorders such as anxiety affect hundreds of millions of people around the world each year. Research has identified cellular damage by oxidative stress to be a contributing factor in the physiological manifestation of cognitive dysfunction. Current pharmaceutical treatments are uncertain and sometimes ineffective. Metabolic defense systems, such as the blood brain barrier, prevent a majority of synthetic drugs from reaching the brain. Natural antioxidants are favorable neurotherapeutics for their biocompatibility with the body and capacity to bypass most molecular deterrents. The traditional Chinese herb, Rhizoma Anemarrhena (ZM), is a potential neuroprotective agent that has expressed the ability to penetrate the the blood brain barrier but few studies have been done to quantify the antioxidant efficiency of this species. To further investigate the medicinal characteristics of ZM, a series of scavenging assays was done for the following reactive oxidative species (ROS): DPPH, OH-, NO-, O_2-, and H_2O_2. Spectroscopy was used to measure solution color changes induced by chemical transformation upon reduction. Results indicate the tendency of the herb to seek out and reduce the different types of reactive oxidative species. The antioxidant capacity results from these experiments will be used to support a subsequent in-vivo procedure to evaluate the capability of ZM as a behavioral treatment. A reduction of ROS presence in the brain could be implicated as a preventative or healing remedy. Positive findings highlight Rhizoma Anemarrhena herbs to be assessed for use in neurological treatments.

Disclosures: **S. Sowa:** None. **N. Swalve:** None.

Poster

596. Stress and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 596.13/V46

Topic: G.05. Anxiety Disorders

Title: Neuropharmacological actions of the diterpene tilifodiolide

Authors: *C. ALBA-BETANCOURT[1], **A. RUIZ-ARREDONDO**[2], M. GONZÁLEZ-CHÁVEZ[3], D. GASCA-MARTÍNEZ[4], M. DEVEZE-ÁLVAREZ[1], Á. ALONSO-CASTRO[1]; [1]Univ. De Guanajuato, Guanajuato, Mexico; [2]Univ. de Guanajuato, Guanajuato, Mexico; [3]Autonomus Univ. of San Luis Potosi, San Luis Potosí, Mexico; [4]Inst. of Neurobio., Querétaro, Mexico

Abstract: Tilifodiolide (TFD) is a clerodane diterpenoid obtained from *S. tiliifolia*. Several studies have reported an *in vivo* antidiabetic activity, and *in vitro* antioxidant effects from *Salvia tiliifolia* Vahl (Lamiaceae), a plant native to the American continent. *S. tiliifolia* is used as a folk medicine for the treatment of neurodegenerative diseases, among others. In this work, the sedative, anxiolytic, and antidepressant effects of 1-100 mg/kg TFD were evaluated with the pentobarbital-induced sleeping time assay, the elevated plus maze test (EPM), the light-dark test, the cylinder exploratory test, and the forced swimming test. TFD did not disturb the start of sleep or extended the length of sleep, 1.5 mg/kg clonazepam (CNZ) diminished the start of sleep by 74% and extended the length of sleep by 2.4-fold. In the EPM, 50 and 100 mg/kg TFD augmented ($p<0.05$) the time consumed in open arms but showed no effects on the number of entries in open arms. In the light-dark test, TFD augmented ($p<0.05$) the time in the light chamber with similar action in comparison to CNZ (1.5 mg/kg). Nonetheless, this effect was no dose-dependent. TFD showed no actions on the amount of entries in the light compartment. TFD reduced the quantity of rearings in a dose-dependent manner: 10 mg/kg (37%), 50 mg/kg (67%), and 100 mg/kg (65%). CNZ (1.5 mg/kg) reduced the quantity of rearings by 95%. In the forced swimming test, only 100 mg/kg TFD diminished ($p<0.05$) the immobility time, and 20 mg/kg fluoxetine reduced the immobility time by 60%. In summary, TFD did not have sedative properties but exhibited moderate anxiolytic and antidepressant actions in mice.

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Poster

596. Stress and Anxiety

Location: Hall A

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Program #/Poster #: 596.14/W1

Topic: G.05. Anxiety Disorders

Title: Distinct anxiety outcomes following traumatic brain injury

Authors: *J. POPOVITZ[1], S. P. MYSORE[2], H. ADWANIKAR[1];
[2]Psychological and Brain Sci., [1]Johns Hopkins Univ., Baltimore, MD

Abstract: Traumatic brain injury (TBI) is a prominent health problem and can lead to significant affective deficits. Among those, anxiety-related disorders, such as generalized anxiety disorder and post-traumatic stress disorder, are highly prevalent among TBI patients. Here, we hypothesized that individual variability significantly impacts the development of anxiety phenotype following TBI, particularly over the long term. To test this, we tracked anxiety-like behavior following a moderate injury in adult male mice for a period of 7 weeks using classic behavioral tests: the elevated zero maze, the elevated plus maze, and the open field test. Using clustering-based approaches on the high dimensional dataset, we identified two different behavioral profiles of TBI animals. Animals in one cluster presented an injury-susceptible anxiety phenotype, with significant increases in the proportion of time spent in the open arms/center of field, while those in the other did not present an anxiety phenotype following injury (no change in proportion of time spent in anxiogenic zones). There were no differences between the groups in their anxiety-like behavior prior to injury. Immunohistochemical analysis of GABA (GAD65/67) and glutamate (vGlut1) in key brain regions implicated in the control of anxiety, namely, basolateral amygdala, medial prefrontal cortex, and ventral hippocampus, showed distinct changes in GAD and vGlut signaling in the animals with the injury-susceptible anxiety phenotype, as compared to mice in the unaffected cluster, indicating possibly different mechanisms of injury underlying the different anxiety phenotypes.
Key-words: TBI, anxiety phenotype, variability, elevated plus maze.

Disclosures: J. Popovitz: None. **S.P. Mysore:** None. **H. Adwanikar:** None.

Poster

596. Stress and Anxiety

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Program #/Poster #: 596.15/W2

Topic: G.05. Anxiety Disorders

Support: R01 MH061933; "G protein-gated K+ channels and inhibitory signaling"
Viral Vector and Cloning Core, University of Minnesota

Title: Molecular and cellular mechanisms underlying the contributions of the G protein-gated inwardly rectifying K+ channels to anxiety-related behavior

Authors: *B. N. V. VO, E. MARRON, H. OBERLE, K. WICKMAN;
Univ. of Minnesota, Minneapolis, MN

Abstract: G protein-gated inwardly rectifying K+ (GIRK/Kir3) channels mediate the postsynaptic inhibitory effects of many neurotransmitters in the central nervous system. Dysregulation of GIRK channel activity has been associated with several neurological disorders such as autism, schizophrenia, epilepsy, Down syndrome, Alzheimer's disease, addiction, mood-related disorders, and pain. ML297 is the prototypical small-molecule GIRK channel modulators, and ML297 selectively activates GIRK1/GIRK2 channels, which are the most dominant GIRK channel subtypes in the brain. Systemic administration of ML297 in mice decreased anxiety-related behavior without evoking sedation, and without impacting depression- or reward-related behavior. The anatomic and cellular mechanisms underlying the anxiolytic efficacy of ML297 are not well understood. The present exploratory study seeks to identify the brain region(s) where the selective activation of this GIRK channel subtype contributes to the reduction in anxiety-related behavior. We performed intracranial manipulations to deliver ML297 to two key brain regions implicated in anxiety: the ventral hippocampus (vHPC) and the basolateral amygdala (BLA). We assessed the impact of these manipulations on anxiety-related behavior using the elevated plus maze (EPM). Male mice, ~ 50 d at the time of surgery and ~ 70-80 d at the end of behavior (sample sizes: 8-10 mice/group), are used in this study. ML297 infusion into the ventral hippocampus (vHPC) reduced anxiety-related behavior in mice in the elevated plus maze test in a dose-dependent manner. In contrast, intra-BLA administration of ML297 increased anxiety-related behavior. We next used a viral chemogenetic approach to acutely-inhibit defined neuron sub-populations in the vHPC to identify cell types mediating the anxiolytic influence of ML297 on anxiety-related behavior (male and female mice, same age, group sizes as above). Chemogenetic inhibition of ventral dentate gyrus, but not ventral CA1 pyramidal, neurons reduced anxiety-related behavior, whereas selective inhibition of inhibitory interneurons in the vHPC evoked seizures. Collectively, our data provide insights into the anatomic region and cellular details underlying the contribution of GIRK channels to anxiety-related behavior. This insight into the neural circuits and substrates underlying anxiety highlights GIRK channels as a novel therapeutic target for anxiety disorders and other relevant diseases.

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Poster

596. Stress and Anxiety

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Program #/Poster #: 596.16/W3

Topic: G.05. Anxiety Disorders

Support: R21 MH112081
R01 AA022445
R61 MH111932-01

Title: The role of ventral tegmental area subcircuit in mediating anxiety following repeated social stress

Authors: *C. S. MOREL[1], S. MONTGOMERY[2], S. M. KU[2], B. JUAREZ[2,3], M. FLANIGAN[2], J. J. WALSH[4,2], E. S. CALIPARI[5], L. LI[2], S. J. RUSSO[2], A. K. FRIEDMAN[6], M.-H. HAN[2]; [1]Pharmacol. Sci., [2]Mount Sinai Icahn Sch. of Med., New York, NY; [3]Dept. of Pharmacology, Univ. of Washington, Seattle, WA; [4]Psychiatry, Stanford Univ., Stanford, CA; [5]Pharmacol., Vanderbilt Univ. Sch. of Med., Nashville, TN; [6]Hunter College, City Univ. of New York, New York, NY

Abstract: Anxiety disorders, including generalized anxiety disorder, panic disorder, post-traumatic stress disorder and phobia, affect more than 18% of the American population, and are a major contributor to the global burden of psychiatric diseases. A substantial number of patients (>60%) suffering from anxiety disorders also present depressive-like symptoms. However, the shared or segregated mechanisms underlying both of these diseases remain largely unknown. An increasing body of evidence from human brain-imaging and animal studies implicate the dopaminergic system in the emergence of anxiety disorders and depression. In particular, dopamine (DA) neurons from the ventral tegmental area (VTA) encode rewarding, salient and aversive stimuli and support adaptive behaviors. VTA DA neurons project heavily to the medial prefrontal cortex (mPFC), the nucleus accumbens (NAc), and the amygdala (AMG). We previously described alterations of VTA DA neuronal firing activity following a repeated social defeat stress (RSDS) paradigm, a rodent model that induces different behavioral alterations. Following RSDS, mice can be segregated into two pathological groups: A/D mice that display anxiety and a depressive phenotype (*i.e.* social avoidance behavior, anhedonia, despair and anxiety; susceptible to depression), and A mice that only display anxiety-related behaviors (anxious; resilient to depression). Utilizing neural circuit-probing techniques, we previously observed maladaptive firing activity in VTA-mPFC projecting DA neurons and VTA-NAc projecting DA neurons selectively in A/D mice (depression-susceptible mice), but not in A mice (depression-resilient group). Our current results show that the firing activity of VTA-AMG projecting neurons is dramatically decreased in both A/D and A mice. Additionally, using *in vivo*

calcium imaging in freely moving mice, we correlated VTA-AMG circuit activity with the expression of the anxiety phenotype but not the depressive-related phenotype. Finally, we further demonstrated the causal link between the firing maladaptations in the VTA-AMG subcircuit and anxiety phenotype. Based on our findings, our hypothesis is that the VTA-AMG circuit may play a crucial role in mediating the anxiety-like behaviors observed in both A/D and A mice following RSDS.

Disclosures: **C.S. Morel:** None. **S. Montgomery:** None. **S.M. Ku:** None. **B. Juarez:** None. **M. Flanigan:** None. **J.J. Walsh:** None. **E.S. Calipari:** None. **L. Li:** None. **S.J. Russo:** None. **A.K. Friedman:** None. **M. Han:** None.

Poster

596. Stress and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 596.17/W4

Topic: G.05. Anxiety Disorders

Support: NIH R01 DA027664-08
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NIH K12 H0055885
MUSC Sex Differences SCORE Pilot Grant

Title: Activity regulated cytoskeleton associated protein differentially regulates mood related behavior in the male and female nucleus accumbens

Authors: *R. D. PENROD, C. W. COWAN;
Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract: Anxiety disorders are highly prevalent and increased anxiety is a common symptom in numerous neuropsychiatric diseases. Females experience anxiety at a greater rate than males, and some studies find a nearly 60% greater lifetime risk for anxiety in females compared to males. Given the high prevalence, there is a need for novel therapeutic strategies requiring a better understanding of the underlying neurobiology mediating anxiety disorders. Furthermore, despite the significant sex differences in anxiety (and other stress-related) disorders, we have little understanding of the molecular mediators driving these differences. Recent work from our laboratory has identified Arc in the adult nucleus accumbens (NAc) as a potential mediator of sex differences in anxiety-like behavior. We find that Arc knockdown (shArc) in the NAc reduces anxiety-like behavior in males, but not in females. Interestingly, Arc expression is induced following an anxiety-associated experience in the male, but not female, NAc. Ongoing work is focused on: 1) identifying the mechanism for Arc dependent behavioral regulation in the male NAc, and 2) determining if Arc interacts with estrus to mediate female NAc-associated

behaviors. Using cre-dependent shArc, we are examining the cell type-specific roles for Arc in the NAc for regulating anxiety-like and related behaviors, which will enable future work that focuses on cellular and molecular mechanisms of Arc function in the NAc. To address the relationship between estrus, Arc, and behavior, we are examining whether Arc expression is regulated by sex hormones in the NAc and whether Arc plays an estrus-dependent role in mediating anxiety-like behaviors. Together, these ongoing studies should help advance our knowledge of the novel role for Arc in regulating sex-dependent, anxiety-related behaviors.

Disclosures: R.D. Penrod: None. **C.W. Cowan:** None.

Poster

596. Stress and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 596.18/W5

Topic: G.05. Anxiety Disorders

Title: Dorsal periaqueductal gray and medial hypothalamus involvement in the panic-modulating effects caused by serotonergic activation of dorsal raphe lateral wings

Authors: *M. MATTHIESEN[1], L. DANIEL MENDES[2], H. ZANGROSSI JR[2];
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Abstract: BACKGROUND: A wealth of evidence indicates that the lateral wings (lwDR) subnucleus of the dorsal raphe (DR) is a key structure in the modulation of panic-associated behaviors, such as escape and flight. Pharmacological stimulation of serotonergic neurons in this subnucleus promotes a panicolytic- like effect. It has been hypothesized that this effect is due to serotonin release in two other major panic-associated areas, the dorsal periaqueductal gray (dPAG) and dorsomedial hypothalamus (DMH), where facilitation of 5-HT_{1A} neurotransmission inhibits escape performance. However, it is unknown whether blockade of 5-HT_{1A} receptors in the dPAG or in the DMH interferes with the anti-escape effect caused by lwDR serotonergic neurons stimulation. **METHODS:** Male Wistar rats (280-310 g) were stereotaxically implanted with a guide-cannula directed to the lwDR and other to the dPAG or DMH. Local microinjection of a small volume of the 5-HT1A receptor antagonist WAY-100635 (0.74 nmol/50 nl) was used to indirectly stimulate serotonergic neurons in the lwDR. Ten minutes before the administration in the lwDR, rats were infused with the same drug into the dPAG (0.37 nmol/200 nl) or into the DMH (0.74 nmol/200 nl). Escape behavior was investigated in the elevated T-maze. **RESULTS:** Previous treatment with WAY-100635 in the dPAG or DMH fully blocked the anti-escape effect caused by the injection of this drug in the lwDR [interaction between dPAG and lwDR treatment factors: $F(1,28)=6.40$; $p<0.05$], two way ANOVA; interaction between DMH and lwDR treatment factors: $F(1,25)=5.67$; $p<0.05$], two way ANOVA]. **CONCLUSION:** Our results show that 5-HT_{1A} receptors activation in the dPAG and DMH mediated the panicolytic-like effect

caused by lwDR stimulation. Dysfunctions in the serotonergic pathways that connect the lwDR to the dPAG and to the DMH may be critically involved in the pathophysiology of panic disorder.

Disclosures: M. Matthiesen: None. **L. Daniel Mendes:** None. **H. Zangrossi Jr:** None.

Poster

596. Stress and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 596.19/W6

Topic: G.05. Anxiety Disorders

Title: Neurotrophin modulation of a social circuit to mediate preadolescent stress effects on adult social interaction

Authors: *N. TSE[1], F. S. LEE[2];
[1]Weill Cornell Med. Grad. Sch., New York, NY; [2]Weill Cornell Med. Col., New York, NY

Abstract: Adversity experienced during childhood, such as through emotional abuse and neglect, increases the likelihood that an individual will be diagnosed with a psychiatric disorder later in life. Within these disorders, asocial behavior, characterized by avoidance of or decreased motivation toward social interaction, is a common shared characteristic. Our lab has recently identified a projection from the orbitofrontal cortex (OFC) to the basolateral amygdala (BLA) in which suppression of circuit activity produces a reduction in social interaction. OFC projections to the BLA begin to form during preadolescence, and so adversity suffered within this period may alter the development of this circuit and drive asocial phenotypes in adulthood, though to date, no studies have confirmed this. Additionally, the mechanisms underlying abnormal social circuit development in response to preadolescent stress are unknown. In this current study, we optimized a preadolescent stress paradigm and found that a variable foot shock stress delivered within a specific developmental window produces impairments in social interaction at a remote adult time point. Furthermore, we investigated the molecular mechanisms potentially driving these developed social deficits, namely through post-stress upregulation of the p75 neurotrophin receptor within the OFC. These findings suggest that developing OFC structures and circuits related to sociality are uniquely vulnerable to perturbation during a sensitive preadolescent period, and that imbalance in neurotrophin receptor signaling may underlie the detrimental effect of preadolescent stress.

Disclosures: N. Tse: None. **F.S. Lee:** None.

Poster

596. Stress and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 596.20/W7

Topic: G.05. Anxiety Disorders

Title: Prefrontal cortical control of the paraventricular thalamus

Authors: *N. MACK, W.-J. GAO;
Dept. of Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Altered neurotransmission within the medial prefrontal cortex (mPFC) has long been associated with the pathogenesis of anxiety, yet there is little consensus and even conflicting evidence on the role of the mPFC activation on anxiety-like behaviors. Indeed, lesion studies and pharmacological manipulations in animal models along with functional imaging in the patient population have revealed that both inactivation and activation of the mPFC is related to increased anxiety. One possibility is that these contradictory findings are a consequence of differential effects on distinct subdivisions, neuronal cell types, and projection pathways within the mPFC. Recent evidence suggests that increased excitability in mPFC pyramidal neurons may underly the expression of anxiety-like behaviors. However, a downstream projection pathway from the mPFC where enhanced activity is anxiogenic has yet to be identified. Here we demonstrate that the paraventricular nucleus of thalamus may be a downstream target engaged by the mPFC to modulate anxiety-like behaviors in males. We use chemogenetic manipulations to alter the activity in mPFC-PVT along with multiple well-validated behavioral assays to determine whether modulation of this circuit affects the expression of anxiety-like behaviors. Our preliminary results suggests inhibition the mPFC-PVT has anxiolytic effects on the elevated plus maze (EPM) in male mice without affecting locomotor or exploratory behaviors. Using both chemogenetics and optogenetics, our future directions include probing whether bidirectional modulation of this circuit in male and female mice alters the expression passive-like anxiety behaviors. We also aim to probe the cellular excitability of mPFC neurons that project to the PVT.

Disclosures: **N. Mack:** None. **W. Gao:** None.

Poster

596. Stress and Anxiety

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 596.21/W8

Topic: G.05. Anxiety Disorders

Support: MOST 106-2320-B-007 -006 -MY3

Title: Physiological characterization of lateral orbitofrontal cortical projection neurons to nucleus accumbens and basolateral amygdala

Authors: *C.-W. LAI[1], C.-H. CHANG[2,1];
[1]Inst. of Mol. Med., Natl. Tsing Hua Univ., Hsinchu, Taiwan; [2]Inst. of Systems Neurosci., Natl. Tsing Hua Univ., Hsinchu (city), Taiwan

Abstract: The lateral orbitofrontal cortex (lOFC) projects to the nucleus accumbens (NAcc) and the basolateral nucleus of the amygdala (BLA). The two projections regulate different behaviors, for example, compulsive drug seeking and reward outcome encoding. In series of studies, we started to investigate the lOFC collateral modulation of these downstream targets and the physiological characterization. We used in vivo extracellular single unit recordings in anaesthetized rats in the experiments. In Experiment 1, we recorded a total of 19 neurons from 10 rats. Among our sampled units, eight neurons projected from lOFC to NAcc, while five neurons projected from NAcc to lOFC. We found one neuron projected from lOFC to BLA, while four neurons projected from BLA to lOFC. Among all the neurons recorded, we only found one lOFC neuron collaterally projected to both NAcc and BLA. Under our filter settings (bandpass 300-10K Hz), 17 of the sampled neurons had low firing rate with relative long spike duration, suggesting the majority of these units were putative projections neurons. In our on-going Experiment 2, we further characterize the physiological characteristics of NAcc- or BLA-projecting lOFC neurons by testing the thresholds (the stimulation current to evoke spike response probability of 2 - 12%) and stimulus intensity-response probability curves (I-O curves). The stimulation electrode was placed in lOFC in search of orthodromic responsive units in NAcc or BLA. So far, we found 4 neurons in NAcc from 8 rats, with a threshold at 0.54 ± 0.19 mA (range 0.35 to 0.70 mA). We did not find any responsive units in BLA yet in 8 rats. Our preliminary results supported the idea that the lOFC to BLA projections were sparse. We will combine tracer study to examine if there is topographic segregation of NAcc- and BLA-projecting neurons in lOFC.

Disclosures: C. Lai: None. **C. Chang:** None.

Poster

596. Stress and Anxiety

Location: Hall A

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Program #/Poster #: 596.22/W9

Topic: G.07. Other Psychiatric Disorders

Support: National Natural Science Foundation of China (Y73BN11171)
The National Key R&D Program of China (Y72FN91171)

Title: Physiological function abnormal of anterior dorsal bed nucleus of the stria terminalis and ventromedial hypothalamus contribute to the social-isolation-induced behavioral deficits

Authors: *C. ZHENG, L. WEI, B. BO, Z. LIANG, Z. WANG;
Inst. of Neuroscience, Chinese Acad. of Sci., Shanghai, China

Abstract: Sociality is an indispensable property among most species. The reciprocal links between individuals and social network contribute to the improvement of the cognition capability and maintenance of the mental health. The sociality is vital for individual to live in the society, however, the underlying neural mechanism of sociality still largely unknown. In this study, by utilizing the model of post-weaning social isolation (PWSI), we established the social interaction deficit rats. The results of elevated plus maze test confirmed that the rats of PWSI show high level of anxiety. The results of social preference test show that social preference ratio reduced in PWSI group. In addition, there is a negative correlation between the anxiety level and social preference ratio. The rest-state functional magnetic resonance imaging data show that the functional connectivity between bed nucleus of the stria terminalis (BNST) and ventromedial hypothalamus (VMH) reduced after PWSI. By using in vitro slice recording, we found that the frequency of miniature excitatory postsynaptic current (mEPSC) increased while the decay time decreased in anterior dorsal BNST after PWSI. Furthermore, we found that rest membrane potential and the threshold of action potential in VMH decreased in PWSI group. These results suggested that function abnormal of adBNST and VMH and synaptic transmission between these two nucleuses contribute to the social isolation-induced behavioral deficits.

Disclosures: C. Zheng: None. **L. Wei:** None. **B. Bo:** None. **Z. Liang:** None. **Z. Wang:** None.

Poster

596. Stress and Anxiety

Location: Hall A

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Program #/Poster #: 596.23/W10

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: This study was part of the Canadian Biomarker Integration Network in Depression (CAN-BIND) program (www.canbind.ca). CAN-BIND is an Integrated Discovery Program carried out in partnership with, and financial support from, the Ontario Brain Institute.

Title: Effects of combined psychological and metabolic stress on behavior and physiology

Authors: *B. MELANSON, T. LAPOINTE, F. LERI;
Psychology, Univ. of Guelph, Guelph, ON, Canada

Abstract: Chronic stress is highly implicated in the development of depression, possibly through elevation of inflammatory cytokines such as interleukin (IL)-6, IL-1β, IL-17A and tumour necrosis factor (TNF)-α. The primary objective of the current project in laboratory rats was to explore the relationship between combined psychological and metabolic stressors, inflammatory cytokines, and depressive-like behavior to uncover markers of response to antidepressants. Two experiments have been performed in male Sprague-Dawley rats. In Experiment 1, rats were exposed to repeated sessions of inescapable swimming stress to explore behavioral indices of despair (forced swim test), as well as circulating levels of inflammatory cytokines. In Experiment 2, repeated swimming stress was combined with exposure to a metabolic stressor (0, 200 and 300 mg/kg 2-deoxy-D-glucose; 2DG) to explore impact on behavioral despair, anhedonia (saccharin preference), as well as circulating levels of corticosterone and inflammatory cytokines. Experiment 1 indicated that multiple sessions of swimming stress induced long-lasting behavioral despair ($p < 0.001$), but levels of inflammatory cytokines were not affected ($p > 0.05$). In Experiment 2, the addition of the metabolic stressor dose-dependently increased despair responses ($p = 0.048$), corticosterone ($p = 0.001$) and TNF-α ($p = 0.020$). Moreover, rats treated with 200 and 300mg/kg 2DG displayed a significant reduction in saccharin consumption ($p < 0.001$). In summary, the current results in laboratory rats suggest that inflammatory cytokines may play a role in depressive-like behaviors when exposure to uncontrollable stress is of considerable intensity and duration. Moreover, establishing a functional protocol for inducing a significant inflammatory response to multimodal stress allows further investigation into the effects of conventional and novel antidepressant medications.

Disclosures: B. Melanson: None. **T. Lapointe:** None. **F. Leri:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 597.01/DP11/W11

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: G.08. Drugs of Abuse and Addiction

Support: P30AI078498
T32-AI-049851

Title: Putting on the brakes: An EEG investigation of inhibitory control and action monitoring in HIV+ abstinent substance users

Authors: *K.-M. WAKIM-TAKAKI[1], N. VIEYTO[1], C. J. MOLLOY[2], Z. CAO[1], E. G. FREEDMAN[3], J. J. FOXE[4];
[1]Neurosci., Univ. of Rochester, Rochester, NY; [2]Psychiatry, Trinity Col., Dublin, Ireland; [3]Del Monte Inst. for Neurosci., Univ. of Rochester - Neurosci., Rochester, NY; [4]Neurosci., Univ. of Rochester Sch. of Med., Rochester, NY

Abstract: Individuals with human immunodeficiency virus (HIV) with a history of substance use are at risk of engaging in behaviors that interfere with treatment, such as relapse, medication non-adherence, unprotected sex, and needle sharing. Active users of cocaine, both with and without HIV, show clear perseverative response patterns, as well as deficits in the ability to implement flexible problem-solving strategies. The executive functions of "inhibitory control"—the ability to withhold a thought, action or feeling—and "action monitoring"—the ability to assess a cognitively demanding situation and entertain response alternatives—are critical for relapse prevention. Although recent behavioral and neuroimaging evidence indicates normalization of these processes in former cocaine users as function of drug abstinence, it is unknown whether this recovery trajectory persists in former users with comorbid HIV. To better understand the executive changes underlying risky behavior in the high-risk population of individuals with comorbid HIV and history of substance dependence, we collect high-density EEG recordings as patients perform a 'Go/NoGo' response inhibition task. Outcome measures of interest include task performance, as well as amplitude and onset times of the fronto-central N2/P3 ERP components during correct trials, and ERN/Pe components during error trials. By building a deeper understanding of the neural substrates associated with maladaptive executive function, we hope to pave the way for targeted treatments aimed to reduce risky behavior and facilitate positive health outcomes. Consistent with prior literature, we found that both behavioral performance and electrophysiological markers of inhibitory control at task-relevant scalp sites did not differ substantially between HIV- abstinent cocaine users and healthy controls,

suggesting a partial recovery of inhibitory control capabilities in former cocaine users. Preliminary data suggests that neural and behavioral deficits in inhibitory control are more severe in HIV+ individuals with a history of cocaine dependence compared to HIV+ individuals without former cocaine dependence. These data indicate that inhibitory control capabilities in HIV+ former cocaine users do not normalize to the level of HIV- individuals, suggesting that further or more targeted interventions may be needed to facilitate positive health outcomes in this vulnerable population.

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Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 597.02/W12

Topic: G.08. Drugs of Abuse and Addiction

Support: ERA-NET NEURON-FRQS
CIHR MOP Grant 133537

Title: Cocaine cue-induced brain activations in recreational cocaine users

Authors: *S. G. SCALA[1], S. M. L. COX[1], M. LEYTON[2];
[2]Dept Psychiatry, Psycholology, & Neurol., [1]McGill Univ., Montreal, QC, Canada

Abstract: The development of pathological drug use is thought to reflect an accumulation of difficult-to-disengage habits and sensitized goal-directed behaviors. As part of our research program investigating whether these phenomena occur in humans, we recently reported the first evidence that the presentation of behavior dependent cocaine-paired cues elicits dopamine release in the habit fostering dorsal striatum prior to the development of a substance use disorder (Cox et al, *Sci Reports* 2017). Now we report evidence that recreational cocaine users exhibit activations of the ventral striatum in response to non-contingent cocaine cues. In brief, we used 3T functional magnetic resonance imaging (fMRI) to measure responses to cocaine-themed videos in recreational cocaine users (n=18) and stimulant drug-naïve healthy controls (n=13). Whole brain voxel-wise analyses found that, in the cocaine users, exposure to the drug (*vs.* neutral) videos elicited BOLD responses in the substantia nigra/ventral tegmental area (peak-level, $p < 0.05$, FWE-corrected), ventral caudate (cluster-level, $p < 0.001$, FWE-corrected), posterior cingulate (cluster-level, $p < 0.001$, FWE-corrected), premotor cortex/supplementary motor area (cluster-level, $p < 0.05$, FWE-corrected), supramarginal gyrus (peak-level, $p < 0.001$, FWE-corrected), precuneus (cluster-level, $p < 0.001$, FWE-corrected), and angular gyrus (cluster-level, $p < 0.001$, FWE-corrected). Controls showed cocaine cue-induced activations in

the angular gyrus only (cluster-level, $p < 0.05$, FWE-corrected). To our knowledge, these findings characterize for the first time brain regional responses to non-contingent drug cues in recreational cocaine users.

Disclosures: S.G. Scala: None. **S.M.L. Cox:** None. **M. Leyton:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 597.03/W13

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R15DA038295

Title: Conditioned place preference with low dose mixtures of 3,4-methylenedioxypyrovalerone (MDPV) and 3,4-methylenedioxymethamphetamine (MDMA) in male and female Sprague-Dawley rats

Authors: *H. I. RISCA, C. N. CONWAY, J. D. SHAYKIN, L. E. BAKER;
Psychology, Western Michigan Univ., Kalamazoo, MI

Abstract: 3,4-Methylenedioxypyrovalerone (MDPV) is a novel synthetic cathinone reported to have a high abuse potential and to produce adverse medical consequences when used recreationally. Preclinical research indicates the psychopharmacology of MDPV is comparable to both cocaine and 3,4-methylenedioxymethamphetamine (MDMA). MDPV is commonly used as a substitute or in combination with other psychostimulants, which may be a contributing factor to MDPV-related toxicity. Despite the prevalence of concomitant use of synthetic cathinones and other psychostimulants, few studies have investigated the combined behavioral effects of these substances. The current study evaluated the combined effects of MDPV and MDMA in a rodent model of conditioned place preference (CPP). Adult male (n=72) and female (n=60) Sprague-Dawley rats underwent an eight-day biased CPP procedure. Treatment groups consisted of saline, MDPV (1 or 3.2 mg/kg), MDMA (3 mg/kg), 1 mg/kg MDPV + 3 mg/kg MDMA, or 3.2 mg/kg MDPV + 3 mg/kg MDMA. Activity was monitored during all conditioning trials. To assess evidence for CPP, difference scores were calculated by subtracting time spent in the drug-paired chamber pre-conditioning from time spent in the same chamber post-conditioning. Activity levels during drug conditioning trials were highest among the 3.2 mg/kg MDPV-treated animals. A two-way ANOVA on the difference scores indicated a statistically significant treatment effect. Sex and the treatment by sex interaction were not statistically significant. Although difference scores were higher in all MDPV and MDPV+MDMA treatment groups compared to the saline control groups, only the females treated with 3.2 mg/kg MDPV + 3 mg/kg MDMA exhibited statistically significant evidence for

CPP. Interestingly, 3 mg/kg MDMA appeared to attenuate the locomotor stimulant effects of 3.2 mg/kg MDPV but increase its effects on conditioned reward. These findings indicate females are more sensitive to the rewarding effects of MDPV and these effects may be enhanced by co-administration of MDPV and MDMA. Moreover, concurrent use of MDPV and MDMA may pose an enhanced risk for abuse, particularly in females.

Disclosures: **H.I. Risca:** A. Employment/Salary (full or part-time):; Western Michigan University (part-time). B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NIDA Drug Control Supply. **C.N. Conway:** None. **J.D. Shaykin:** None. **L.E. Baker:** A. Employment/Salary (full or part-time):; Western Michigan University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NIDA Drug Control Supply.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

Location: Hall A

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Topic: G.08. Drugs of Abuse and Addiction

Support: VA Biomedical Laboratory Research and Development CDA2 award IK2BX002531.

Title: Blockade of hypocretin/orexin receptors prevents sleep deprivation-induced enhancement of cocaine conditioned place preference

Authors: *T. E. BJORNESS[1,2], R. W. GREENE[3];
[1]VA Med. Ctr. of North Texas, Dallas, TX; [2]Univ. of Texas Southwestern, Dallas, TX; [3]Dept Psychiatry & Dept Neurosci., UTSW, Peter O'Donnell Brain Inst., Dallas, TX

Abstract: Cocaine, a psychostimulant with abuse potential due to blockade of dopamine transporters, alters sleep under active use, withdrawal, and abstinence conditions. Furthermore, recovery of lost SWS time during abstinence is associated with an increase in relapse such that there may be a bidirectional influence of sleep and addiction-related behaviors. We have previously demonstrated that acute sleep deprivation both enhances the rewarding properties of cocaine using the conditioned place preference task and induces preference to a low, subthreshold dose of cocaine. However, the mechanism(s) by which sleep deprivation influences

reward-related behavior are still unknown. Here, we investigated a possible role of orexin, a neuromodulator which facilitates waking and has been implicated in reward related behavior, including both natural rewards and drugs of abuse. Adult male C57BL/6 mice underwent unbiased conditioned place preference (CPP) training using a three chambered CPP box. CPP expression was tested using a protocol consisting of a pre-test (doors open) to ensure a lack of side bias, followed by alternating daily cocaine and saline conditioning trials (doors closed), and a 20 min post-test (doors open). Mice were sleep deprived via a slowly moving treadmill belt for 4 hours immediately prior to the post-test (experimental group), or allowed to sleep undisturbed (control group). All animals were injected with 1 mg/kg SB334867 (selective orexin 1 receptor antagonist), approximately 15 min prior to the post-test. A moderate cocaine dose (8 mg/kg) was used; this dose is typically reinforcing and supports CPP in mice. Several days after the end of the CPP protocol, mice underwent an additional experiment in which weight was used as an indirect measure of SB334867 efficacy based on reports of potential hydrolysis leading to an orexin 1-inactive product. Mice were weighed daily and then injected with vehicle (DMSO in sterile water) or 1 mg/kg SB334867 approximately 15 min before the end of the light phase. All mice experienced both vehicle and SB334867 injections. Both control and sleep deprived mice showed preference for the cocaine-paired chamber; however, there was no significant difference in degree of preference between groups. This differs from previous experiments in which acute sleep deprivation enhanced expression of cocaine conditioned place preference. Weight change was significantly lower following 1 mg/kg SB334867 compared to vehicle suggesting that the SB334867 was effective in influencing orexin activity. Overall, these results suggest involvement of the orexin system as a mediator of sleep disturbance's influence on reward behavior.

Disclosures: T.E. Bjorness: None. **R.W. Greene:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH R01 DA038042
NIH NIGMS #2R25GM082406
NIM HD 007579
Ponce Research Institute

Title: Effects of aromatase inhibition on cocaine-seeking behavior in male rats

Authors: *J. K. ALVARADO TORRES[1], F. MONTALVO-LOPEZ[1], J. WILSON[1], J. PLA-TENORIO[1], A. ECHEVARRIA-RIVERA[1], M. T. SEPULVEDA-ORENGO[2], D. MUELLER[3];

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Abstract: Females are more susceptible to cocaine abuse but more responsive to treatment than males. In females, low estrogen levels impair extinction learning of drug seeking behavior suggesting that estrogens are critical mediators of extinction memory formation. Males also utilize estrogens within the brain through aromatase conversion of circulating androgens. However, it is unclear whether estrogens mediate extinction in males as in females. Thus, we determined if estrogens regulate extinction of cocaine seeking in males, and whether epigenetic changes are responsible. We hypothesized that males lacking estrogens would show impaired extinction and decreased histone H3 acetylation within reward-related brain structures. To test, we examined the effects of a potent aromatase inhibitor, Fadrozole (FAD), on extinction of cocaine-conditioned place preference (CPP). Following conditioning, male rats were injected with FAD (0.5, 1 or 2.5 mg/kg) or vehicle before each CPP test across days. Tissue from the infralimbic medial prefrontal cortex was subsequently screened for 21 different histone 3 modifications with colorimetric assay. Naïve context-exposed rats were used as a control. We observed a dose-dependent effect of FAD, where 0.5 and 1.0 mg/kg doses facilitated extinction and 2.5 mg/kg impaired extinction as compared to vehicle. These findings suggest that estrogens modulate extinction of cocaine seeking in male rats. Preliminary epigenetic data shows high levels of histone 3 modifications in cocaine-vehicle group compared to naive control group. In addition, H3K36 me1 and me2 differed in 1.0 mg/kg FAD group compared to vehicle. This epigenetic data may reveal how estrogens mediate gene transcription important for extinction of cocaine seeking in males.

Disclosures: J.K. Alvarado Torres: None. **F. Montalvo-Lopez:** None. **J. Wilson:** None. **J. Pla-Tenorio:** None. **A. Echevarria-Rivera:** None. **M.T. Sepulveda-Orengo:** None. **D. Mueller:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 597.06/W16

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH NIDA T32DA007288
NIH NIDA R01DA037327

Title: The role of serotonin 5-HT_{2C} receptors at the RMTg in cocaine conditioned avoidance

Authors: *Y. S. CHAO, J. PARRILLA-CARRERO, M. EID, P. J. VENTO, T. C. JHOU; Med. Univ. of South Carolina, Charleston, SC

Abstract: The neurobiology of cocaine's rewarding effects has been extensively characterized, but relatively little is known about the pathways and processes that underlie cocaine's aversive effects. Aversive responses to cocaine are significant because they may modulate both the acquisition of drug-seeking, and later behaviors such as relapse in experienced animals, and may underlie individual differences in susceptibility to cocaine addiction. Prior work from our lab showed that activation of the rostromedial tegmental nucleus (RMTg) by cocaine critically drives cocaine conditioned avoidance. While some of this cocaine-induced RMTg activation is due to glutamatergic inputs from the lateral habenula (LHb), a majority arises from unknown mechanisms. Using RNAseq we made the unexpected discovery that the RMTg expresses robust and enriched levels of mRNA for the serotonin 2C receptor (gene name *htr2c*) relative to surrounding regions. Because cocaine binds to both serotonin and dopamine uptake transporters, we postulate that 5-HT_{2C}R activation at the RMTg might be a novel mechanism by which cocaine activates the RMTg and drives avoidance. To test the hypothesis that activation of 5-HT_{2C}R following cocaine administration is critical for RMTg excitation that in turn drives conditioned avoidance responses to cocaine, we use a runway operant task developed by Ettenberg and colleagues, in which rats traverse a 5-foot long corridor to obtain a single cocaine infusion. We find that intra-RMTg injection of SB-242084 (a specific 5-HT_{2C}R antagonist) and RMTg site-specific shRNA knockdown of the *htr2c* gene block the development of cocaine conditioned avoidance, while injection of Ro60-0175 (a specific 5-HT_{2C}R agonist) is sufficient to induce conditioned place aversion. In addition to behavioral studies, we use slice electrophysiology to examine the *in vitro* effects of cocaine and 5-HT_{2C}R antagonist and agonist on RMTg neurons. Preliminary data show both cocaine and 5-HT_{2C}R agonist induce delayed depolarization of RMTg neurons that project to the VTA. Future studies will focus on further testing and establishing the specificities of these *in vitro* responses, since another serotonin receptor gene *htr2a* was also identified at the RMTg, albeit expressed at a significantly lower quantity, and studying the role of the 5-HT_{2C}R in RMTg neuron *in vivo* functions via live single cell wire recording. Preliminary data in our lab and prior findings support the notion that aversive effects of cocaine contribute to subsequent relapse drug seeking behaviors. The current studies may identify a valid target for treating cocaine's aversive effects and relapse drug seeking behaviors.

Disclosures: Y.S. Chao: None. **J. Parrilla-Carrero:** None. **M. Eid:** None. **P.J. Vento:** None. **T.C. Jhou:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 597.07/W17

Topic: G.08. Drugs of Abuse and Addiction

Support: NIMH Grant 106912

Title: Behavioral and biochemical studies of novel allosteric modulators of the dopamine transporter with therapeutic potential

Authors: *C. D. RICE[1], S. LEWANDOWSKI[1], X. LIU[1], S. AGGARWAL[1], J. SALVINO[2], *O. V. MORTENSEN[1];
[1]Pharmacol. and Physiol., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Wistar Inst., Philadelphia, PA

Abstract: Repetitive cocaine seeking, and use is attributed to cocaine's ability to inhibit the dopamine transporter (DAT). Many attempts have been made to prevent cocaine's actions on DAT but this resulted in drugs that also had addictive properties. By understanding DAT functionality, and more specifically how DAT interacts with cocaine we will be better positioned to develop therapeutics for treating cocaine use disorders. Dopamine and cocaine bind to the primary orthosteric binding pocket on DAT, S1, and previous studies from our lab and others have elucidated a second allosteric binding pocket on DAT, S2. We speculate that modulation of the S1 binding pocket by an allosteric site, S2, can affect the way cocaine binds to the S1 site. Computational modeling and virtual screening of a chemical library against the S2 site of DAT identified a compound, KM822 that acts as an allosteric modulator of DAT function. To further understand the mechanism of allosteric modulation of DAT, analogs of KM822 were designed and synthesized. In this study we show that one of these analogs, NP-1-152, interacts with the S2 site in our computational model and we have confirmed *in vitro* that NP-1-152 binds to the allosteric site by using the substituted cysteine accessibility method (SCAM). We also find that like KM822, NP-1-152 decreases the apparent affinity of cocaine for DAT in dopamine uptake studies. To test the behavioral effects of NP-1-152, we used two different cocaine-associated paradigms. One being cocaine-induced locomotion, testing the psychostimulatory effects of cocaine. The other being cocaine conditioned placed preference, testing the rewarding effects of cocaine. In both assays, we found that NP-1-152 attenuated the effects of cocaine by decreasing cocaine-induced locomotion and cocaine-induced association with a specific environment. We conclude that allosteric modulation of DAT can affect not only cocaine's primary mechanism of action *in vitro* but the psychotropic effects of cocaine *in vivo.* Our work has implications of a novel therapeutic for cocaine use and abuse.

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Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

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Program #/Poster #: 597.08/W18

Topic: G.08. Drugs of Abuse and Addiction

Support: NRF Grant
UKZN-CHS Grant

Title: Effects of indirect cocaine exposure and early postnatal fostering on epigenetic DNA modification and behavioural phenotypes of drug naive mice

Authors: *D. C. AJONIJEBU[1], M. V. MABANDLA[2], W. M. DANIELS[3];
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Abstract: Here, we explored the hypothesis that parental cocaine exposure could alter epigenetic machinery in drug-naïve offspring while early postnatal fostering may further modify the accompanied neurochemical and functional components. Variant drug naïve pups were produced from cocaine exposed or non-drug exposed C57BL/6 female mice that were matched with their male counterpart for mating. Within three days of birth, some of the pups were fostered and nurtured by non-biological lactating dams. The pups were initially examined for locomotor activity and memory performance and subsequently for changes in DNA methylation in promoter regions of cAMP response element modulator (*Crem*) and *Fosb* in the prefrontal cortex (PFC) at 48 days postnatum. The impact of postnatal fostering on these parameters was also investigated to further evaluate the influence of the environment on epigenetic expression. Our results showed that cocaine exposure significantly decreased both *Crem* and *Fosb* methylation in the prefrontal cortex of the progenitor mice compared to their controls. We also found that similar patterns of methylation in the parents were replicated in the same brain region of all groups of drug naïve non-fostered offspring mice. Whereas, fostering the offspring at early life did not only prevent expression of epigenetic marks associated with parent's cocaine experience but also impaired recognition memory, especially in descendants lineally inclined with either paternal (ME) and/or both progenitors' (MFE) cocaine exposure, as opposed to intact memory performance in their non-fostered counterparts. We also found that locomotor activity was unaltered in all groups of mice tested in the open field. Our data provide some evidence that indirect exposure to cocaine may cause marked epigenetic changes within the cortical networks of drug naïve descendants and that mediation by *Crem*/*Fosb* signalling in this brain region may be beneficial, while early postnatal fostering may further engineer molecular switching that may predispose the individual to future risky behaviours as well as accumulative potential to developing cognitive impairment later in life.

Disclosures: D.C. Ajonijebu: None. **M.V. Mabandla:** None. **W.M. Daniels:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

Location: Hall A

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Intramural Research Program
NIH/NIDA DA026472
VA BLR&D 1IO1BX000782

Title: Cocaine-induced structural brain changes in rhesus monkeys: Lasting changes and regions of recovery after two years of abstinence

Authors: *H. P. JEDEMA[1,2], X. SONG[1], H. J. AIZENSTEIN[2], E. A. STEIN[1], Y. YANG[1], C. W. BRADBERRY[1,2];
[1]Intramural Res. Program, NIH, Baltimore, MD; [2]Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: In order to provide insight into the observed differences in gray matter between cocaine users and control subjects that are observed clinically, we previously examined the longitudinal changes in gray matter density (GMD) in brains of rhesus monkeys following a 12-month period of intravenous cocaine self-administration (n=8 cocaine group vs n=6 controls). Using a novel analysis pipeline optimized for longitudinally collected structural imaging data and voxel-based morphometry, we observed reduced GMD in the cocaine group in multiple brain regions, including orbitofrontal cortex, thalamus, temporal cortex, and insula. In addition, we found increased GMD in the temporal pole, ventral frontal cortex, caudate, cerebellum, and occipital cortex. In a select subset of cortical clusters, the decreases in GMD correlated with impairment in cognitive function in these subjects, highlighting the functional impact of the GMD changes. The clusters of longitudinal GMD changes in monkeys correspond well to the cross-sectional differences in gray matter observed clinically and suggest that chronic cocaine use likely contributes to the reduced gray matter in cocaine users. Following a 2-year period of abstinence from cocaine, a 3rd MRI scan on a subset of the subjects (n=6 cocaine groups vs n=5 controls) revealed that the changes in GMD following cocaine exposure had largely reversed in most regions, including the thalamus, occipital cortex, and cerebellum. This reversal is consistent with recovery of cognitive function we observed after 3-5 months of abstinence. However, we observed a lack of change in GMD in temporal cortical regions, the caudate, and insula after this prolonged abstinence, suggesting that these areas reflect more lasting alterations that might contribute to an enhanced risk of relapse observed in drug addiction.

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Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 597.10/W20

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH/NIDA R15DA040809

Title: Sex differences in cocaine reward and estradiol-mediated hypersensitivity to cocaine cues are associated with changes in ERK activity within the mesolimbic reward pathway

Authors: *S. S. KOKANE, A. C. HOCH, R. J. ARMANT, L. I. PERROTTI;
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Abstract: Previous research has shown that the increased vulnerability of women and female animals to the subjective effects of cocaine and hypersensitivity to cocaine-associated cues is mediated by estradiol. Estradiol mediates these effects of cocaine by potentiating dopaminergic synaptic transmission in the mesolimbic reward pathway. At the neuronal level, estradiol-mediated neuroadaptations in dorsal striatum (dStria), nucleus accumbens shell (NAc shell) and core (NAc core) are implicated in regulating these effects. Previous studies from our group have demonstrated the ability of estradiol to enhance cocaine-cue associations in a cocaine-conditioned place preference (cocaine-CPP) paradigm. Studies conducted in males animals have well established that activation of extracellular signal-regulated kinase (ERK) plays an important role in mediating neuroadaptations within the mesolimbic pathway that are important for the development of cocaine-cue associations. However, studies exploring the induction of ERK in females and the influence of gonadal hormones on the induction of ERK in the mesolimbic system in response to cocaine-CPP are severely lacking. Thus, the goal of the present study was to identify sex differences in the induction of ERK activation after cocaine-CPP and to examine the influence of estradiol's enhancement of cocaine-cue associations on ERK induction in the mesolimbic system. Intact adult male and female, and ovariectomized (OVX) female rats were subjected to a cocaine-CPP paradigm using a 3/3 conditioning procedure with 10mg/kg of cocaine hydrochloride (i.p.). To systematically compare the effects of estradiol on cocaine-cue associations, OVX female rats were treated with estradiol benzoate (EB; 5 µg; s.c.) 30 minutes prior to the start of each cocaine-conditioning session. Expression of cocaine-CPP was assessed under a drug- and hormone-free state 24h after the last conditioning session. Immediately after the CPP test, animals were euthanized and brain tissue comprising ventral tegmental area (VTA), NAc and dStria was isolated to assess the expression of phosphorylated ERK (pERK) protein. Overall, females exhibited a higher preference for cocaine and had higher levels of pERK in VTA, NAc, and dStria than males. EB-treatment during cocaine-conditioning potentiated cocaine-CPP and increased pERK in dStria and NAc shell in females. In conclusion, our results

demonstrate, that **sex differences in cocaine preference and estradiol-mediated potentiation of cocaine-cue associations may be due to increased ERK activation in the nucleus accumbens shell and dorsal striatum.** Funding support: NIH/NIDA R15DA040809 (LIP).

Disclosures: S.S. Kokane: None. **A.C. Hoch:** None. **R.J. Armant:** None. **L.I. Perrotti:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

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Program #/Poster #: 597.11/W21

Topic: G.08. Drugs of Abuse and Addiction

Support: F32-DA041778
T32-GM800111
R01-MH114990
DP1-DA039650
R00-DA034681
R21-ES024850

Title: The role of Gadd45b in striatal physiology and cocaine reward

Authors: *M. E. ZIPPERLY, F. SULTAN, G.-E. GRAHAM, N. A. SIMPKINS, K. E. SAVELL, J. S. REVANNA, J. J. DAY;
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Abstract: Exposure to drugs of abuse leads to alterations in neuronal activity and synaptic organization, which outlive the direct effects of the drug and may contribute to addiction. Furthermore, drug experience contributes to activity-dependent changes in DNA methylation, an epigenetic modification that is critical for synaptic plasticity and plays an important regulatory role in the function and development of the mammalian nervous system. The *Gadd45* (Growth arrest and DNA-damage inducible) family is involved in activity-dependent DNA demethylation, but little is known about how this family regulates the activity of brain reward circuits and subsequent behavioral responses to drugs of abuse, such as cocaine. The present study utilizes unbiased genome-wide transcriptional profiling, pharmacological manipulations, electrophysiological recordings, and CRISPR tools in both *in vitro* and *in vivo* rodent model systems to characterize the importance of *Gadd45b* in dopamine-dependent epigenetic regulation and cocaine reward. In primary rat striatal cultures *in vitro*, acute dopamine treatment increased *Gadd45b* mRNA. This increase was blocked by the dopamine receptor type 1 (Drd1) antagonist SCH-23390 and was mimicked with the Drd1 agonist SKF-38393, suggesting that Drd1 activation is required for dopamine-induced increases in *Gadd45b*. Furthermore, RNAi knockdown of *Gadd45b* in cultured striatal neurons resulted in downregulation of immediate

early genes (IEGs), such as *Fos*, *Fosb*, and *Arc*, as well as reduced action potential bursting activity, compared to scrambled controls. *In vivo, Gadd45b* and IEGs were upregulated in the rat nucleus accumbens following acute cocaine reward. CRISPR/Cas9-driven *Gadd45b* knockdown attenuated cocaine-paired place preference *in vivo*, suggesting that *Gadd45b* action is required for cocaine memory. Ongoing studies aim to further investigate the role of *Gadd45b* by characterizing the effects of overexpression on neuronal activity and IEG expression. Overall, our results suggest that *Gadd45b* is induced by dopamine receptor activation and regulates transcriptional and physiological dynamics in striatal neurons.

Disclosures: M.E. Zipperly: None. **F. Sultan:** None. **G. Graham:** None. **N.A. Simpkins:** None. **K.E. Savell:** None. **J.S. Revanna:** None. **J.J. Day:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 597.12/W22

Topic: G.08. Drugs of Abuse and Addiction

Title: The role of fragile X mental retardation protein in striatal plasticity and drug-related behavior

Authors: *J. HUEBSCHMAN[1], L. N. SMITH[2];
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Abstract: Cocaine, and other drugs of abuse, are known to alter dendritic spine density and synaptic strength of medium spiny neurons (MSNs) in the nucleus accumbens (NAc) and dorsal striatum (DS), implicating such changes in connectivity in the development and/or maintenance of addiction. However, key regulators of this process remain unclear. The fragile X mental retardation protein (FMRP), an RNA binding protein which controls the translation of hundreds of brain RNAs, has been shown to regulate spine density in multiple brain regions. Our work has highlighted FMRP's function in the promotion of basal spine stability, as well as in limiting cocaine-induced increases in dendritic branching and spine density, in multiple striatal sub-regions. Here, we continue to examine the role of FMRP in striatal cell plasticity and how this process relates to the development of addiction-related behaviors in mice, using both embryonic mouse cortical-striatal cell co-culture and *in vivo* mouse drug self-administration models. In the absence of FMRP, cultured striatal cells show no differences in synaptic puncta density after 10 days *in vitro* (DIV) but develop a significant deficit in puncta by 14 DIV, suggesting that FMRP plays an important role in striatal cell synapse formation and maintenance. Further, our preliminary *in vivo* drug self-administration data suggest that FMRP may be required for shifts in hedonic preferences associated with repeated drug exposure. Ongoing work in our lab is

examining the role of FMRP's specific RNA-binding regions in regulating striatal plasticity, which will provide insight into the FMRP targets involved in this process. We are also investigating the role of FMRP in D1- and D2-receptor expressing MSN's and how its activity in each of these cell types may regulate drug-related behaviors.

Disclosures: J. Huebschman: None. **L.N. Smith:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

Location: Hall A

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Program #/Poster #: 597.13/W23

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH P50 DA039841
NIH R01 DA037927

Title: Correlation among striatum coexpression networks and drug-related sensation-seeking behaviors in diversity outbred mice

Authors: *M. C. SAUL, P. E. DICKSON, L. H. GAGNON, T. WILCOX, T. ROY, U. DATTA, E. J. CHESLER;
The Jackson Lab., Bar Harbor, ME

Abstract: Novelty-related and sensation-seeking behaviors are strong predictors of drug use phenotypes in both mice and humans. These behaviors are heritable in both species, implying conserved brain gene regulatory networks for drug use predisposition. To enumerate genes whose brain expression covaries with such behaviors in a genetically diverse population, we measured open field, novel place preference, light-dark box, and hole board behaviors in the Diversity Outbred population. We correlated these behavioral traits with striatum gene expression using bulk RNAseq. We found varying distributions of association between global transcript abundance and novelty and sensation-seeking phenotypes. Open field and light-dark box traits showed many statistically significant associations (at FDR < 0.10) with striatum transcript abundance, hole board exploratory traits showed fewer associations, and novel place preference traits showed almost no associations. Effect sizes were lower than previously observed behavioral associations with striatum gene expression in less diverse mouse stocks, suggesting that diversity expands mechanisms of gene regulatory stabilization relative to inbred mice. However, coexpression network analysis revealed strong correspondance among gene networks membership and behavioral correlations with genes. For example, within one module containing a large cluster of synaptic genes, module membership showed a very strong (r = 0.67) correspondance with gene correlation to novel place preference. Among the most highly connected nodes within this module was the synaptotagmin gene *Syt13*, which was strongly

coexpressed with multiple glutamatergic and GABAergic receptor genes. These results reinforce that in genetically diverse populations, behaviorally relevant gene expression phenomena arise at the network level.

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Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 597.14/W24

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA040777

Title: Novelty facilitates formation of long-term extinction memory of cocaine-associated context

Authors: *J. LIU, R. WU, J.-X. LI;
SUNY At Buffalo, Buffalo, NY

Abstract: Repeated exposure to drug-associated cues would induce extinction. Extinction of drug-associated cues is a new associative memory that inhibits original drug reward memory. It is believed that facilitating extinction memory is an effective strategy to control drug addiction. Previous studies showed that extinction can be promoted or enhanced by non-pharmacological strategies such as a brief exploitation of a novel context (novelty). However, it is unclear whether novelty would affect extinction memory of drug-associated cues. Here, we investigated the effect of novelty on extinction memory of cocaine-associated contextual cue in cocaine-induced conditioned place preference (CPP) in rats. After the conditioning of cocaine-induced CPP, rats were allowed to freely move (30 min per day) in the CPP chambers for three days to induce extinction. We found that the three-day extinction had no effect on subsequent expression of cocaine-induced CPP. Interestingly, exposure to novelty 1 hour before extinction sessions (novelty-extinction) suppressed subsequent expression of cocaine-induced CPP, suggesting that novelty facilitated formation of long-term extinction memory of the cocaine associated contextual cue. However, exposure to novelty 6 hours before extinction had no effect on extinction memory, indicating that novelty affected extinction in a time-dependent manner. Furthermore, we found that the long-term extinction memory induced by “novelty-extinction” procedure persisted for at least three weeks. “Novelty-extinction” procedure did not disrupt cocaine reward memory, since cocaine reward memory recovered 6 weeks after extinction. Although long-term exposure to drug-associated cues induce extinction, brief exposure to drug-associated cues retrieves drug reward memory and may trigger reconsolidation. Extinction and

reconsolidation are two opposite processes. We then examined whether exposure to novelty before memory retrieval would affect cocaine reward memory. Rats were placed in the cocaine-paired side for 10 min to retrieve cocaine reward memory. We found that exposure to novelty 1 hour before retrieval for three days had no effect on subsequent expression of cocaine-induced CPP. Taken together, these results indicate that novelty facilitates formation of long-term extinction memory of cocaine-associated context, suggesting that "novelty-extinction" may be a novel behavioral strategy to regulate drug addiction.

Disclosures: **J. Liu:** None. **R. Wu:** None. **J. Li:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

Location: Hall A

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Program #/Poster #: 597.15/W25

Topic: G.08. Drugs of Abuse and Addiction

Support: 1 R01 DA045023-01A1

Title: The effects of escalated cocaine intake on decision-making dynamics

Authors: *M. J. STEPHENS, J. S. BECKMANN;
Psychology, Univ. of Kentucky, Lexington, KY

Abstract: Cocaine Use Disorder (CUD) is characterized partly by the use of cocaine at the expense of other alternatives; in other words, it is a decision-making pathology (Kalivas and Volkow, 2005). Probabilistic reinforcement-learning choice (PRLC) tasks are able to assess decision-making behavior in a dynamic scenario that more closely resembles the conditions of daily human life. In order to compare decision making in rats with regulated and dysregulated cocaine intake, a PRLC task was run in tandem with an escalation procedure. First, animals were trained on a PRLC task until responding was stable, and they were then implanted with an indwelling jugular catheter and trained on a cocaine self-administration procedure (0.3mg/kg to the animal's weight) using a fixed ratio 1 schedule under 1-hr access until responding was stable. For the escalation procedure, some animals remained on 1-hr access and others were given 6-hr access to cocaine for 21 days. Then all rats returned to 1-hr access. The animals were trained such that they performed the PRLC task in the morning (while not under the influence of drugs) then were taken to rest in their home-cage and were later put back into the operant boxes for self-administration sessions.
Escalation of cocaine intake was evident in the 6-hr exposed animals while intake was stable in the 1-hr exposure animals. Preliminary analyses indicate that the choice behavior between groups did not differ over the 21-day period, despite differences in intake between the groups. The results suggest that despite dysregulated drug taking, when not under the influence of drugs

and when making choices for non-drug alternatives, the rats decision making was unaffected. Thus, drug-associated decision-making may be context dependent and any drug-related changes in decision making are not necessarily universal.

Disclosures: M.J. Stephens: None. **J.S. Beckmann:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 597.16/W26

Topic: G.01. Appetitive and Aversive Learning

Support: NIH R21 DA043190

Title: Activation of GABA projection neurons from the ventral tegmental area to the nucleus accumbens attenuates incubation of cocaine craving

Authors: *M. SUAREZ[1], E. CANTRELL[2], C. E. BASS[3];
[1]Pharmacol. and Toxicology, [2]Neurosci., Univ. at Buffalo, Buffalo, NY; [3]Univ. at Buffalo SUNY, Buffalo, NY

Abstract: The symptoms of cocaine use disorder are often expressed, or only expressed, during periods of prolonged abstinence, leading to relapse. Several brain areas play a role in sensitivity to both cocaine and cocaine-associated cues; the Ventral Tegmental Area (VTA) is heterogeneous midbrain region with dense afferents to the Nucleus Accumbens (NAc) that has been extensively studied for its role in natural- and cocaine-associated behaviors. Most of the neurons in the VTA are dopaminergic, however, the VTA also contains GABA interneurons, as well as GABA projection neurons (GPNs). Approximately one third of mesoaccumbal afferentss are GABAergic and are critical for cue-motivated responding. Using a combinatorial viral approach to target activating designer receptors exclusively activated by designer drugs (DREADDs) to VTA glutamate decarboxylase 1 (GAD1)-positive neurons in rats, our lab has previously demonstrated that chemogenetic activation of VTA GABA neurons decreases motivation for sucrose-predictive cues. Furthermore, when reward value was unexpectedly reduced by decreasing the volume of sucrose earned, clozapine N-oxide (CNO) in the NAc reduced responding to the sucrose-predictive cue when compared to controls. Currently, the role of these GPNs in cocaine-mediated behaviors is unknown. Rats were trained to self-administer cocaine (0.5 mg/kg/inf), by lever pressing, for 14 days and then were tested in early (< 3 days) or late (> 30 days) forced abstinence, to establish the expression of incubation of craving. At both test times, we chemogenetically activated either all VTA GABA neurons by giving the CNO systemically (0.3 mg/kg i.p.), or just the VTA GABA neuron terminals in the NAc by microinfusion of CNO. Our results show that rats readily express incubation by increased

responding on the previously active lever when tested > 30 days, compared to < 3 days. Additionally, systemic CNO, which simultaneously activates all VTA GABA neurons locally and at their distal projection sites, decreased responding on the active lever on all test days. Interestingly, microinfusion of CNO into the NAc, which activates only accumbal terminals of VTA GABA projection neurons, normalized the incubation response to levels seen at < 3 days. CNO had no effect in virus control rats. These results clearly establish that mesoaccumbal GABA neurotransmission facilitates either a reduction in motivation for a previously active lever, or an enhancement of extinction learning to a previously drug-paired environment.

Disclosures: M. Suarez: None. **E. Cantrell:** None. **C.E. Bass:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

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Topic: D.09. Multisensory Integration

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Title: Posterior parietal cortex inactivation abolishes the acquisition of cocaine reward-context association

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Abstract: Reward-induced behavior is closely affected by the learned context in a particular environment. However, the neural substrates for reward-context relations have not yet been fully elucidated. The posterior parietal cortex (PPC), known to act as a multisensory integrating area, receives inputs from various areas that accept contextual elements (e.g., visual cortex, auditory cortex, thalamus). To investigate a novel role of the PPC in cocaine reward-context associations, we performed cocaine conditioned place preference (CPP) after manipulating PPC neurons by irreversible lesion, temporary inhibition, and optogenetic inactivation. We observed that excitotoxin N-methyl-D-aspartic acid (NMDA) lesion to PPC induced the diminished the expression of cocaine CPP (p<0.01). To determine which session of the CPP is associated with the PPC function, muscimol was infused for temporary inhibition before training or preference

test session, respectively. As a result, we found that PPC plays a role in the acquisition, not in the expression, of cocaine CPP ($p<0.05$). In addition, the optogenetic inactivation of PPC during the training session also abolished the expression of cocaine CPP ($p<0.05$). However, inactivation of PPC did not have any effects in cocaine-induced locomotion, suggesting the inhibition of PPC was not due to a motor effect. Together, these results suggest that the PPC plays an important role in reward-context association during the pair formation rather than retrieval procedure.

Disclosures: S. Jeong: None. **S. Xu:** None. **U. Kang:** None. **J. Koo:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

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Title: Histone deacetylase 5 (HDAC5) in the prelimbic cortex regulates cocaine self-administration and seeking behaviors

Authors: *S. M. BARRY[1], N. AGNIHOTRI[2], J. D. WOLFE[3], M. TANIGUCHI[1], C. W. COWAN[1];
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Abstract: Relapse to drug-seeking remains a major obstacle in the treatment of cocaine addiction in individuals suffering from substance use disorders. Underlying this clinical obstacle are neuroadaptations and changes in gene expression within limbic structures critical for reward and goal-directed behavior. Drug-induced changes in gene expression in the medial prefrontal cortex (mPFC) promote drug-seeking or develop as a compensatory mechanism to oppose drug reward. These changes occur in part through epigenetic mechanisms such as histone acetylation and deacetylation, which changes chromatin structure through post-translational modifications. Expression of a nuclear-localized Histone Deacetylase 5 (HDAC5) in the nucleus accumbens (NAc) reduces drug seeking after cocaine self-administration (SA). However, the role and regulation of HDAC5 in addiction-relevant NAc efferents has not been investigated. We tested the hypothesis that nuclear HDAC5 in the prelimbic (PrL) cortex, a subregion of the mPFC associated with the promotion of drug-seeking behavior, would decrease cocaine-seeking, but have an opposing role in a related subregion, the infralimbic cortex (IL). We found that

expression of nuclear HDAC5 in the PrL augmented cocaine SA behavior, but it suppressed context-related drug seeking without altering cued or cocaine-primed reinstatement of drug seeking following extinction training. Interestingly, no significant effects on cocaine SA behavior were observed in rats expressing nuclear HDAC5 in the IL. Ongoing studies are investigating the role of the HDAC5 target gene, *Npas4*, in cocaine SA, and the possibility that HDAC5 in the PrL might regulate cocaine-context associations via regulation of NPAS4. Together our findings suggest that HDAC5 plays a region-specific role in the mPFC to regulate cocaine SA in a context-dependent manner, and ongoing studies will elucidate the mechanisms through which this regulation occurs.

Disclosures: S.M. Barry: None. **N. Agnihotri:** None. **J.D. Wolfe:** None. **M. Taniguchi:** None. **C.W. Cowan:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

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Title: The cell type-specific role of nucleus accumbens NPAS4 in cocaine-conditioned behaviors

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Abstract: Substance use disorder is a chronic, relapsing behavioral disorder that is characterized by compulsive drug seeking and use despite negative consequences to the individual. During the course of drug use, persistent neuroadaptations develop in the nucleus accumbens (NAc), a brain region predominately composed of dopamine D1 receptor- and D2 receptor-expressing medium spiny neurons (MSNs) and whose activity is associated with reward and motivation. The progression from casual drug use to abuse is mediated in part by the strong association between the rewarding effects of the drug and the environmental contexts and cues linked to drug use experiences. As such, these external cues can become powerful triggers for relapse in abstinent addicts. However, the molecular and cellular mechanisms underlying these drug-context memories are not well understood. One possible regulator of neuroadaptations in the NAc responsible for drug reward-related learning is the activity-dependent transcription factor, neuronal PAS Domain Protein 4 (NPAS4). In the forebrain, NPAS4 regulates excitatory and

inhibitory synapse balance and synaptic transmission in a cell type-dependent manner. Here, we show that following exposure to a novel drug-paired environment, a small population of NAc neurons induce NPAS4 and, of those, ~50% are D1R- or D2R-expressing MSNs. Cell type-specific reduction of NPAS4 in the adult NAc, using a cre-dependent shRNA virus in D1- or D2-cre mice, revealed a critical role for NPAS4 in D2-MSNs for cocaine reward-context learning and memory without altering sensitivity to cocaine-induced locomotor responses and sensitization. In addition, ongoing studies reveal important roles for NPAS4 in MSN synaptic transmission. Together, our current findings suggest an important cell type-specific role for NPAS4 in the NAc for regulating the development of drug reward-context associations.

Disclosures: B.W. Hughes: None. **M. Taniguchi:** None. **C.W. Cowan:** None.

Poster

597. Cocaine: Behavior, Circuits, and Mechanisms

Location: Hall A

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ControlExtraData.DynamicPosterDisplay:
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Topic: I.08. Methods to Modulate Neural Activity

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Title: Double dissociation of two PPTg neuron populations mediating prepulse inhibition and reward

Authors: *N. FULCHER, E. AZZOPARDI, C. DE OLIVEIRA, R. HUDSON, S. LAVIOLETTE, S. SCHMID;
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Abstract: The pedunculopontine tegmental nucleus (PPTg) is a complex structure involved in many innate functions, such as arousal, reward association, and sensorimotor gating. Accordingly, PPTg neurons project to a host of brain regions, including the basal ganglia, the ventral tegmental area (VTA) and the pontine reticular formation. The PPTg is a cholinergic structure, however, it also contains a considerable number of glutamatergic and GABAergic neurons. It has also been assumed for a long time that cholinergic projections to the reticular formation mediates sensorimotor gating, i.e. prepulse inhibition (PPI) of the startle response. PPI deficits accompany many neuropsychiatric illnesses, such as schizophrenia, autism spectrum disorder (ASD), and Tourette's Syndrome, yet underlying mechanisms are unclear. Additionally, literature suggests that cholinergic PPTg projections to the VTA mediate opioid-induced

dopamine activation via VTA M5 muscarinic receptors. While prior studies find chronic lesions of PPTg neurons block conditioned place preference (CPP) and disrupt PPI and, we and others provide recent evidence that transient selective inhibition of PPTg cholinergic neurons does *not* alter PPI. Here, we aim to further decipher the differential role of PPTg glutamatergic and cholinergic neurons in reward association and PPI by intracranially delivering cholinergic- or glutamatergic-neuron specific inhibitory DREADDs bilaterally into the rat PPTg. Subjects were tested for startle, PPI, and morphine-induced CPP after receiving an i.p. injection of DREADD activator, clozapine-N-oxide (CNO), or saline (control). We provide evidence that DREADD inhibition of cholinergic PPTg neurons does not disrupt PPI, but impedes the acquisition of morphine-induced CPP. In contrast, transient inhibition of glutamatergic PPTg neurons significantly disrupts PPI, but has no effect on the acquisition of morphine-induced CPP. Our results highlight, for the first time, a double dissociation between the role of PPTg glutamatergic and cholinergic neuron populations in reward association versus sensorimotor gating. It further corroborates the evidence that cholinergic PPTg neurons do *not* mediate PPI, suggesting that instead glutamatergic PPTg neurons mediate PPI.

Disclosures: **N. Fulcher:** None. **E. Azzopardi:** None. **C. De Oliveira:** None. **R. Hudson:** None. **S. Schmid:** None. **S. Laviolette:** None.

Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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NIDA-IRP (ES)
DA023248 (CSL)
DA044749 (CSL)

Title: Lower insula gray matter volumes in females (but not males) with cocaine use disorder: Data from the Enigma Addiction Working Group

Authors: *R. A. RABIN[1], S. MACKEY[3], M. A. PARVAZ[2], H. GARAVAN[4], C.-S. R. LI[5], G. PEARLSON[6], L. SCHMAAL[7], R. SINHA[8], E. A. STEIN[9], D. VELTMAN[10], N. ALIA-KLEIN[2], R. GOLDSTEIN[11];
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Abstract: Introduction: Despite lower rates of cocaine use disorder (CUD), females experience a more severe course of the disorder, have greater difficulty quitting, and are at increased risk for relapse following abstinence compared to males. Notably, sex differences in addiction have not only been reported clinically, but also in the context of neural responses to cue-induced craving and stress reactivity. Neuroanatomical alterations may underlie sex differences given that gray matter volume (GMV) varies in select brain areas between males and females (e.g., limbic regions). This study applied voxel-based morphometry to investigate potential sex differences in GMV using the largest prospective sample of individuals with CUD derived from the ENIGMA Addiction Consortium.
Method: Structural T1-weighted MRI scans and clinical data were pooled from 7 sites. Participants received a clinical interview for DSM Axis I Disorders; CUD participants met for cocaine dependence. The final sample was 420 sex- and age-matched (mean age= 37.7±9.8) participants: CUD males (CUDM, n=140); CUD females (CUDF, n=70); control males (CTLM, n=140); control females (CTLF, n=70). Images were prepared for voxel-based morphometry with modulation using the CAT12/SPM12 toolbox. Differences in GMV were assessed using a 2×2 (sex by diagnosis) ANCOVA that included age, total intracranial volume, and site as covariates. Variables that differed between groups and correlated with GMV regions showing significant interaction effects were also included as covariates (education, race). Whole-brain voxel-wise linear regressions were conducted to explore relationships between GMV and lifetime cocaine use. The voxel-wise threshold was $p<0.001$ uncorrected with clusters >50 contiguous voxels and family-wise error (FWE) rate of $p<0.05$ cluster-level corrected.
Results: Significant GMV diagnosis differences were replicated in frontal regions, inferior temporal gyrus, and supplementary motor cortex (CUD<controls). The sex × diagnosis interaction revealed lower left anterior insula (x=-32, y=23, z=8, $p_{FWE}=0.013$) and left lingual gyrus (x=-2, y=-84, z=-8, $p_{FWE}=0.007$) GMV in CUDF compared to CTLF but not in males. A whole-brain negative relationship emerged between cocaine use and GMV in the right hippocampus (x=36, y=-36, z=-12, $p_{FWE}=0.003$) in CUDM, but not CUDF.
Conclusion: Given the importance of the insula to interoception and the hippocampus to extinction of no-longer rewarded associations and craving, results suggest differential sexually dimorphic mechanisms may be associated with cocaine addiction. The development of gender-tailored interventions for CUD remains to be explored.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Topic: G.08. Drugs of Abuse and Addiction

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Title: Psychophysiological and neural correlates of cognitive reappraisal mediated down-regulation of attention to drug-related cues in addicted individuals and the role of negative emotionality

Authors: *P. MALAKER, R. A. RABIN, N. ALIA-KLEIN, R. Z. GOLDSTEIN, M. A. PARVAZ;
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Abstract: Background: Cognitive reappraisal (CR), an adaptive technique associated with personality traits through which the value and emotional impact of stimuli are modified through self-distancing or reinterpretation, has shown to be effective in down-regulating biased attention to drug-related cues in addicted individuals. Reduction of EEG-derived late positive potential (LPP) amplitude has previously shown to track CR-mediated down-regulation of drug cue-reactivity. While its neural underpinnings using task-related functional MRI have been explored, the underlying structural integrity of these neural correlates in addicted individuals is still not well understood. **Methods:** EEG data was collected on 30 individuals with cocaine use disorder (iCUD) and 28 healthy controls (HC) during a CR task. CR was measured as the difference in LPP between 'Look' (i.e., passive viewing) and 'Decrease' (i.e., down-regulation using CR) conditions. Separately, T1-weighted MRI scans were also acquired on 29 iCUD and 26 HC and regional gray matter volumes (GMV) were assessed using voxel-based morphometry. Whole-brain regression was conducted to investigate the relationship between extent of CR (LPP amplitude difference) and GMV. In addition, given prior associations with both CR and regional GMV, moderation effects of trait negative emotion (NEM; assessed via Multidimensional Personality Questionnaire-Brief Form) on LPP - GMV association were also explored. **Results:** Whole-brain group by LPP amplitude difference interaction revealed that greater down-regulation of drug cue-reactivity via CR (increased LPP difference) was positively associated with higher GMV in the right orbitofrontal gyrus (p_{FDR}=0.004), inferior frontal gyrus (p_{FDR}=0.019), post-central gyrus (p_{FDR}=0.021), cuneus (p_{FDR}=0.005), and left thalamus (p_{FDR}=0.014) in iCUD compared to HC. Additionally, thalamic GMV in iCUD was negatively correlated with NEM ($p<0.001$), and the moderation analysis revealed that iCUD with lower

NEM demonstrated a stronger association between CR and thalamic GMV (p=0.002). **Conclusions:** We show that greater structural integrity of regions typically implicated in cognitive control, value attribution and mindfulness is also associated with improved CR of drug-related cues in iCUD. In addition, iCUD with lower NEM showed stronger thalamic GMV-LPP association. These results highlight the importance of morphological integrity of select brain regions, and emotional functioning in the ability to use CR to down-regulate attention, perhaps via a corticothalamic pathway, to drug-related cues in iCUD.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Topic: G.08. Drugs of Abuse and Addiction

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Title: Lorcaserin inhibits cocaine-induced changes in brain functional connectivity

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Abstract: The 5HT2C/2A agonist lorcaserin has been shown to attenuate the abuse-related behavioral effects of drugs of abuse; however, little is known about its underlying neural mechanisms. The present study aimed to determine the neural correlates of lorcaserin's effects in nonhuman primates self-administering cocaine during functional magnetic resonance imaging (fMRI) sessions. Three adult rhesus macaques (2 male, 1 female) were trained to self-administer intravenous cocaine in a mock MRI scanner under a fixed ratio 3 schedule of reinforcement. During test sessions, monkeys were transported to a 3.0 Tesla MRI scanner in which they could earn two injections of 0.1 mg/kg/inj cocaine during a 30-min scan session. The effects of pretreatment with 1.0 mg/kg lorcaserin on cerebral blood volume (CBV) response to self-administered cocaine was analyzed in two ways: (1) using an empirically derived pharmacological regressor (phMRI) to elucidate patterns of neural activation in response to bolus cocaine injections, and (2) using a seed-based approach centered in the bilateral putamen to determine alterations in functional connectivity following cocaine self-administration. Results found that all subjects self-administered both cocaine injections during all scan sessions. The CBV response to cocaine injections indicate functional inhibition of putamen, motor/pre-motor cortex, prefrontal areas, and temporal regions. Cocaine self-administration also altered functional connectivity with increased connectivity observed between the putamen and other striatal regions

(e.g., nucleus accumbens, caudate), and decreased connectivity between putamen and regions involved in motoric and/or cognition-related behavior (e.g., primary motor cortex and anterior cingulate). Pretreatment with lorcaserin did not appreciably alter the pharmacologic response to cocaine but did alter cocaine self-administration-induced changes in putamen functional connectivity. Specifically, lorcaserin attenuated the increased striatal connectivity and also decreased putamen connectivity with insula following cocaine self-administration. These results suggest that lorcaserin may not alter the direct pharmacological effects of cocaine but rather, disrupt processing of information related to pharmacological stimuli.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Support: DA041668

Title: Tmod2 is a regulator of cocaine responses through control of striatal and cortical excitability, and drug-induced plasticity

Authors: *V. KUMAR[1], A. MITRA[1], S. P. DEATS[1], P. E. DICKSON[2], B. J. NIEMAN[3], J. ZHU[4], N.-P. TSAI[5], E. J. CHESLER[2], Z.-W. ZHANG[2];
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Abstract: Drugs of abuse induce neuroadaptations, including synaptic plasticity, that are critical for transition to addiction, and genes and pathways that regulate these neuroadaptations are potential therapeutic targets. *Tropomodulin 2* (*Tmod2*) is an actin-regulating gene that plays an important role in synapse maturation and dendritic arborization and has been implicated in substance-abuse and intellectual disability in humans. Here we mine the KOMP2 data and find that *Tmod2* knockout mice show emotionality phenotypes that are predictive of addiction. Detailed addiction phenotyping showed that *Tmod2* deletion does not affect the acute locomotor response to cocaine administration. However, sensitized locomotor responses are highly attenuated in these knockouts, indicating a potential lack of necessary drug-induced plasticity. In addition, *Tmod2* mutant animals do not self-administer cocaine indicating lack of hedonic responses to cocaine. Whole brain MR imaging shows differences in brain volume across multiple regions although transcriptomic experiments did not reveal perturbations in gene co-expression networks. Detailed electrophysiological characterization of *Tmod2* KO neurons,

showed increased spontaneous firing rate of early postnatal and adult cortical and striatal neurons. Cocaine-induced synaptic plasticity that is critical for sensitization is either missing or reciprocal in *Tmod2* KO nucleus accumbens shell medium spiny neurons, providing a mechanistic explanation of the cocaine response phenotypes. Combined, these data provide compelling evidence that *Tmod2* is a major regulator of plasticity in the mesolimbic system and regulates the reinforcing and addictive properties of cocaine.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Support: NIH IRP

Title: Prior cocaine self-administration differentially alters state encoding in distinct dorsomedial striatal neuron populations in rats

Authors: *L. MUELLER[1,2], A. M. WIKENHEISER[3], M. SHARPE[3], D. M. DIETZ[2], T. A. STALNAKER[1], G. SCHOENBAUM[1];
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Abstract: When the rules that govern our actions change, it is useful to learn about the new situation in a way that preserves old learning, building a library of associations that can be deployed as needed to match the current context. One way to achieve this is to compartmentalize learning about different contexts into distinct “states”, each containing information relevant to a particular scenario. Using inputs from the orbitofrontal cortex, cell populations within the dorsomedial striatum (DMS), including medium spiny neurons (MSNs), fast-spiking interneurons (FSIs), and cholinergic interneurons (CINs), work together to maintain such state-specific rules. Since drugs of abuse are known to disrupt state-dependent behaviors and decision making, neural encoding of state within the DMS may be impaired by drug exposure.
Here, we assessed how a history of cocaine self-administration affected neural representations of state in MSNs and FSIs, the major cell populations of the DMS. Single-unit activity was recorded from rats that had self-administered either sucrose or cocaine for several weeks prior to recording. Units were recorded while rats performed an odor-guided decision making task comprised of two blocks of trials, or “states”. In one state, odor cues were delivered to a central port and signaled the availability of a large reward from one fluid well and a small reward from

another well. In the second state, the odor-reward size contingencies were reversed. We found that cocaine-experienced rats were slower to adjust responding for large rewards following a state change as compared to sucrose-experienced controls. This behavioral change was accompanied by differences in state encoding by DMS MSNs and FSIs. Prior to odor onset, MSNs in the cocaine-experienced group exhibited decreased trial type classification accuracy, suggesting a loss of state representation relative to sucrose controls. However, following odor onset, FSIs in the cocaine group displayed increased trial type classification accuracy, demonstrating enhanced outcome representation. Together, these results indicate that DMS state encoding is disrupted by cocaine experience. These findings are consistent with a role for DMS cell populations in the regulation of behavioral flexibility and suggest that alterations in task encoding may contribute to the poor decision-making observed in individuals following exposure to drugs of abuse.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Title: Role of anterior dorsal lateral hypothalamic area perineuronal nets in VTA neuron excitability

Authors: *J. M. BLACKTOP[1], B. A. SORG[2], J. T. WILLIAMS[3], S. L. INGRAM[4];
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Abstract: Addiction involves drug-induced neuroplasticity of the circuitry for motivated behavior, which includes the medial forebrain bundle and the lateral hypothalamic area (LHA). Emerging at the forefront of neuroplasticity regulation are specialized extracellular matrix structures that form perineuronal nets (PNNs) around parvalbumin positive (PV^+) fast-spiking interneurons, making them a promising target for the regulation of drug-induced neuroplasticity. We previously reported that the dorsal anterior lateral hypothalamic area (LHAad) exhibits robust PNN expression using the PNN marker *Wisteria floribunda* agglutinin (WFA), and that approximately two-thirds of WFA positive neurons co-expressed PV. Removal of PNNs with the enzyme chondroitinase ABC (Ch-ABC) blocks the acquisition of cocaine- but not sucrose-

induced behavior (conditioned place preference and self-administration) and cue-induced reinstatement of cocaine- but not sucrose-seeking behavior. LHAad PNN-surrounded neurons receive dense glutamatergic input and are predominantly GABAergic. The LHAad receives robust prelimbic prefrontal cortex (PL PFC) input, while providing moderate input into both the PL PFC and ventral tegmental area minimal input into the nucleus accumbnes. The overarching hypothesis is that PNNs in the LHAad are a necessary substrate for drug-induced plasticity. One possible mechanism by which LHAad PNN removal inhibits cocaine-induced behavior is increasing VTA dopamine neuron inhibition. The goal of this first set of experiments is to determine if LHAad neurons project onto DA or non-DA neurons of the VTA, if these projections are GABAergic or glutamatergic, and whether PNN-removal alters the activity of this projection. Here we report 1) the effects of light-activated Chronos-induced LHAad terminal excitation of VTA neurons, and 2) the effect of LHAad PNN-removal on excitation of VTA neurons. The results of these studies will define the circuit at cellular and synaptic levels to provide a better understanding of the mechanisms underlying PNN modulation of drug-seeking behaviors.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Title: Perineuronal net removal in the rat medial prefrontal cortex alters cocaine reinstatement and fast-spiking interneuron excitability

Authors: *E. T. JORGENSEN[1], A. N. TOURTELLOT[1], J. A. AADLAND[1], T. E. BROWN[2]; [1]Neurosci., [2]Sch. of Pharm., Univ. of Wyoming, Laramie, WY

Abstract: Our laboratory is interested in the molecular underpinnings that mediate pervasive drug memories. Perineuronal nets (PNNs) are specialized extracellular matrix structures that primarily surround parvalbumin-containing fast-spiking interneurons (FSI). Our research group previously published that removal of PNNs within the medial prefrontal cortex (PFC) attenuates cocaine-induced reinstatement of cocaine-conditioned place preference (cocaine-CPP) and increases the firing rate of pyramidal neurons within the prelimbic PFC. Our on-going research suggests that PNNs have a time-dependent effect on modulating firing activity of FSIs to

influence pyramidal neuron activity. Rats underwent cocaine-CPP training and extinction. After meeting extinction criteria, rats were microinjected into the prelimbic PFC 3d prior to cocaine-induced reinstatement with either vehicle or chondroitinase ABC (ch-ABC) to degrade PNNs. This procedure has shown to previously reduce cocaine-CPP. 2 hr following reinstatement, brain slices containing the mPFC were prepared for whole-cell electrophysiological recordings. PNN degradation resulted in an attenuation in the number of current-induced action potentials (APs) (vehicle: 99.0±7.31; ch-ABC: 53.33±1.43). In addition, we found significant changes in both the halfwidth and afterhyperpolarization potential (AHP) of APs in FSIs following ch-ABC treatment when compared to controls. Differences in these specific intrinsic properties suggest that there could be alterations in the currents responsible for the AHP and halfwidth. Through this work, we aim to further identify how PNNs are altering intrinsic and synaptic transmission following cocaine-associated learning, which contributes to persistent drug craving.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Program #/Poster #: 598.08/W38

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Support: KAKENHI 18K06520

Title: Acute restraint stress augments the rewarding effect of cocaine through the activation of α1 adrenoceptors in the medial prefrontal cortex of mice

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Abstract: Stress augments cocaine craving in addicted individuals. To elucidate neural mechanisms underlying this effect of stress, we have developed an experimental paradigm combining cocaine-induced conditioned place preference (CPP) test with restraint stress in mice. After cocaine conditioning, acute (30 min) restraint stress exposure immediately before posttest significantly increased cocaine CPP scores. During stress exposure, the level of extracellular noradrenaline (NA) has been reported to be increased in the medial prefrontal cortex (mPFC). Thus, we hypothesized that NA in this brain region plays a critical role for stress-induced

augmentation of cocaine CPP. Whole-cell recordings from layer V pyramidal cells in mPFC slices demonstrated that bath-application of NA induced depolarization and increased frequency of excitatory postsynaptic currents (EPSCs). Blockade of α1, but not α2 or β, adrenoceptor suppressed these excitatory effects of NA. Additionally, NA did not increase EPSC frequency in the presence of tetrodotoxin, suggesting that the effects of NA are mediated by a postsynaptic mechanism. Intra-mPFC injection of an α1 adrenoceptor antagonist reduced the stress-induced enhancement of cocaine CPP. Moreover, silencing the neuronal activity of mPFC pyramidal cells with DREADD attenuated the stress-induced enhancement of cocaine CPP. Taken together, our findings suggest that stress-induced increase in NA transmission excites pyramidal cells in the mPFC via α1 adrenoceptor stimulation, resulting in the enhancement of cocaine craving.

Disclosures: **S. Wada:** None. **J. Yanagida:** None. **H. Sasase:** None. **T. Zhang:** None. **H. Kamii:** None. **M. Domoto:** None. **X. Li:** None. **S. Deyama:** None. **E. Hinoi:** None. **A. Yamanaka:** None. **N. Nishitani:** None. **K. Nagayasu:** None. **S. Kaneko:** None. **M. Minami:** None. **K. Kaneda:** None.

Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 598.09/W39

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA034684
NIH Grant MH095972

Title: Cocaine extinction induces dendritic spine alterations in projection-specific sub-populations in the rat infralimbic cortex

Authors: *K. NETT[1], S. A. ROMIG-MARTIN[2], J. J. RADLEY[2], R. T. LALUMIERE[2]; [1]Interdisciplinary Grad. Program in Neurosci., [2]Dept. of Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA

Abstract: Prior studies suggest ventral medial prefrontal cortex (mPFC), known as the infralimbic cortex (IL), mediates the extinction and inhibition of cocaine seeking, particularly through a small population of projections to the nucleus accumbens (NA) shell. Previous work from our laboratory indicates cocaine self-administration, but not passive receipt of cocaine, induces regressive plasticity within the dorsal mPFC, as indicated by dendritic spine density reductions in pyramidal neurons. These results suggest an intersection between cocaine itself and learned instrumental behavior in terms of prefrontal plasticity. However, it is unclear whether similar changes occur in the IL and whether extinction training reverses or further alters dendritic plasticity in the IL. Moreover, it is unknown whether structural alterations induced by behavior

globally affect dendritic plasticity within the IL or specific subpopulations of projection neurons. To address this issue, male Sprague-Dawley rats (250-275 g) received bilateral microinjections of a retrograde virus containing a GFP tag into the NA shell and were implanted with intrajugular catheters. Rats then underwent two weeks of daily 6 h cocaine self-administration, in which active lever presses produced a cocaine infusion (400 μg/infusion) and light/tone cues, or served as yoked-saline controls. Rats then underwent 3 weeks of extinction training (1 h per day), in which active lever presses had no consequence, or 3 weeks of homecage withdrawal, prior to being euthanized. We then used an intracellular dye cell-loading technique to fill NAshell-projecting IL pyramidal neurons with Lucifer yellow. Neurons were imaged with 3D confocal imaging followed by deconvolution and analysis using NeuronStudio software to classify individual spine subtypes, quantify each subtypes' density on basal, proximal and distal dendrites, and analyze spine clustering. Preliminary results suggest that extinction learning rescues reductions in dendritic spine density and clustering that are observed following cocaine self-administration and withdrawal. Specifically, this rescue effect was observed only in IL neurons that project to NA shell. Ongoing work is determining the extent of these changes and whether the behavioral manipulations differentially alter specific subtypes. These findings point to an important interplay between cocaine self-administration and behavioral training that can alter and reverse plasticity within the mPFC in a functionally specific manner. Moreover, as spine morphology alterations often accompany learning events, these changes may be indicative of extinction encoding.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

Location: Hall A

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Program #/Poster #: 598.10/W40

Topic: G.08. Drugs of Abuse and Addiction

Support: R01AA023183
R01DA037294
T32 AA007456
NIAAA R21 021549

Title: Neuronal activity-based brain-wide profiling of relapse-promoting and relapse-suppressing afferents to the infralimbic cortex in rats trained to self-administer cocaine or ethanol

Authors: *H. NEDELESCU[1], G. E. WAGNER[1], H. C. CHANG[1], G. DE NESS[1], A. CARROLL[1], Y. LIU[1], A. THAN[1], C. RICHIE[2], B. T. HOPE[3], F. WEISS[1], N. SUTO[1];
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Abstract: Environmental cues modulate appetitive behavior, an effect that extends to maladaptive behaviors including drug addiction. In the context of addiction, environmental cues predictive of drug availability can promote learned drug seeking responses; conversely, environmental cues predictive of drug non-availability can suppress this behavior. This bidirectional modulation of drug-motivated behavior is mediated by two distinct coactive groups of neurons - neuronal ensembles - within the infralimbic cortex (IL). These two IL neuronal ensembles are reactive selectively to either relapse-promoting or relapse-suppressing cues. However, the neuroanatomical source of afferents that activate these ensembles remains unknown. To address this gap in knowledge, we conducted brain-wide neuroanatomical analysis to identify neuronal ensembles that project to IL and that are differentially reactive to relapse-promoting or relapse-suppressing cues. To this end, we first delivered a retrograde tracer (AAV2retro) into the IL in order to identify somata and their axonal projections with direct input to the IL. We then trained the rats to press a lever for cocaine or alcohol. Next, drug availability and non-availability was conditioned to the presence of distinct environmental cues. While the cue predictive for drug availability promoted lever-pressing, the cue predictive for drug non-availability suppressed drug-seeking behavior. After behavioral testing, we used Fos to identify the IL afferent ensembles that were reactive to either the cue predictive of drug availability or the cue predictive to drug non-availability. We found IL-projecting Fos-expressing ensembles in different brain areas that were selectively activated by either relapse-promoting or relapse-suppressing cues. Together, this study expands our current knowledge of cue-reactive IL neuronal ensemble circuitry contributing to cocaine- and alcohol-seeking behavior.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

Location: Hall A

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA033436
NIH Grant GM118272
NIH Grant DA037270

Title: The effects of cocaine self-administration and ceftriaxone on nucleus accumbens GLT-1 trafficking

Authors: *Y. PADOVAN HERNANDEZ, L. A. KNACKSTEDT;
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Abstract: Ceftriaxone is a beta-lactam antibiotic which increases the expression and function of the glutamate transporter GLT-1. We have demonstrated that expression of GLT-1 is decreased in the nucleus accumbens core (NAc) following extinction from cocaine self-administration. We have also shown that ceftriaxone attenuates cue- and cocaine-primed reinstatement while restoring GLT-1 in the NAc. While there is evidence that ceftriaxone upregulates GLT-1 mRNA in cell cultures continually treated with ceftriaxone, we recently found that neither cocaine self-administration itself or the later treatment with chronic ceftriaxone altered NAc GLT-1 mRNA. Here we utilized proteomic approaches to decipher the mechanism of action of both cocaine and ceftriaxone in the NAc following cocaine self-administration and extinction. Male Sprague-Dawley rats self-administered intravenous cocaine or received yoked-saline infusions for 12 days. Rats underwent extinction training for 21 days. During the last 6 days of extinction, half of the cocaine rats and half of the saline rats received ceftriaxone (200 mg/kg IP) immediately after the extinction session, while the remaining rats received vehicle. Rats were euthanized 24-hrs following the last ceftriaxone/vehicle injection, in agreement with the timing of our previous assessments of behavioral and molecular effects of ceftriaxone treatment. The NAc was dissected and frozen for global proteomic analysis. In a separate group of rats, following NAc dissection, tissue underwent immunoprecipitation of GLT-1 or tandem ubiquitin binding entities. In agreement with the publications of our labs and others, following cocaine, ceftriaxone downregulated proteins associated with glutamate signaling and long termdepression. Novel pathways for ceftriaxone action included clathrin mediated endocytosis and ubiquination. Follow-up immunoprecipitation and western blotting established that surface, intracellular and total protein expression of GLT-1 is reduced by cocaine and restored by ceftriaxone. Ubiquitin c-terminal hydrolase-1 was reduced by cocaine and restored by ceftriaxone, indicating a potential mechanism underlying the changes in GLT-1 expression. In conclusion, we have identified both novel and established pathways as being affected by ceftriaxone in rats with a history of cocaine self-administration. Future work will determine mechanistic roles for these pathways in the ability of ceftriaxone to attenuate cocaine reinstatement.

Disclosures: Y. Padovan Hernandez: None. **L.A. Knackstedt:** None.

Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 598.12/W42

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH R01 DA034684

Title: Characterization of infralimbic cortical neurophysiological dynamics during the extinction of cocaine-seeking behavior in rats

Authors: *V. A. MULLER EWALD, J. KIM, R. T. LALUMIERE;
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Abstract: Prior work has implicated the infralimbic cortex (IL) in the consolidation of extinction learning following cocaine self-administration. However, most studies investigating this role for the IL have *manipulated* this cortical region, and little work has *observed* IL activity during the extinction of cocaine seeking. To determine how activity in the IL relates to the extinction of cocaine-seeking behavior, we used *in vivo* electrophysiology to record from the IL of behaving rats as they underwent extinction training. Male Sprague-Dawley rats (250 - 275 g) underwent surgery for implantation of an intravenous catheter and a fixed 9-channel electrode array aimed at the IL. Animals then underwent cocaine self-administration for a minimum of 15 d. During self-administration, animals lever pressed for cocaine in 30s epochs during which the lever remained extended (availability window). If animals failed to respond within this availability window, the lever was retracted and an intertrial interval ensued. Extinction training directly followed self-administration and lasted a minimum of 5 d. During extinction, lever presses did not produce cocaine infusions. Neural recordings were conducted every day, and data were analyzed for the early, middle and late extinction time points. Single unit findings indicate largely separate subpopulations of IL units that are responsive to lever presses and availability-window onset. Local field potential findings indicate theta-band oscillations in the IL throughout the task during all extinction time points, suggesting the importance of hippocampal inputs into this region throughout extinction training. Spectrogram analyses revealed increases in theta power following availability-onset, which were especially prominent during early extinction training. Together with prior work using brain-based manipulations, these findings suggest that IL activity guides behavioral outcomes during extinction of cocaine-seeking behavior.

Disclosures: V.A. Muller Ewald: None. **J. Kim:** None. **R.T. LaLumiere:** None.

Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 598.13/W43

Topic: G.08. Drugs of Abuse and Addiction

Support: Netherlands Organisation for Scientific Research (NWO) grant ,project number 019.163LW.011

Title: Escalation of cocaine self administration requires norepinephrine

Authors: *H. BELDJOUD, G. DE GUGLIELMO, M. KALLUPI, O. GEORGE;
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Abstract: Understanding how and what are the changes in neuronal plasticity that underlie the switch from a regular drug intake to inadaptive compulsive, drug intake is critical for investigating any potential drug treatment. Although there is no doubt that the reward aspect of drug addiction is mediated by dopamine, we still need to consider how other neuromodulators such as norepinephrine might modulate these primary dopaminergic effects. The aim of this study was to interfere with the escalation of cocaine intake, a model of cocaine dependence, and disturb the development of dependence by the administration of the β−adrenergic receptor antagonist propranolol. Rats acquired cocaine self-administration with 2 h daily access for 5 days after which two groups, equated for acquisition levels, were defined according to treatments prior to sessions, and switched to 6h self-administration for an additional 15 days. In the first phase one group of rats was treated with Propranolol, before the start of each 6h session, whereas the control group received saline. Upon completion of phase 1, the treatment was switched: half of the rats from the saline group then received propranolol instead of saline, and the previous propranolol group was switched to saline treatment. The motivation for cocaine was also tested. In order to control for propranolol effects on a natural reward, another group of rats was trained to press for saccharin solution. Then, underwent the same experimental procedure and propranolol treatment as for cocaine. Results Following acquisition, the control group displayed a robust escalation of cocaine intake whereas, the propranolol prevented the escalation and maintained a lower cocaine intake as well as a lower motivation to cocaine. The Saline group that subsequently was switched to propranolol did not show any significant variation when compared to controls. Switching the propranolol group to saline increased cocaine intake without reaching the intake level of the escalated cocaine group. The motivation for cocaine was maintained lower long after propranolol treatment was stopped. Propranolol had no effect on saccharin rewards and did not alter the motivation for it. Conclusions Propranolol prevented cocaine escalation and the motivation for cocaine. The propranolol effect was restricted to escalation. Propranolol reduced the motivation for cocaine and this effect was maintained long after propranolol treatment was stooped. These results show that propranolol, had affected the neuronal plasticity related to the escalation and the motivation for cocaine intake without affecting the hedonic property of cocaine.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 598.14/W44

Topic: G.08. Drugs of Abuse and Addiction

Support: BBRF NARSAD Young Investigator Award #22811

Title: Epigenetic effects of sex and early-life stress on cocaine addiction vulnerability

Authors: D. ROCKS[1], I. JARIC[1], D. SHOSHAN[1], J. M. GREALLY[2], M. SUZUKI[2], ***M. KUNDAKOVIC**[1];
[1]Dept. of Biol. Sciences, Fordham Univ., Bronx, NY; [2]Ctr. for Epigenomics, Dept. of Genetics, Albert Einstein Col. of Med., Bronx, NY

Abstract: Early-life stress, such as neglect and abuse, increases the risk for drug abuse and addiction in later life. In addition, there are sex differences in cocaine addiction with females progressing more rapidly into substance use disorder, which is at least in part related to estrogen effects. The mechanisms underlying stress- and sex hormone-induced addiction vulnerability are poorly understood although epigenetic mechanisms provide a plausible candidate. To address this question, we performed the early-life stress (maternal separation) paradigm in mice from postnatal day (PD) 1-14 and examined the risk for cocaine addiction in later life (PD50-60) using cocaine-induced conditioned place preference (CPP). Our study shows that early-life stress increases cocaine preference in a dose- and sex-dependent manner. Male mice exposed to early-life stress show increased cocaine CPP after a low (2.5 mg/kg) cocaine dose that is not sufficient to induce cocaine preference in control males. On the contrary, both low (2.5 mg/kg) and high (10 mg/kg) cocaine doses have a more profound effect in stress-exposed female mice compared to control females. Interestingly, we found that the cocaine CPP results in females vary with the estrous cycle, with early-life stress shifting this behavior in favor of increased cocaine preference. To address whether epigenetic mechanisms may be involved in sex-specific cocaine effects, we performed chromatin accessibility (ATAC-seq) assay on purified neuronal nuclei isolated from the nucleus accumbens of proestrus (high-estrogenic) females, diestrus (low-estrogenic) females, and male mice following 1-hour and 4-hour cocaine (10 mg/kg) treatments. We found sex-specific chromatin organizational changes in response to cocaine, which included the loci nearby genes implicated in the reward pathway and cocaine addiction. The glutamate transporter 1 gene (Glt1, *Slc1a2*), which is strongly implicated in addiction, showed a sex-specific chromatin accessibility profile both at baseline and following cocaine exposure, and this was associated with a sex difference in Glt1 gene expression. This study has implications for improving our understanding of the role of early-life stress in addiction vulnerability and reveals a candidate epigenetic mechanism underlying sex differences in drug abuse and addiction.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH/NIDA Grant DA003906
NIH/NIDA Grant DA012513
NSF Grant OIA-1539034

Title: Single cell Ca^{2+} activity of dopamine D1 and D2 receptor expressing medium spiny neurons of the nucleus accumbens core during extinction and relapse of cocaine seeking

Authors: *R. M. CHALHOUB[1], C. GARCIA-KELLER[1], J. A. HEINSBROEK[2], A.-C. BOBADILLA[1], P. W. KALIVAS[1];
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Abstract: The nucleus accumbens core (NAc) plays a central role in drug addiction. Its constituent D1- and D2- expressing GABAergic medium spiny neurons (D1- and D2-MSNs) integrate cortical and limbic inputs to regulate drug seeking behavior. Recent data challenge the functional dichotomy of these cells in the direct/indirect pathways hypothesis. To investigate the functional role of D1- and D2-MSNs during drug seeking, we recorded single cell Ca^{2+} dynamics in D1- and D2-MSNs of freely behaving D1- and D2-cre transgenic mice using a miniature microscope (nVista) and virally expressed Cre-dependent Ca^{2+} indicator (GCaMP6f). Mice were trained to self-administer cocaine in daily 2 hours-session during which a single nose-poke (FR1) resulted in an intravenous cocaine injection and presentation of drug-contingent cue. Following a brief abstinence period, drug seeking was assessed during a post-abstinence test (PA), wherein cues but not cocaine were present. Drug seeking behavior was then extinguished to the cocaine-associated context over 8-10 days, before undergoing a second cue-induced reinstatement session. Calcium activity was recorded throughout representative sessions of the entire behavioral paradigm; recordings were pre-processed and normalized, and single cell calcium activity were isolated and aligned to behavioral responses (i.e. nose-pokes). We found that during PA test, individual nose-pokes were associated with a significant change in the activity of D1-MSNs. This change in activity gradually decreased in the absence of cocaine-associated cues during extinction training. In contrast to D1-MSNs, changes in Ca^{2+} activity in D2-MSNs preceded nose-pokes during PA session. D2-MSNs retained their response during extinction training, but the response pattern gradually shifted to follow the active nose-pokes. Our data suggest that NAc encodes drug-seeking behavior through an interaction between both D1- and D2-MSNs during behavioral reinstatement following abstinence. On the other hand, extinction training is associated with a sustained D2-MSNs response, and a decrease in D1-MSNs response. These data set the stage for further analyses into the population coding of drug seeking by NAcore subpopulations of neurons.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant DA034696
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NIH Grant F31-DA041767
NIH Grant T32-GM008471

Title: Dissecting the influence of D_2 dopamine and $GABA_B$ receptor signaling pathways in ventral tegmental area dopamine neurons on drug-induced behavior

Authors: *M. C. DEBAKER, E. MARRON, N. M. MCCALL, A. M. LEE, K. WICKMAN; Univ. of Minnesota Twin Cities, Minneapolis, MN

Abstract: Dopamine (DA) neurons of the ventral tegmental area (VTA) play critical roles in reward and motivation and are key targets of drugs of abuse. In addition to enhancing VTA DA neurotransmission, drugs of abuse such as cocaine engage inhibitory G protein-dependent signaling pathways mediated by D_2 DA receptors (D_2R) and $GABA_B$ receptors ($GABA_BR$) in VTA DA neurons. However, the relative influence of D_2R and $GABA_BR$-dependent signaling pathways on VTA DA neuron excitability and cocaine-related behaviors is unknown. To investigate this issue, we developed CRISPR/Cas9 tools to ablate $GABA_BR$ or D_2R in VTA DA neurons in the adult mouse. Adeno-associated viral vectors harboring guide RNAs (gRNAs) targeting either $GABA_BR$ or D_2R, or a control vector, were injected into the VTA of young adult (50 d) male and female DATCre(+):Cas9GFP^{flox} mice. Following a 5 wk viral incubation period, the impact of viral treatment on $GABA_BR$- or D_2R-dependent signaling in VTA DA neurons was assessed by measuring postsynaptic somatodendritic whole-cell currents (V_{hold} = -60 mV) evoked by the $GABA_BR$ agonist baclofen (200 µM) or the D_2R agonist quinpirole (20 µM). Currents evoked by baclofen (365 ± 50 pA, n=6) and quinpirole (59 ± 16 pA, n=4) were reliably observed in VTA DA neurons from control subjects, but were absent in neurons from mice treated with $GABA_BR$ (5 ± 1 pA, n=10; t_{14}=9.5, P<0.0001) or D_2R (4 ± 1 pA, n=5; t_7=4.0, P<0.01) gRNA, respectively. Importantly, D_2R-dependent responses were preserved in VTA DA neurons treated with the $GABA_BR$-specific gRNAs, and vice versa, confirming the specificity of the CRISPR/Cas9-mediated target ablation. Having established the efficacy and selectivity of this viral CRISPR/Cas9 approach, we are currently testing the behavioral sensitivity of mice lacking either D_2R or $GABA_BR$ in VTA DA neurons to cocaine. In preliminary studies, we have found that mice lacking $GABA_BR$ in VTA DA neurons exhibit significantly increased motor activity responses to acute systemic cocaine (15 mg/kg i.p.) compared to control subjects

($F_{3,12}$=5.8, P<0.05, Bonferroni posttest, n=3/group). We intend to use this approach to probe the impact of D_2R- and $GABA_B$R-dependent signaling in VTA DA neurons on other cocaine-induced behaviors, and to explore how these inhibitory receptors impact sensitivity to other drugs of abuse. Understanding the relative influence of D_2R- and $GABA_B$R-dependent signaling pathways on the actions of drugs of abuse may suggest drug-specific approaches for treating certain behavioral aspects of addiction.

Disclosures: M.C. DeBaker: None. **E. Marron:** None. **N.M. McCall:** None. **A.M. Lee:** None. **K. Wickman:** None.

Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 598.17/X3

Topic: G.08. Drugs of Abuse and Addiction

Title: Cocaine conditioning induces alterations in ventral hippocampal synaptic function and plasticity mediated by the presence of calcium-permeable AMPA receptors during abstinence

Authors: *C. J. PRESTON[1], K. A. BROWN[2], J. J. WAGNER[2];
[2]Dept Physiol. & Pharmacol., [1]Univ. of Georgia, Athens, GA

Abstract: We investigated the incubation of drug-seeking by utilizing an escalating i.p. cocaine dosing schedule with the conditioned place preference (CPP) paradigm to assess synaptic function and plasticity in the ventral hippocampus (vH) after various abstinence periods. CPP was achieved 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). CPP and vH function were assessed either 2, 9, or 28 days after the final injection of cocaine. When CPP was assessed after a 28 day abstinence period there was a significant increase in time spent in the cocaine-paired compartment on the second test day compared to the first test day which occurred one day after the final injection. This incubation of cocaine craving has been previously observed following self-administration of cocaine and is thought to be caused by progressive changes in synaptic function and plasticity. Slices prepared from the vH and fEPSPs were recorded in the CA1 region up to 28 days after the final injection day to assess changes in vH function during abstinence. We observed significantly decreased vH long-term potentiation (LTP) in animals that received cocaine conditioning compared to those that received the saline vehicle. Interestingly, the cocaine- treated animals also exhibited a significant leftward shift in the input-output 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 28 days after the final drug exposure (Preston et al, 2019). To further investigate this

change in basal synaptic transmission, whole-cell voltage clamp was used to record from CA1 pyramidal neurons from cocaine-treated animals after 28 days of abstinence. These neurons exhibited an increase in the rectification index compared to saline-treated animals suggesting the presence of calcium-permeable AMPA receptors (CP-AMPARs). When NASPM (a CP-AMPAR specific antagonist) was bath applied to the vH slices, there was a significant decrease in EPSC amplitude in cocaine treated animals compared to saline-treated animals. Here, we have shown a decrease in ventral hippocampal LTP and increased basal synaptic transmission associated with the presence of CP-AMPARs following 28 days of abstinence from cocaine conditioning.

Disclosures: C.J. Preston: None. **K.A. Brown:** None. **J.J. Wagner:** None.

Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Program #/Poster #: 598.18/X4

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA R01DA037327
U01DA044468

Title: The role of RMTg-mediated cocaine aversion in addiction

Authors: *M. EID[1], J. PARRILLA-CARRERO[1], H. LI[2], A. THOMAS[1], T. C. JHOU[1];
[2]Neurosci., [1]Med. Univ. of South Carolina, Charleston, SC

Abstract: Although cocaine's aversive responses are relatively less widely acknowledged than its rewarding effects, they are experimentally robust. Particularly elegant experiments by Ettenberg and his group have shown that single doses of cocaine produce an initial rewarding phase followed by an aversive crash about 15' later that is sufficient to condition a net aversion to cocaine, that in most (but not all) animals, is strong enough to overcome cocaine's rewarding effects. In our lab, we investigated behavioral responses to cocaine in rats performing a runway operant task that is particularly suited for assessing the combined rewarding and aversive properties of cocaine. In this task rats traverse a 5-foot long corridor to obtain a single daily dose of cocaine. After 4-7 trials, we found large variations in animals responses to cocaine, where some animals slowed down dramatically (high avoiders) and others remained fast (low avoiders). In recent years, our lab and others have demonstrated that cocaine avoidance depends critically on the rostromedial tegmental nucleus (RMTg) and its afferents. The RMTg is a major GABAergic midbrain input to midbrain dopamine (DA) neurons that plays major roles in avoidance. We have thus shown that there are individual differences in RMTg neurons firing rate that correlate with cocaine-conditioned avoidance behavior. Indeed, compared to low cocaine avoiders, high avoider animals have similar RMTg inhibition during the rewarding phase of the

drug (5’ post injection), but have significantly higher RMTg firing rates during its aversive phase (15’ post-infusion). To investigate the molecular driver of these differences in the RMTg, we used *in vitro* electrophysiology and demonstrated that low avoiders have less RMTg firing during the aversive phase of cocaine, partly driven by downregulation of the GluR1 subunit of the AMPA receptor. Indeed, when we inhibited this subunit pharmacologically using NASPM, all animals shift to becoming low avoiders on the runway task. These results imply the existence of a phenotypical organization of cocaine evoked plasticity in VTA projecting RMTg neurons that might be critical to signal aversion to cocaine. Thus, RMTg neurons adaptations are in a crucial position for relaying aversive information to the mesocorticolimbic DA neurons, and these changes might contribute to cocaine addiction vulnerability. We are planning on using the DLight sensor to investigate if differences in RMTg firing between high and low avoiders translate in differences in dopamine levels in the accumbens during the aversive phase of cocaine.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Program #/Poster #: 598.19/X5

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Title: Histone Deacetylase Inhibitors (HDACi) modulate biophysical properties of DA neurons in the VTA in cocaine-sensitized rats

Authors: *C. A. JIMENEZ-RIVERA[1], **D. CONSUEGRA-GARCIA**[1], C. CALO-GUADALUPE[1], K. Y. BOSQUE- CORDERO[2], F. ARENCIBIA-ALBITE[3], C. YOU[4], M. S. BRODIE[5];
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Abstract: Drugs of abuse are known to cause long-term neuroadaptations in the brain that possibly contribute to the individual's vulnerability to addiction. These modifications of brain normal function are mediated by epigenetic regulations in gene expression such as chromatin remodeling. One type of chromatin remodeling is histone acetylation, which is under the control of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Cocaine sensitization alters the intrinsic properties of dopamine (DA) neurons of the ventral tegmental area (VTA), which in turn alter dopamine transmission in the mesocorticolimbic network. One intrinsic property of VTA neurons affected by exposure of drugs of abuse is the hyperpolarization-activated cation current (Ih), which is mediated by HCN channels. Previously, our laboratory has demonstrated a reduction in Ih and cell capacitance in VTA DA neurons from cocaine-sensitized rats. Little is known about epigenetic regulation of ion channels by drug exposure. No studies of epigenetic regulation of h-current have been performed. Using the whole-cell patch clamp technique, we investigated the effects of an HDAC inhibitor (SAHA) on cocaine-induced changes in Ih current. Additionally, we explored the effect of SAHA on rebound excitation and cell capacitance in brain slices from cocaine-sensitized rats. *In vitro* incubation of midbrain slices with SAHA (3 μM for two hours) reversed the cocaine-induced reduction in VTA DA Ih to baseline levels (cocaine-control 250 ± 5.0 pA vs cocaine-SAHA 460 ± 8.3 pA, $p<0.001$). Current clamp traces also demonstrated SAHA reversal of cocaine-induced Ih reduction concomitant with a reduced action potential firing (cocaine-control 5 ± 1.4 pA vs cocaine-SAHA 1 ± 0.34 pA, $p<0.01$). Interestingly, the membrane capacitance was significantly increased in the cocaine-SAHA group (cocaine-control 112 ± 30 vs cocaine-SAHA 306 ± 6, $p<0.003$). These results support the idea that the reduction of Ih current and cell size in VTA DA neurons after cocaine sensitization is epigenetically regulated and suggest the possibility that HDAC inhibitors could reverse cocaine-induced neuroadaptations in reward circuits.

Disclosures: C.A. Jimenez-Rivera: None. **D. Consuegra-Garcia:** None. **C. Calo-Guadalupe:** None. **K.Y. Bosque- Cordero:** None. **F. Arencibia-Albite:** None. **C. You:** None. **M.S. Brodie:** None.

Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 598.20/X6

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant 2R01DA031900

Title: Cell type-specific knockdown of hypocretin receptor 1 in ventral tegmental area neurons leads to contrasting effects on dopamine responses to cocaine

Authors: *E. M. BLACK[1], D. L. BERNSTEIN[2], J. R. BARSON[1], C. E. BASS[3], R. A. ESPAÑA[1];
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Abstract: Extensive evidence indicates that the hypocretin system impacts the reinforcing effects of cocaine via actions on hypocretin receptor 1 in the ventral tegmental area. For example, our lab has shown that hypocretin receptor 1 antagonists or hypocretin receptor 1 knockdown in the ventral tegmental area decreases the motivation for cocaine and that these effects are associated with disrupted dopamine responses to cocaine. In general, these findings have been interpreted as an indication that the effects of hypocretin receptor 1 antagonism occur via actions on dopamine neurons of the ventral tegmental area. However, this assumption is complicated by the observation that hypocretin receptor 1 are located on both dopamine and GABA neurons of the ventral tegmental area where hypocretin acts in an excitatory manner on both of these neuronal populations. Consequently, it remains unknown to what extent hypocretin actions at dopamine versus GABA neurons of the ventral tegmental are necessary to drive alterations in cocaine-associated behavior and dopamine responses to cocaine. To address this gap in knowledge, we employed a combinatorial viral approach to selectively knockdown hypocretin receptor 1 on either dopamine or GABA neurons in the ventral tegmental area. We used *ex vivo* fast scan cyclic voltammetry to examine the effects of cell type selective hypocretin receptor 1 knockdown on downstream dopamine dynamics in the nucleus accumbens. Our preliminary observations suggest that knockdown of hypocretin receptor 1 on dopamine neurons leads to disrupted dopamine dynamics at baseline and reduced dopamine responses to cocaine, while knockdown of hypocretin receptor 1 on GABA neurons enhances the effects of cocaine. These findings provide a more comprehensive understanding of hypocretin modulation of dopamine neurotransmission and may uncover potential targets for future development of treatment strategies for cocaine use disorder.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Topic: G.08. Drugs of Abuse and Addiction

Support: FRM Grant DPA20140629806

Title: Dynamic dopaminergic activity during abstinence from extended- and limited-access of cocaine self-administration

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Abstract: The chronic relapsing nature of cocaine addiction suggests that chronic cocaine exposure produces persistent neuroadaptations in brain areas such as the dopaminergic system, a main actor in motivated behaviors. Throughout abstinence, neuroadaptations may be temporally and regionally dynamic. For example, early cocaine abstinence is characterized by a negative emotional state whereas with extended abstinence, the sensibility to drug-associated cues increasing leading to incubation of craving. Recent A PET-imaging study by our group (Nicolas et al., 2017) showed that the metabolism of dopaminergic-targeted structures, the nucleus accumbens and the dorsal striatum, is differentially altered after early and late abstinence, respectively. However, because of the resolution of this technique, we were not able to measure the specific changes within the midbrain dopamine system (VTA/SNc). We thus hypothesized that time and region-specific changes in the VTA and SNc dopaminergic neurons could be associated with short and long-time abstinence. Male rats had either an extended access to cocaine (Long-Access group (LgA); 6h/session) or a recreational cocaine use (Short-Access group (ShA); 1h/session) for 25 sessions. We then used *in vivo* electrophysiological recordings isoflurane anesthetized rats and recorded spontaneously active VTA and SNc DA neurons during early (D7) and late (D30) abstinence. No change in DA neuron population activity was found in ShA rats in the VTA and the SNc at any time of abstinence. In contrast, a significant decrease in the number of spontaneously active VTA DA neurons of LgA rats was found after 7 days and 28 days of abstinence. After 7 days of abstinence we also found a significant decrease in the bursting activity of VTA DA neurons of LgA but this effect disappeared after 28 days. In the SNc of LgA rats, we found a significant increase in the firing rate of DA neurons during early abstinence but no significant change was found in all three parameters of DA activity during late abstinence. These findings first suggest that dopaminergic activity state is altered only in rats that experimented extended addiction-like access to cocaine self-administration. These effects were time- and region-specific. The present study also suggests that during early abstinence, the negative state could be mediated by both a decrease in VTA DA activity and a decreased signal-to-noise ratio in SNc DA neurons target structures. Interestingly, we found no change in SNc activity after prolonged abstinence, but a persistent decrease in VTA activity suggesting a persistent role of VTA DA activity in enhanced cocaine seeking.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Title: Cocaine reshapes the physiology of ventral CA1 afferents to nucleus accumbens that underlie drug seeking and reward

Authors: *A. L. EAGLE[1], K. L. BRANDEL-ANKRAPP[1], M. A. DOYLE[2], E. S. WILLIAMS[3], C. E. MANNING[2], R. M. BASTLE[4], I. S. MAZE[4], A. J. ROBISON[1];
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Abstract: Ventral CA1 hippocampus (vCA1) afferent neurons play a critical role in drug behavior, and activation of ventral CA1 glutamatergic projections to nucleus accumbens (NAc) drive seeking for cocaine. However, the mechanism by which cocaine shapes the function of this vCA1-NAc circuit is poorly understood. Evidence suggests that cocaine drives synaptic plasticity in this circuit and our preliminary evidence suggests that it reduces vCA1 excitability. We propose an innovative role for ΔFosB, a transcription factor, in the activity of vCA1-NAc neurons and cocaine behavior. ΔFosB is induced in hippocampus by chronic cocaine and we show that it regulates hippocampal function and reduces CA1 excitability. Here, we used viral-mediated, circuit-specific fluorescent labeling and whole cell patch-clamp electrophysiology to determine chronic cocaine effects on vCA1-NAc physiology. We found that cocaine, similar to ΔFosB expression, reduces vCA1-NAc excitability, suggesting that cocaine induces ΔFosB leading to decreased neuronal excitability. Studies are ongoing to identify the ion channel mechanism underlying this change. Using circuit-specific CRISPR-mediated gene editing , we have also determined that ΔFosB expression in vCA1-NAc neurons is necessary for cocaine reward and seeking. *FosB* KO in vCA1-NAc neurons specifically decreased cocaine reward and seeking. Ongoing studies are currently identifying the pattern of gene expression regulated by cocaine in the vCA1-NAc circuit. Collectively, these findings demonstrate that cocaine functionally reshapes the vCA1-NAc circuit to drive cocaine-dependent behaviors. Furthermore, they suggest that ΔFosB and its gene targets in hippocampus afferents may serve as promising therapeutic inroads for drug addiction.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Whitehall Foundation Research Grant APP131146
2014 NARSAD Young Investigator Award

Title: Cocaine alters gene expression in ventral ca1 afferents to nucleus accumbens that underlie drug seeking and reward

Authors: *K. L. BRANDEL-ANKRAPP[1], A. L. EAGLE[1], M. A. DOYLE[1], R. M. BASTLE[2], I. S. MAZE[3], A. J. ROBISON[1];
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Abstract: Cocaine use remains a massive public health concern. Cocaine dependence and cocaine-seeking behavior are widely studied, and drug dependency drives drug-seeking behavior. Pyramidal neurons of the ventral hippocampus (vHPC) - a key region for memory -project to the nucleus accumbens (NAc) - a significant reward center - and facilitate drug seeking behavior. Additionally, chronic cocaine use leads to physiological changes within the vHPC-NAc circuit that reinforce seeking behavior, but the role of gene expression in these physiological changes is not well understood. We have identified that the transcription factor ΔFosB, which is induced by cocaine in the hippocampus, drives changes in drug-seeking behavior and the physiology of this circuit. This suggests that ΔFosB induction in vHPC-NAc is a key mechanism by which cocaine drives changes in physiology and drug-seeking behavior. We aimed to determine how gene expression is altered by chronic cocaine in vHPC-NAc neurons and the potential role of ΔFosB in this process. First, we used circuit-specific TRAP-Seq with viral-mediated gene manipulation and transgenic mouse lines to identify altered patterns of gene transcription in vHPC-NAc neurons after chronic cocaine. Furthermore, we used conditional knockout models under cocaine and drug-free conditions to determine whether transcriptional changes were regulated by ΔFosB. We are currently validating gene targets via traditional molecular assays, including immunohistochemistry, to identify novel gene expression regulated by cocaine within the vHPC to NAc circuit. This will ultimately lead to future studies to assess the role of specific gene targets in vHPC-NAc physiology and subsequent effects on drug seeking behavior.

Disclosures: **K.L. Brandel-Ankrapp:** None. **A.L. Eagle:** None. **M.A. Doyle:** None. **R.M. Bastle:** None. **I.S. Maze:** None. **A.J. Robison:** None.

Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

Location: Hall A

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Program #/Poster #: 598.24/X10

Topic: G.08. Drugs of Abuse and Addiction

Support: Trinity University
Mindlin Foundation

Title: Dopamine receptor dependence of cocaine-mediated plasticity in specific excitatory synapses onto midbrain dopamine neurons

Authors: *A. R. KARLA[1], C. Y. GUO[1], L. D. MUZYKA[1], A. C. TOLER[1], A. J. DAVIS[1], G. M. BEAUDOIN, III[2];
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Abstract: Dopamine plays an important role in communication between neurons, notably in the neural pathway that is involved in motivation and reward-seeking behavior. The mesolimbic dopaminergic pathway is activated by excitatory inputs, which are affected by a single exposure to cocaine. Our research is characterizing cocaine's mechanism within these excitatory inputs by studying the synapses between the midbrain regions pedunculopontine tegmental nucleus (PPN) and substantia nigra pars compacta (SNc). Prior research has shown that cocaine induces changes in receptor composition at synapses between glutamatergic neurons in PPN and dopaminergic neurons in SNc. The ratio between two glutamate receptors, NMDA and AMPA, is used to assess this synaptic plasticity in response to in vivo cocaine exposure in mice. A virus encoding a fluorescent protein (YFP) and a light-operated cation channel (ChR2) is injected via stereotaxic surgery, allowing us to selectively excite PPN-innervated synapses on SNc dopamine neurons. Using electrophysiological recordings, in vivo cocaine exposure causes a decrease in the AMPA to NMDA receptor ratio after 24 hours. It is unknown, however, whether excitatory D1-like or inhibitory D2-like receptors are involved in this change. We are investigating the effect of a D1-like receptor antagonist (SCH 23390) and D2-like receptor antagonist (eticlopride) on the cocaine-induced decrease in the AMPA/NMDA ratio. Based on cocaine's established role in inhibiting the dopamine transporter, we suspect that one or both of these receptors are required. Preliminary evidence suggests that D1 receptors are involved in cocaine-mediated plasticity of PPN-SNc synapses.

Disclosures: **A.R. Karla:** None. **C.Y. Guo:** None. **L.D. Muzyka:** None. **A.C. Toler:** None. **A.J. Davis:** None. **G.M. Beaudoin:** None.

Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Topic: G.08. Drugs of Abuse and Addiction

Support: Trinity University

Title: Cocaine-induced structural and functional changes of input-specific excitatory synapses on nigral dopaminergic neurons

Authors: J. F. MORENO[1], S. R. RODRIGUEZ[1], K. E. WINDSOR[1], A. C. TOLER[1], P. VOIT[1], A. B. LITCH[1], A. R. KARLA[1], C. Y. GUO[1], S. HEMANI[1], *G. M. BEAUDOIN, III[2];
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Abstract: *In vivo* cocaine exposure has been shown to induce changes in excitatory synaptic responses to mesostriatal dopamine neurons. These neurons may be a part of the reward pathway and could be important for controlling motivation and addictive behavior. In early work, cocaine was shown to initially change excitatory synapses on dopaminergic neurons without identification of the source of the glutamate. Using optogenetics, we are able to label and activate PPN by injecting in mice a virus encoding a light operated cation channel, channelrhodopsin (ChR2), and yellow fluorescent protein (YFP). Using this system, we have shown that glutamatergic projections from the pedunculopontine tegmental nucleus (PPN) onto dopamine neurons in the substantia nigra pars compacta (SNc) have altered glutamatergic receptor ratios one day after a single injection of cocaine administered *in vivo*. Specifically, the PPN-SNc synapse has an increase in N-methyl-d-aspartate (NMDA) receptor function, as tested using electrophysiology. We are now further characterizing the underlying structural and functional changes at this synapse that underlies this increase in NMDA receptor-mediated currents. We are using a combination of electrophysiology and immunofluorescence with confocal imaging to ascertain if the increased NMDA receptor-mediated current is due to one of several hypotheses including, but not limited to, an increase in the number of synapses, an increase in the number of NMDA receptors at the same synapse, a change in localization of receptors at the synapse and/or a change in subunit composition. Thus, we have begun to characterize the postsynaptic responses of SNc dopamine neurons to excitatory projections from PPN to identify the receptor subunit composition at these glutamatergic subtypes. As expected, NMDA receptors (NMDARs), have a typical, outward rectifying I-V relationship suggesting the presence of standard NMDAR1/2 heteromers. Additionally, distribution of NMDAR1 subunit localization is not globally affected by cocaine in SNc. We are using the YFP-labeled PPN axons to identify changes in localization of glutamatergic subunits at these synapses on dopamine neurons. We have developed an automated image analysis routine to identify putative synapses

between PPN and dopamine neurons from confocal images in order to assay changes in localization, size, and quantity of specific glutamate receptor subunits. By measuring the synaptic response of dopamine neurons and imaging localization of NMDA receptors to putative synapses, we are able to identify what is affected by cocaine at these synapses.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Support: NIH Grant DA038613

Title: Blood mitochondrial copy number as a biomarker for altered motivational states in mouse models of stress and drug addiction

Authors: ***C. A. CALARCO**[1], R. CHANDRA[1], S. VAN TERHEYDEN[1], M. E. FOX[1], M. ENGELN[1], G. MORAIS-SILVA[2], M. F. PAGLIUSI, JR[3], M. TURNER[1], M. LOBO[1]; [1]Anat. and Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD; [2]Sch. of Pharmaceut. Sci., Sao Paulo State Univ., Araraquara, Brazil; [3]Biol. Inst., State Univ. of Campínas, Campinas, Brazil

Abstract: Exposure to chronic stress changes many aspects of the reward pathways in the brain and their functions. These changes in neuronal morphology and electrophysiological function are influenced and supported by available cellular energy stores, provided to the cell by mitochondria. Mitochondrial health and function are dynamically regulated in a cell-type and brain region selective manner, and impacted by environmental changes. While understanding the changes that occur in reward processing regions of the brain, such as the nucleus accumbens, are fundamental to understanding the motivational changes associated with chronic stress or exposure to drugs of abuse, this data is not readily available in a clinical population. Therefore, the use of biomarkes as proxies for changes in the brain are necessary. Recently, the proliferation of mitochondria in blood leukocytes has emerged as a potentially useful biomarker for depression, bipolar disorder, and substance abuse, with the added benefit that this metric can be remeasured over multiple stages of disease, recovery or relapse. Increased copy number of mitochondrial DNA relative to nuclear DNA, indicating an increase in the number of mitohcondria per cell, has been linked to depression severity as well as other diseased states. In the current study we examined mitochondrial copy number in blood from animals that have

undergone chronic social defeat stress (CSDS). Mitochondrial copy number is significantly increased in animals that have undergone CSDS, with the largest increases in animals observed to be susceptible to the stress, as determined by their behavior in a social interaction test. Further, blood mitochondrial copy number is significantly correlated with time spent interacting with the social target in this social interaction test. Additionally, we examined the relationship between blood mitochondrial copy number and CSDS-induced changes in mitochondrial copy number and gene expression in the nucleus accumbens. Finally, we examined if this relationship between blood mitochondrial copy number and behavior is specific to CSDS or if there is a comparable relationship after exposure to drugs of abuse, such as after cocaine self-administration or exposure to the opioid, fentanyl.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Support: NIH Grant R01DA047843

Title: Transcriptional adaptations in the ventral pallidum following cocaine self-administration

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Abstract: Growing evidence suggests the ventral pallidum (VP) is critical for drug intake and seeking behavior. Receiving dense projections from the nucleus accumbens as well as dopamine inputs from the midbrain, the VP plays a central role in the control of motivated behaviors. Repeated exposure to cocaine is known to alter VP neuronal firing and neurotransmission. Surprisingly, there is limited information on the molecular adaptations occurring in VP neurons following cocaine intake. To provide insight into cocaine-induced transcriptional alterations we performed RNA-sequencing on VP of mice that underwent 10 days of cocaine self-administration (0.5mg/kg/infusion) followed by twenty-four hours of abstinence. We observed differential gene expression in 363 genes between animals that self-administered cocaine and saline controls. Subsequent Gene Ontology analysis pointed toward alterations in dendrite- and spine-related genes. Searching for a common regulator for these sets of genes, we found that the expression of the transcription factor Nr4a1 showed a robust increase following cocaine self-

administration. Further, we observed an increase in the Nr4a1 transcriptional target Plk2, a molecule important for synaptic and structural plasticity. Analysis of Plk2 molecular targets showed alterations in Actin and Rap2 dynamics after cocaine exposure, confirming alterations in dendritic and spine functions. Overexpression of Nr4a1 in the VP reduced cocaine seeking supporting its role in drug-related behavior. Using fluorescent *in situ* hybridization, we are now determining which VP projection neuron population displays increased Nr4a1 and Plk2 levels after cocaine self-administration. This includes VP- ventral tegmental area, VP-lateral habenula, VP-mediodorsal thalamus, or VP-nucleus accumbens projection neuron populations. Additionally, we are using adenoassociated virus (AAV) overexpression and CRISPR knockdown manipulation of Nr4a1 and Plk2 to interrogate the role of these molecules in VP circuits during cocaine self-administration and relapse-like behavior. Altogether, our work can provide crucial information into the molecular adaptations occurring in VP neuron supporting cocaine self-administration and relapse-like behavior.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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Support: NIDA CEBRA R21DA046227

Title: Optically induced CRISPR tool for epigenome editing in cocaine abuse

Authors: *E. Y. CHOI[1], R. CHANDRA[2], M. MCGLINCY[2], A. CHOW[2], M. LOBO[2];
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Abstract: Drug abuse is a debilitating chronic disease which is a leading cause of disability around the world. Drug seeking after repeated drug exposure is prevalent despite the devastating personal consequences. Studies have shown that repeated exposure of drugs, such as cocaine, leads to changes in epigenetic processes, including nucleosome modifications. Such changes can alter cocaine-induced behavior as well as other motivational behaviors. However, the lack of tools to induce histone modifications with precise spatiotemporal control, *in vivo,* is a major barrier in studying the complex molecular and behavioral dynamics occurring during the addictive process. In this study, we developed an optically induced CRISPR mediated histone modification tool that can be targeted to precise loci in selective neuron subtypes using the CRY2-CIBN blue light heterodimerizing complex system. These novel constructs are packaged

into AAVs for *in vivo* delivery into the brain. In cell culture, our novel constructs, which code for catalytically dead (d)Cas9-CIBN and CRY2-KDM1A fusion proteins on a Cre dependent backbone (termed Opto-CRISPR-KDM1A), were co-transfected into Neuro2A cells along with sgRNA targeting for early growth response 3 (Egr3) and NGFIA-binding protein 2 (Nab2). We focus on Egr3 and Nab2 because we observe differential induction of these molecules in nucleus accumbens (NAc) dopamine receptor 1 vs 2 medium spiny neurons (D1-MSNs vs D2-MSNs) after repeated cocaine. After 1 hour of blue light exposure, Egr3 mRNA level was significantly down-regulated in cells transfected with the sgRNA targeting Egr3, and Egr3 mRNA was significantly up-regulated in cells that were transfected with sgRNA targeting Nab2. Consistent with this, Nab2 mRNA level was significantly up-regulated in cells with Egr3 targeting sgRNA, and down-regulated in cells with Nab2 targeting sgRNA. To confirm that the system is interchangeable across multiple histone modifying enzymes, we created a new fusion protein, CRY2-p300, which contains the truncated functional core of histone acetylation enzyme p300 fused with CRY2. After 1 hour or 4 hours of blue light exposure with Opto-CRISPR-p300, Egr3 mRNA level was significantly increased in cells transfected with sgRNA targeting Egr3, and significantly reduced in cells transfected with sgRNA targeting Nab2. Nab2 mRNA expression was significantly increased in cells transfected with Nab2 targeting sgRNA. We can now begin to confirm and utilize the Opto-CRISPR systems *in vivo*, including during cocaine self-administration and relapse like behavior.

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Poster

598. Neural Mechanisms Underlying Cocaine Use and Abuse

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UTMB IHII Pilot Grant

Title: Cocaine impacts CNS innate immune responses via MAVS and STING regulation during HIV-1

Authors: C. EZEOMAH[1], A. L. PERSONS[2], T. NAPIER[3], ***I. E. CISNEROS**[1];
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Abstract: Cocaine, a highly addictive psychostimulant, negatively impacts the users' ability to initiate an innate immune response to invading pathogens such as human immunodeficiency

virus (HIV)-1. Cocaine and HIV-1 act through multifaceted processes from increased Ca^{+2} dysregulation, oxidative stress, gliosis, mitochondrial dysfunction and generation of proinflammatory mediators. Astrocytes, the most abundant cell in the central nervous system, potently respond to foreign substances, and induce neuroimmune adaptations that transpire across a scattered set of neural circuits and contribute to assorted outcomes related with cocaine exposure and dependence, including participation in the development in the plasticity of dendritic spines, synapses and neurotransmission. Reactive astrocyte phenotypes that occur during cocaine-dependent states and/or HIV-1, may drive the behavioral transformations that lead to cocaine dependence and addiction. Astrocytes express a plethora of pattern recognition receptors (PRR)s that may dictate these neuroimmune alterations. These include cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) that are canonically activated by pathogen or self-genetic material, and mitochondrial antiviral signaling (MAVS) protein, which is regulated by mitochondrial events. Whether these mechanisms contribute to astrocyte-induced neuroimmune adaptations during cocaine use disorder (CUD) remains elusive. As the shared neurotoxic outcomes of cocaine and HIV-1 regulate both MAVS and STING, w**e hypothesized that MAVS and STING activate cocaine-induced inflammation in the context of HIV-1.** Our preliminary data, in primary human astrocytes shows that cocaine +/- HIV-1 differentially regulate IL6, IL8, IL10, results in phosphorylation of NF-κB, increases TNFα and results in activation of type I interferon signaling, including increases in IFNβ1, phosphorylation of TBK1 and phosphorylation and translocation of IRF3. Moreover, we observed that MAVS and STING expression and localization in the frontal cortex of HIV-1 transgenic rats, with or without cocaine, is significantly altered. Taken together, our *in vitro* and *ex vivo* data demonstrate that cocaine and HIV-1 activate neuroimmune signaling pathways that may partly be dictated through MAVS and STING.

Disclosures: C. Ezeomah: None. **A.L. Persons:** None. **T. Napier:** None. **I.E. Cisneros:** None.

Poster

599. Decision Making and Action Selection

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 599.01/X16

Topic: H.01. Animal Cognition and Behavior

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Tatiana Pérez de Guzman el Bueno Foundation

Title: Cortical and subcortical local field potencials involved in a go/no-go task in rats

Authors: *C. MUÑOZ REDONDO, A. GRUART, J. DELGADO-GARCIA;
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Abstract: Go/No-Go tasks allow to assess decision making in behaving rats and, in addition, help to determine their ability to suppress a specific action according to the context, or their ability to cancel an action in progress when an unpredictable cue indicates that it should be avoided. In many of these experimental procedures, food is used as a positive reinforcement to study associative learning or decision-making processes. In the present experiments, Lister Hooded male rats were used. Animals had to discriminate in an iPad screen between two visual stimuli (Go or No-Go) disposed in horizontal or vertical ways and in white or green colors. In this situation, the execution (Go) or non-execution (No-Go) of the behavioral selected action (to touch or not to touch the visual display) would be reinforced. Rats were trained in a modified Skinner box equipped with an iPad, where stimuli appeared. The maingoal was to record and to analyze local field potentials (LFPs) collected from different cortical and subcortical brain structures, when the visual stimuli were shown in the iPad screen and during the subsequent behavioral activities. Animal behavior was videotaped and quantified. Following an introductory tone, the rat had to press a white horizontal rectangle (Go) or to avoid touching a green vertical one (No-Go), getting in this way a pellet as reward. Previously, rats had gone through caloric restriction and maintained to 85-90% of their initial weight. The experiment consisted of five phases, two pure phases and then mixed. In the first one, rats learned to approach the iPad and touch the stimulus in the case of Go trials as well as not to approach it in No-Go phase trials. In the next phases, Go and No-Go stimuli were mixed in an increasing way (50%, 25%, and intermingled specified patterns). Rats were implanted with recording electrodes in motor and prelimbic (PLc) cortices, accumbens nucleus core (Acc), dorsolateral and dorsomedial striatum, hippocampus, mediodorsal thalamic nucleus (MD), and basolateral amygdala (BLA). Each animal was implanted with recording electrodes in five of the indicated sites. Preliminary results indicate that rats were able of acquiring this rather complicate task with a significant performance even when stimuli were mixed at a 25%. Spectral analyses of collected LFPs indicate the specific involvement of PLc, Acc, BLA, and striatum, but not hippocampus, during the proper execution of Go and No-Go tasks. Spectral power changes were observed mainly in delta, theta and gamma bands. Thus, these brain areas are involved in cognitive and motivational processing, execution of motor responses, and contribute to reward-directed behaviors.

Disclosures: C. Muñoz Redondo: None. **A. Gruart:** None. **J. Delgado-Garcia:** None.

Poster

599. Decision Making and Action Selection

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Topic: H.01. Animal Cognition and Behavior

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Title: Neuronal activity in the primate gustatory cortex during economic choices

Authors: *A. JEZZINI, C. PADOA-SCHIOPPA;
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Abstract: The gustatory cortex (GC), located in the anterior insula, receives anatomical projections from sensory and associative thalamic nuclei (VPMpc, MD, Pulvinar) and is densely interconnected with the amygdala, the orbitofrontal cortex (OFC) and the anterior cingulate cortex. Classic work showed that neurons in GC respond to the chemosensory properties of foods. More recently, it was suggested that GC participates in more complex processes such as the representation of the food's subjective or hedonic value (Jezzini et al., 2013). Importantly, the behavioral paradigms used in previous studies of GC did not provide any operational measure of subjective value. Furthermore, it remains unclear whether and how the GC might contribute to food-related and/or value-driven behaviors. To address these outstanding questions, we recorded the activity of neurons in the GC of monkeys performing an economic choice task. In each session, a monkey chose between two juices, labeled A and B, offered in variable amounts. Offers were represented by sets of squares on a monitor and the animal indicated its choice with a saccade. For each session, the relative value of the juices was inferred from the choice pattern. We recorded and analyzed the activity of 912 cells. Roughly 50% of neurons were significantly modulated by the offer type and/or by the animal's choice. In contrast, only few cells were modulated by the spatial contingencies of the task. As in previous studies of OFC, we defined and examined a large number of variables. Our analyses revealed that neurons in GC encoded two variables: the *chosen value* (i.e., the value of the chosen option independently of the juice type) and the *chosen value A|B* (i.e., the juice-specific chosen value). For both variables, neuronal modulation in GC started during the delay intervening between offer presentation and the go signal, and was most pronounced upon juice delivery. More specifically, neurons encoding the *chosen value* peaked shortly before juice delivery; neurons encoding the *chosen value A|B* peaked after juice delivery. Additional analyses confirmed that *chosen value* responses reflected the subjective nature of value, as distinguished from the physical and chemical properties of the juices. Thus neurons in GC reflect the integration of chemosensory inputs and the motivational state of the animal. Conversely, our results indicate that GC does not contribute to the formation of the current economic decision.

Disclosures: A. Jezzini: None. **C. Padoa-Schioppa:** None.

Poster

599. Decision Making and Action Selection

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

Support: MH002886-11

Title: Afferent projections of frontal cortical area 12o in rhesus macaques

Authors: C. CLEVELAND, M. MOYER, E. MURRAY, *R. C. SAUNDERS;
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Abstract: The medial and lateral subdivisions of orbitofrontal cortex (OFC) are thought to support distinct components of reward-based learning and decision making, and the anatomical connections of these subdivisions appear to support their distinct roles. Although much is known about the anatomical connections of lateral OFC areas 11 and 13, much less is known about the adjacent area 12o, the portion of area 12 lying on the orbital surface. Until recently, 12o has not been considered part of the decision making circuit. To gain a better understanding of how area 12o interacts with other brain regions, we mapped the anatomical connections of area 12o in rhesus monkeys. 1 µl injections of standard retrograde neuronal tract tracers were placed in different levels of 12o as well as in nearby frontal cortical areas (e.g. 11, 13, 12l). Retrograde label after 12o injections suggest a robust set of projections from the frontal pole area 10, adjacent OFC areas 11 and 13, with only a light projection from area 14. On the medial surface area 32 had fairly dense label while area 24 had dense label rostrally but only light label caudal to the genu of the corpus callosum. Lateral PFC contained only sparse retrograde label in area 46, along the banks of the principal sulcus, and in areas 9 and 8. As expected, outside of the frontal lobe we found dense retrograde label within the rostral temporal cortical areas, particularly the temporal pole areas 38 and 36p. The rostral auditory cortical area, TS1, had substantially more label as compared with the rostral visual association cortical area TE. Caudal to the pole the multi-sensory area of the upper bank of the STS had heavy label throughout. In the medial part of the temporal lobe there was light label in the parahippocampal cortical areas including rostrally the perirhinal cortex and intermediate entorhinal cortex. There was also light label more caudally in areas TF/TH. Subcortically, the most prominent label was found in the basal nuclei of the amygdala and the medial thalamic region including the midline nuclei, mediodorsal nucleus, and the medial pulvinar. Labeled cells were also found in the source nuclei of many of the neuromodulators such as the substantia nigra, the raphe nuclei, and the basal forebrain. In summary, area 12o in macaques receives inputs from frontal cortex regions similar to those of both the proposed medial frontal and orbital frontal cortical networks (Ongur and Price, Cerebral Cortex, 2000), from the temporal lobe, as well as the medial thalamus, and from regions containing cholinergic, serotonergic and dopaminergic neurons. Future studies should address the role of area 12o in reward-based learning and decision making.

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Poster

599. Decision Making and Action Selection

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Program #/Poster #: 599.04/X19

Topic: H.01. Animal Cognition and Behavior

Support: DA031695

Title: A modified actor-critic learning model suggests anterior cingulate cortex maintains eligibility traces for learning

Authors: *D. R. SCHUWEILER, D. VAZQUEZ, M. R. ROESCH;
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Abstract: We have established a task to study fundamental neural signals related to learning and decision-making and their disruption in addiction. During this task, rats are presented one of three odor cues that direct them to go to a left fluid well, a right fluid well, or either to receive reward. The task is divided into four blocks of trials, and there are no cues indicating the current block or block switches. In the first block the left side, for example, is paired with a short delay before reward and the right side with a long delay. This pairing is reversed for the second block. In the third block, the left side is paired with a large reward and right side with a small reward. The pairing is reversed for the last block. Thus, rats experience unexpected changes in reward value every time a new block begins.
During this task, we have recorded distinct types of learning-related neural signals. Dopamine (DA) neurons in the ventral tegmental area (VTA) increase or decrease firing when rewards are better or worse than expected, respectively. Thus, VTA DA neurons appear to signal classic reward-prediction errors (RPEs). Neurons in the basolateral amygdala (BLA) increasing firing when rewards are better or worse than expected. Thus, BLA neurons appear to signal unsigned RPEs. Neurons in the anterior cingulate cortex (ACC) increase firing at the start of the trial, and the firing rate decays to baseline after the cue is presented. For many ACC neurons, this cue-related activity increases after unexpected changes in value, and the increase correlates with response latency, a measure of attention. We have hypothesized that DA activity drives learning, while BLA activity encodes how surprising an outcome is; this latter information is sent to the ACC to modulate attention, and ACC activity converges with striatal DA to direct behavior. However, it is still unclear exactly what is being encoded by the ACC in this context.
We fit a modified actor-critic learning model to the behavior observed in our task. In our model DA-like RPEs drive Pavlovian learning by the critic, as usual, but we have added BLA-like unsigned RPEs which set the learning rate for the operant actor and the magnitude of the eligibility traces. The eligibility traces included in actor-critic models control how well a cue becomes associated with a reward, and they enable the model to associate cues with rewards that

are delivered after a delay. Our model produces eligibility traces which appear similar to the activity of the ACC units that is thought to encode attention. Thus, our model generates the novel hypothesis that one function of the ACC is to maintain neural representations of cues that enable the development of cue-outcome associations.

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Poster

599. Decision Making and Action Selection

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Program #/Poster #: 599.05/X20

Topic: H.01. Animal Cognition and Behavior

Title: The effect of ventral striatum lesions on choices based on reward availability versus desirability in rhesus macaques

Authors: *M. S. PUJARA[1], B. M. BASILE[2], V. D. COSTA[3], B. B. AVERBECK[4], E. A. MURRAY[5];
[1]Natl. Inst. of Mental Hlth., NIH, Bethesda, MD; [2]Lab. of Neuropsychology, Natl. Inst. of Mental Health, NIH, Bethesda, MD; [3]Dept. of Behavioral Neurosci., OHSU/ONPRC, Portland, OR; [4]NIMH/NIH, Bethesda, MD; [5]Lab. of Neuropsychology, NIMH, NIH, Bethesda, MD

Abstract: Reward value is determined by the likelihood of reward receipt as well as the current worth of the reward. The ability to use existing knowledge about a reward — whether it is likely to become available or whether it is desirable or not — represents two distinct processes that are both critical for driving adaptive choices. Though the ventral striatum (VS) has been implicated in guiding reward-based learning, the extent to which it is necessary for guiding choices based on information about reward availability, desirability, or both, has not been fully explored in rhesus macaques. We therefore compared monkeys with VS lesions (n=3) and intact controls (n=4) on two touchscreen tasks where reward value changed as a function of either availability or desirability. Choice based on reward availability was tested using a three-arm bandit task, wherein monkeys learned to choose between three probabilistically rewarded images. Periodically, one of the options was replaced with a novel image that had not yet been associated with reward. Monkeys therefore had to choose between exploring the novel option or exploiting their existing knowledge about the two familiar options that remained available, where the availability of reward was known. Impairments in optimizing rewards via novelty exploration present as either increased novelty seeking or novelty aversion. Choice based on desirability was tested using a reinforcer devaluation task, wherein monkeys learned to choose between two stimuli, each associated with a unique food reward. Critically, monkeys were sated on one of the two outcomes, and stimulus choice was assessed immediately following satiety. Monkeys that are impaired on this task are unable to shift choices away from stimuli that predict the outcome

they were sated on, relative to their choices at baseline, before satiety. We found that monkeys with VS lesions were impaired on the probabilistic three-arm bandit task, showing increased novelty seeking as indexed by choice and reaction times upon the first presentation of a novel stimulus, especially when the overall probability of reward was greatest prior to the presentation of a novel image. However, VS lesions produced only mild impairments in stimulus choice following selective satiety. The results of these experiments suggest that the VS may be specialized to guide choices based on information about reward likelihood rather than reward palatability in rhesus macaques.

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Poster

599. Decision Making and Action Selection

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Title: Hippocampal-related memory deficits in Sprague-Dawley rats with spontaneous ventriculomegaly

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Abstract: Purpose. Spontaneous ventriculomegaly has been observed in rats that were presumably normal. While external phenotype of these animals is unremarkable, they show considerable enlargement of the ventricular system and hippocampal atrophy. Given the role of the hippocampus in memory consolidation, we evaluated long-term memory retention while decision-making in rats with spontaneous ventriculomegaly.
Methods. Animals included (adult male Sprague-Dawley rats) were those identified as having spontaneous ventriculomegaly while performing baseline MRI scanning intended for a different research protocol. Control (n=8) and lesioned (n=8) animals were submitted to a delayed-alternation task (no-delay, 30, 60, and 180s) and to an object-in-context recognition task. During

the first one, we evaluated the number of correct choices as well as the latency to find the reward during each trial. The second task assessed the rodents' ability to remember where they had previously encountered a specific object, calculating the context recognition index (0.5 reflects no preferences for any of the objects while higher values show a preference for familiar objects in novel contexts).
Results. When compared to Control animals, rats with ventriculomegaly showed a significantly reduced delayed-alternation performance in each of the four evaluated times ($p<0.0001$), as well as increased latencies while trying to reach the reward ($p<0.01$). When evaluated the long-term memory formation during the object-in-context recognition task, subjects with ventriculomegaly spent less time ($p<0.05$) investigating the familiar object. Recognition index value was 0.8 and 0.5 for Control and lesioned animals, respectively.
Conclusion. Our results are the first to show how spontaneous ventriculomegaly-induced hippocampal damage impacts upon decision-making behaviors, in particular, when deciding between immediate and delayed rewards. Moreover, this lesion disrupts the animals' ability to recall or express contextual information.Thanks to Juan Ortiz Retana and Carlos Flores Bautista for technical support.

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Poster

599. Decision Making and Action Selection

Location: Hall A

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Program #/Poster #: 599.07/X22

Topic: H.01. Animal Cognition and Behavior

Title: Stimulus specific value coding in motivational circuits is not a bug, it's a feature

Authors: *V. D. COSTA;
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Abstract: Motivational brain regions, such as the amygdala, ventral striatum, and orbitofrontal cortex encode stimulus and action values. A prevalent view is that value coding in these regions is general and not stimulus or action specific. However, prior studies have typically only examined responses to a limited set of stimuli or actions, sometimes confounded value with the identity of an action or stimulus, or relied on statistical rather than experimental controls. To determine the extent to which value coding in motivational regions is general or stimulus specific we recorded activity in the amygdala, ventral striatum, and orbitofrontal cortex in rhesus macaques as they played a multi-arm bandit task where they had to learn visual stimulus-outcome relationships. Every so often an existing choice option was randomly replaced with a novel option, allowing us to assess how individual neurons encoded the value of choices across

35 stimuli assigned different reward probabilities. The proportion of task responsive neurons in each brain region that showed evidence of general value coding did not exceed chance. Rather the majority of neurons in each brain region showed evidence of stimulus specific value coding. Neuronal preferences for specific stimuli were not readily discernable from natural image statistics. Despite weak evidence of general value coding at the level of individual neurons, we were still able to decode the value of choices from pseudo-populations constructed for each region. These results are consistent with increasing evidence that value coding in the brain is heterogenous and multidimensional.

Disclosures: V.D. Costa: None.

Poster

599. Decision Making and Action Selection

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Support: Yale Center for Clinical Investigation Multidisciplinary Post-Doctoral Training Program in Translational Research TL1 TR001864
Yale Center for the Translational Neuroscience of Alcoholism P50 AA012870
NIH Grant R01 DA041480

Title: Investigating the role of the gut microbiome in decision-making in mice

Authors: *S. L. THOMPSON, S. M. GROMAN, J. H. MEYERS, G. HUANG, J. R. TAYLOR; Psychiatry, Yale Univ. Sch. of Med., New Haven, CT

Abstract: Goal-directed, or model-based, behavior is a type of decision-making that is vital for flexibly updating choices in a dynamic environment. In contrast, habitual or automatic, also known as model-free, behavior is efficient but inflexible. Rigid, repetitive behaviors that persist in the absence of a goal have been observed in individuals with various psychiatric disorders. These compulsive behaviors may arise from disruptions in the reinforcement learning (RL) systems that enable flexible, adaptive decision-making. The dynamics between model-based and model-free RL systems can be quantified in multi-stage decision-making (MSDM) tasks. MSDM tasks consist of sequential decisions, whereby choices made in one stage transition probabilistically (i.e., common or rare) to the options available in the next stage, and ultimately to the possibility of reward based on reinforcement probabilities assigned to the final stage options. The gut microbiome has recently emerged as a major modulator of neuropsychiatric phenotypes. However, the role of the gut microbiome in decision-making is unknown. Here, we adapted a version of the MSDM task developed in rats for use in mice and assessed the role of the gut microbiome in decision-making. Adult male C57BL/6 mice were water-restricted, trained

using water as the reinforcer, and tested on the MSDM task using a probabilistic, alternating block schedule of reinforcement. Mice were then provided with a cocktail of nonabsorbable antibiotics in the chow or a control diet for one week and then retested on the MSDM task while maintained on the antibiotic regimen. Mice were then placed back on the control diet and retested on the MSDM task eight weeks later. Mice were able to learn the state transitions and reinforcement schedules in the MSDM task and exhibited strikingly similar decision-making strategies compared to those observed in humans and rats, suggesting that mice use both model-free and model-based RL systems when making decisions. Exposure to antibiotics reduced both model-based and model-free strategies in the MSDM task, which persisted eight weeks after washout of antibiotics. These results provide preliminary evidence of a role for the gut microbiome in RL strategies of decision-making that may be relevant to psychiatric disorders in which compulsivity is a core behavioral feature.

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Poster

599. Decision Making and Action Selection

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant P50MH100023

Title: Prefrontal cortico-amygdalar interactions are required for social associations to guide operant behavior

Authors: H. W. KIETZMAN, *S. L. GOURLEY;
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Abstract: Navigating a complex world requires the formation of associations between cues, our behaviors, and their outcomes. Over the past 50 years, the circuitry underlying the ability of Pavlovian cues to motivate instrumental behavior has been carefully dissected utilizing procedures such as Pavlovian-to-instrumental transfer (PIT). We have discovered that social associations, such as experience with a novel conspecific, can motivate food-reinforced operant behavior in mice, through PIT-like processes. We hypothesized that the prelimbic (PL) subregion of the medial prefrontal cortex, known to process social information, but not classically associated with PIT, might be necessary for social associations to guide instrumental behavior. Chemogenetically silencing the PL, when social associations would otherwise be expected to motivate operant behavior, ablated such “social PIT.” PL inactivation also reduced social approach in a social interaction test, while leaving social memory intact. Next, we

chemogenetically silenced PL projections to the basolateral amygdala (BLA), rendering mice again unable to utilize social associations to guide instrumental decision making. Meanwhile, social approach remained intact. Together, these results suggest that top-down communication from the PL to BLA is not necessary for attending to social stimuli per se, but enables social associations to guide operant behavior.

Disclosures: S.L. Gourley: None. **H.W. Kietzman:** None.

Poster

599. Decision Making and Action Selection

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Program #/Poster #: 599.10/X25

Topic: H.01. Animal Cognition and Behavior

Title: Signal dynamics corresponding to transformation from value to choice in midbrain dopamine neurons and orbitofrontal neurons during economic decision-making in monkeys

Authors: *M. YUN[1], T. KAWAI[2], M. NEJIME[2], H. YAMADA[2], M. MATSUMOTO[2];
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Abstract: In economic decision-making, individuals evaluate the value of options, and then decide to choose or not to choose the options based on the value. To identify the neural mechanism underlying this behavior, it is critical to understand how the brain transforms value information into choice commands. Yet, although many studies have reported brain regions that participate in the valuation process, the value-to-choice transformation mechanism remains unclear. Here we focused on midbrain dopamine (DA) neurons that are well-known as a part of the valuation system, and examined whether and how these neurons contribute to the value-to-choice transformation process. We recorded single-unit activity from DA neurons in monkeys performing an economic decision-making task in which the monkey was required to decide to choose or not to choose an option based on its value immediately after the option was offered. We found that DA neurons represented diverse signals related not only to the option's value but also to the animal's choice; some neurons represented the value of the offered option, some represented whether the animal would choose or not choose the option, and some represented the value of the option only when the option was chosen by the monkey -we therefore called this activity pattern as *choice-dependent value* signal that was influenced by both value and choice. We next analyzed the time course of these DA signals and found that the order of signal representations corresponded to the value-to-choice transformation. Shortly after the onset of the option, the value signal rapidly appeared, which was followed by the choice-dependent value signal. The choice signal arose at last. For comparison, we also recorded single-unit activity from the orbitofrontal cortex (OFC) that has been implicated in economic decision-making, and found that OFC neurons also represented the three signals and exhibited the same order of signal

representations. Notably, the last-arising choice signal appeared before the monkey executed a motor action to choose the option in both DA and OFC neurons. Thus, both neurons could regulate the monkey's choice behavior. On the other hand, the choice signal of DA neurons preceded that of OFC neurons, suggesting the value-to-choice transformation process has completed earlier in DA neurons. We finally observed that the choice signal of DA neurons did not simply reflect the monkey's motor action using a control motor task in which the monkey just executed the same motor action without economic decision-making. Our findings provide evidence that not only prefrontal regions but also the subcortical DA system plays a crucial role in value-based choice formation.

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Poster

599. Decision Making and Action Selection

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Topic: H.01. Animal Cognition and Behavior

Support: JST CREST JPMJCR1853

Title: Value and choice representations in the primate ventral striatum during economic decision-making

Authors: *M. NEJIME[1], M. YUN[2], T. KAWAI[1], H. YAMADA[1], M. MATSUMOTO[1]; [1]Fac. of Med., [2]Biomed. Science, Grad Sch. of Comprehensive Human Sci., Univ. of Tsukuba, Tsukuba, Japan

Abstract: To choose an appropriate option in economic decision-making, animals evaluate the value of offered options and then decide to choose or not to choose the options based on the value. Although the ventral striatum (VS) is known as a key structure in the neural network that evaluates reward value, how its value signal regulates choice behavior remains poorly understood. To address this issue, we recorded the activity of phasically active neuron in the VS and electrically stimulated this structure in monkeys performing an economic decision-making task. In this task, six visual cues were associated with different amounts of a liquid reward, and two of them were randomly and sequentially presented to the monkey as available options. When one of the cues was presented as the 1st option, the monkey was required to decide to choose or not to choose the option. Note that the monkey needed to make the decision before seeing the 2nd option. We observed that the monkey more often chose the 1st option as its value became larger. After the decision, the 2nd option was presented. If the monkey had chosen the 1st option, the animal was unable to choose the 2nd option and obtained the reward associated with the 1st

option at the end of the trial. If the monkey had not chosen the 1st option, the animal obtained the reward associated with the 2nd option. Of 131 recorded VS neurons, 43 and 30 neurons encoded the value of the 1st option in manners that these neurons increased and decreased, respectively, their activity as the value became larger. We found that their population activities were modulated not only by the value of the 1st option but also by whether the monkey would choose the 1st option. That is, on average, the 43 positive-value-coding neurons were more strongly activated by the 1st option with the same value when the monkey would choose the option, whereas the 30 negative-value-coding neurons were more strongly activated when the monkey would not choose the option. Next, to examine the causal relationship between the activity of VS neurons and the monkey's choice behavior, we electrically stimulated the VS during the presentation of the 1st option (n = 35 stimulation sites) and compared the choice rate of the 1st option between the stimulation and the non-stimulation conditions. On average, we found that the monkey significantly more frequently chose the 1st option in the stimulation condition, although four and two stimulation sites exhibited a significant increase and decrease, respectively, in the choice rate in the stimulation condition. Our findings suggest that the value signal of the VS supports the brain to regulate value-based choice behavior.

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Poster

599. Decision Making and Action Selection

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Title: Representations and causal contributions of multiple brain regions during context-dependent accumulation of evidence

Authors: ***M. PAGAN**[1], V. D. TANG[1], C. D. BRODY[2];
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Abstract: Our ability to flexibly select, based on context, the relevant information to form decisions is a fundamental cognitive process, yet its underlying neural mechanisms are still largely unknown. To address this issue, we have trained rats to perform a task requiring context-dependent selection and integration of sensory information (adapted from Mante et al., Nature, 2013). As we described in Pagan et al., SFN 2016, on each trial of the task rats are presented

with a train of auditory pulses, where each pulse can either be high-frequency or low-frequency, and each pulse is either played by a speaker to the left or a speaker to the right of the rat. In blocks of "location trials" rats are rewarded if they orient toward the side where the largest number of pulses was played (thus ignoring the frequency of the pulses). In blocks of "frequency trials" rats are rewarded for orienting right if the total number of high-frequency pulses was greater than the total number of low-frequency pulses, and for orienting left if the total number of low-frequency pulses was greater than the total number of high-frequency pulses (thus ignoring the location of the pulses). Therefore on each trial the rat is required to select the relevant feature depending on the task context. Here we present data obtained from electrophysiology and optogenetics experiments targeted at multiple brain regions while the rats performed the task.

Disclosures: M. Pagan: None. **V.D. Tang:** None. **C.D. Brody:** None.

Poster

599. Decision Making and Action Selection

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 599.13/X28

Topic: H.01. Animal Cognition and Behavior

Support: R01MH108358

Title: Connecting the dots: The role of striatal projections from frontal orienting fields during perceptual decision-making

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Abstract: Making decisions based on sequential observations of noisy observations is a fundamental cognitive process. While research across different species has successfully modeled this process as a feedforward computation - graded accumulation of evidence followed by choice categorization (e.g. Hanks and Summerfield 2017), it might be neurally implemented through recurrent dynamics across brain areas. Indeed, strong projections exist from the Frontal Orienting Fields (FOF), a rodent frontal cortical area shown to be involved in late stages of decision-making such as choice maintenance (Hanks et al., 2015) and the anterior dorsal striatum (adStr), an area involved in the early stages of decision-making such as graded evidence accumulation (Yartsev et al., 2018) - suggesting that these brain areas might act in a distributed, recurrent fashion during perceptual decision-making. Here, we investigate the causal role of the FOF-adStr projection by optogenetically silencing it during decisions based on the accumulation of pulsatile auditory evidence (the Poisson Clicks task, Brunton et al., 2013). We injected rats with AAV5-

CaMKIIa-eNpHR3.0-eYFP (halorhodopsin, a light activated chloride pump) in FOF and delivered light (25mW, 594nm) via a sharp fiber optic implanted in adStr to perturb the activity of the axon terminals of FOF-adStr projection neurons. We found that unilateral stimulation throughout the trial impaired decisions by biasing the rats to favor an ipsilateral response relative to the site of inhibition, without affecting movement-related parameters. This demonstrates a causal role for this projection, inconsistent with a purely feedforward account. To better understand the contribution of this projection to various stages in decision-making, and to compare it with direct inhibition of the FOF itself, we explored temporally specific inactivation windows during different epochs within trials of the Poisson Clicks task.

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Poster

599. Decision Making and Action Selection

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Topic: H.01. Animal Cognition and Behavior

Support: Princeton Innovation Fund
Howard Hughes Medical Institute
NIH Grant R01MH108358

Title: Large scale dynamics during evidence accumulation in freely moving rats using functional ultrasound imaging

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Abstract: Evidence accumulation is a well characterized decision making paradigm, in which the subject continually processes evidence until making a specific choice. Drift-diffusion models provide a moment by moment quantitative estimate of the animal's internal accumulation process. Experimenters have investigated a myriad of neuronal mechanisms underlying the accumulation processes, e.g., the contributions of different brains areas such as frontal orbital field, posterior parietal cortex and dorsal striatum that differentially accumulate evidence over time (Hanks 2015; Yartsev 2018). Although evidence accumulation likely involves the coordinated activity of many brain areas, previous studies primarily focus on one area at a time and fail to take into account the contribution of other brain areas during evidence accumulation. To probe a large number of brain areas simultaneously, we used functional ultrasound imaging (fUSi) technology. fUSi has a large spatial coverage (16x20mm^2), high spatial resolution

(~100x100x400 μm^3) and temporal (500ms) resolution. We obtained stable imaging in freely moving rats performing evidence accumulation over many months. Rats were trained on an auditory evidence accumulation task with trials slow enough (spanning up to 5s) to capture the full hemodynamic response. Using fUSi to image during the behavior, we report a number of brain areas with choice-related activity, and directed and temporally ordered activation of brain regions during evidence accumulation.

Disclosures: **A. El Hady:** None. **D. Takahashi:** None. **Y. Zhang:** None. **A. Urban:** None. **G. Montaldo:** None. **C. Brody:** None.

Poster

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Helen Hay Whitney Foundation

Title: Mesoscale cortical dynamics during parametric working memory in freely moving rats using wide-field imaging

Authors: *E. J. DENNIS, A. EL HADY, C. BRODY;
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Abstract: Working memory, the maintenance and manipulation of information over short periods of time, is fundamental to many cognitive processes like language, decision making, and planning. We use a parametric working memory task, where the rat hears a sound, followed by a variable delay period, and then hears a second sound (Akrami *et al.* 2018). After a "GO" cue, the animal then reports whether the first or second sound was louder by poking their nose into either a left or right port and receives a water reward for a correct answer. To receive a reward at the end of a trial, the animal should extract the relevant parameter (loudness) from the first stimulus, retain it through the delay, extract the same parameter (loudness) from the second stimulus, compare them, and report their decision. While previous work identified that the rat posterior parietal cortex (PPC, also called parietal association cortex) is critical for the influence of stimulus history in this task, other regions required for this behavior, notably the memory or persistence of the first stimulus, are unknown. To look at large areas of the dorsal cortex with the goal of identifying additional regions recruited in this task, we used the cScope, a recently developed head-mounted microscope to image Thy-1 transgenic rats broadly expressing GCaMP6f (Scott *et al.* 2018). We implanted a large (4 x 8 mm) glass window into the posterior dorsal surface of the cortex and recorded both hemodynamic and calcium signals at the

mesoscale level during tethered, freely-moving behavior. We report the activity dynamics within this area and correlate it with task parameters.

Disclosures: E.J. Dennis: None. **A. El Hady:** None. **C. Brody:** None.

Poster

599. Decision Making and Action Selection

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Topic: H.01. Animal Cognition and Behavior

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Title: Chronic recording using Neuropixels probes in freely moving rats accumulating auditory evidence

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Abstract: Complex behaviors, such as the gradual accumulation of evidence, depend on the simultaneous activity of many neurons across multiple brain areas. Electrophysiological measurement of large scale neuronal population activity is facilitated by recently developed high-density microelectrode recording probes (Neuropixels). While these probes have been widely applied to record acutely from animals performing tasks when they are head-fixed, chronic use for freely moving behaviors remains limited. An approach for chronic recording from freely moving mice has been recently described (Juavinett and Churchland, 2018). We describe a compact and scalable system for chronic recording and subsequent probe recovery from freely moving rats. The system consists of three components: an internal mount that attaches directly to the probe, an external chassis that encloses the internal mount and attaches to the skull, and a connector that houses the headstage and mates with the external chassis. The probe can be readily removed from the rest of the implant and recovered for future use. During a task that requires the gradual accumulation of auditory evidence, recording from tethered, freely moving rats took place for multiple hours without experimenter supervision. Rats performed at a similar behavioral performance as when they are untethered. Robust spiking signals from up to hundreds of neurons were recorded stably for multiple months. The small size of the system allows multiple probes to be implanted in the same animal, in addition to optical fibers or infusion cannulae for simultaneous recording or pharmacological perturbation. This system thus provides a simple, modular, and scalable approach for deploying Neuropixels probes in freely moving rats. We show data acquired using this system on which aspects of population-level signals related to evidence accumulation are interdependent across brain areas.

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Poster

599. Decision Making and Action Selection

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Title: Anterior and posterior dorsal striatum play distinct roles in evidence accumulation

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Abstract: Sensory-guided decision-making, in particular the accumulation of noisy sensory input across time, is a key cognitive function that remains the subject of intense study. Recent evidence suggests the dorsal striatum is a critical node in evidence accumulation. Firing rates of dorsal striatal neurons correlate strongly with the value of accumulated evidence in either rats integrating auditory evidence toward to a locomotor response or in monkeys accumulating visual evidence toward an eye movement response (Yartsev et al., 2018; Ding and Gold, 2013). Furthermore, optogenetic inactivation of two dorsal striatal subregions in rats, the anterior dorsal striatum (ADS) and posterior dorsal striatum (PDS), produces specific behavioral deficits in auditory evidence accumulation tasks (Yartsev et al., 2018; Znamenskiy and Zador, 2013). However, neuronal activity across the dorsal striatum during evidence accumulation has not been systematically characterized or directly compared. We therefore recorded from single neurons in ADS and PDS in rats performing a task requiring accumulation of competing streams of pulsatile auditory evidence generated by two sound sources . Task-modulated ADS neurons had firing rates that correlated with the value of accumulated evidence favoring a preferred choice during stimulus presentation, as well as strong choice-selective modulations of firing rate around the time of motor execution. By contrast, task-modulated PDS neurons showed less firing rate modulation related to accumulated evidence or choice. Instead, these neurons often responded vigorously and transiently to the individual auditory pulses with very short latencies, consistent with the area's auditory inputs. These pulse-aligned responses were spatially selective and thus can provide task-relevant sensory evidence for downstream brain areas.
We described these neuronal dynamics with a generalized linear model in which all task events, including the auditory pulses as well as motor actions, were used as covariates to predict neuronal spike times. Cross-validated variance explained on single trials was greater than 50% for some neurons, and the model fits captured the distinct relationships between sensory versus motor variables and neuronal spiking across the two areas. This approach will be expanded to

compare neuronal dynamics across many striatal, cortical and brainstem structures to distinguish their roles during auditory evidence accumulation.

Disclosures: **A.G. Bondy:** None. **C.D. Brody:** None. **T.Z. Luo:** None.

Poster

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Title: Neural basis of dynamic risk preferences in rats

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Abstract: Prospect Theory is the predominant behavioral economic theory describing decision-making under risk. We applied Prospect Theory's framework to rodents, using a task in which rats chose between guaranteed and probabilistic rewards. Like humans, rats distorted probabilities and showed diminishing marginal sensitivity, in which they were less sensitive to differences in larger rewards. They exhibited reference dependence, in which the valence of outcomes (gain or loss) was determined by an internal reference point reflecting reward history, and many rats exhibited loss aversion. However, Prospect Theory assumes stables preferences in the absence of learning, an assumption at odds with alternative frameworks such as animal learning theory and reinforcement learning. Rats also exhibited trial history effects, consistent with ongoing learning. A reinforcement learning model in which state-action values were updated by the subjective value of outcomes according to Prospect Theory reproduced rats' nonlinear utility and probability weighting functions, and also captured trial-by-trial dynamics. For example, rats exhibited a "risky win-stay" bias, in which they were more likely to gamble following risky rewards even though they were not more likely to win. Neurons in orbitofrontal cortex (OFC) encoded reward history and whether rats chose risky or safe options. Optogenetic inhibition of OFC eliminated the risky win-stay bias, but spared other sequential dependencies. These trial-by-trial dynamics, mediated by OFC, may reflect faulty inferences about reward contingencies or task states, which were stable but incorrectly inferred to be dynamic. We hypothesize that dynamic subjective preferences, including attitudes towards risk, may at times reflect suboptimal learning mediated by OFC.

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Poster

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Topic: H.01. Animal Cognition and Behavior

Support: CIHR

Title: The medial and lateral subregions of the orbitofrontal cortex play dissociable and opposing roles in cue-guided risk/reward decision making

Authors: M. VAN HOLSTEIN[1], P. MACLEOD[2], ***N. L. JENNI**[1], S. B. FLORESCO[3]; [1]Psychology, Univ. of British Columbia, Vancouver, BC, Canada; [2]Psychology, Univ. of Britsh Columbia, Vancouver, BC, Canada; [3]Psychology, Univ. British Columbia, Vancouver, BC, Canada

Abstract: We often face decisions requiring a choice between options that vary in terms of reward magnitude and uncertainty. In some situations, the probabilities of obtaining a desirable outcome can be inferred from environmental cues. For example, an experienced Blackjack player knows the odds of winning a hand are better when the dealer is showing a “6” compared to an “ace”. Studies with humans, where subjects are often presented with explicit cues informing about the probabilities of winning a gamble, have revealed these types of risk evaluations are supported by the orbitofrontal cortex (OFC). Previous work from our group has implicated the medial subregion of the OFC in probabilistic discounting, where the odds of receiving the large reward change gradually across blocks of trials. Here, the mOFC tempers the urge to chase large/risky rewards when profitability is low. In contrast, lateral OFC inactivations did not affect choice on this task. This adds to mounting evidence that the OFC is made up of functionally heterogenous subregions. Another region known to modulate risky choice, at least in the context of losses, is the agranular insula. (AI). However, it is unclear how these regions contribute to cue-guided risky/reward decision making. To assess how the mOFC, lOFC and AI contribute to risky decision making when odds are explicitly cued, we used a novel “Blackjack” task. Rats were well-trained to choose between a certain 1 pellet or a large/risky 4 pellet reward. Critically, distinct auditory stimuli informed the rat of the probability of obtaining that large reward on a given trial: either 50% (good odds) or 12.5% (poor odds). mOFC inactivation reduced risky choice, and this effect was accompanied by an increase in sensitivity to feedback when the odds were good. This suggests that activity in the mOFC dampens the impact of the previous outcome on choice, specifically when choosing risky is the most advantageous strategy. In stark contrast, lOFC inactivation increased risky choice, accompanied by a reduction in the tendency to choose

the small/certain option after a recent loss. Thus, the lOFC may facilitate adaptation of choice strategy after negative feedback. AI inactivation had no effect on any decision variables measured. The mOFC and lOFC appear to play opposing roles in risky decision-making, specifically in situations where probabilistic odds are both previously learnt, and explicitly cued. These functions vary greatly compared to their role in risky choice guided by internal representations of changes in reward probabilities. These findings highlight novel roles for the m/lOFC and highlight the complexity with which the OFC functions to promote profitable choice.

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Poster

599. Decision Making and Action Selection

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Title: The abused inhalant toluene disrupts activity of medial prefrontal cortex (mPFC) glutamatergic neurons under conditions of uncertainty

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Abstract: Volatile organic solvents like toluene cause intoxication and changes in brain function similar to those produced by classic drugs of abuse. For example, we previously demonstrated that toluene, applied acutely to medial prefrontal cortex (mPFC) brain slices, caused a long-lasting depression in glutamatergic synaptic transmission in deep-layer pyramidal neurons. The consequence of this effect is unknown, but would be expected to disrupt behaviors that require a functional mPFC. The present set of experiments used the mPFC-dependent probabilistic discounting task combined with *in vivo* fiber photometry to study decision making in the face of uncertain outcomes. In brief, Sprague-Dawley rats were trained to lever press for a reward (20% sweetened condensed milk): one lever delivered a small, certain reward (30 µl, 100% of the time) while a second lever delivered a large, uncertain reward (90 µl, reinforcement probability

shifts incrementally from 100% to 6.25%). We previously reported that the effect of toluene on this task depends on the order in which odds were presented, a pattern of responding that mimics pharmacological inactivation of the mPFC. It is not known, however, which portions of the task (e.g. generalized attention, choice selection, consumption encoding) depend on mPFC activity. To address this, we virally expressed the genetically encoded calcium sensor GCaMP6f in glutamatergic mPFC neurons and monitored calcium transients in real-time using *in vivo* fiber photometry. During free choice trials, mPFC activity peaked before either lever press. However, during forced choice trials, a peak only occurred when that lever produced an optimal outcome based on reward probabilities (shifting from risky lever to safe lever throughout the session). Toluene pretreatment caused a delayed and incomplete shift of this activity pattern. During reward consumption, mPFC activity decreased proportionally with time spent in the food well, and the depression following a risky win was larger than following a safe win. Following toluene exposure, mPFC activity also decreased during reward consumption, but it was not correlated with consumption time, resulting in no distinction between signal during safe vs risky wins. These results provide a physiological basis for the mPFC's theorized role in updating action - outcome contingencies and further implicate mPFC dysfunction in the behavioral flexibility deficits caused by toluene. More importantly, understanding this physiology may help guide the treatment of neuropsychiatric diseases marked by aberrant choice. Funding: NIDA R01 DA013951, NIAAA T32 AA007474, NIDA 2T32 DA007288, and NIDA F31DA045485.

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Poster

599. Decision Making and Action Selection

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Support: CIHR

Title: Mesocortical dopamine modulation of cue-guided, risk/reward decision making

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Abstract: The ability to make optimal choices between options that vary in terms of reward magnitude and uncertainty is a critical survival skill. Probabilistic decision-making paradigms often require human subjects to utilize external cues to guide decisions. On the other hand, studies of probabilistic decision making in rodents typically use tasks such as probabilistic discounting where choice is guided by internal representations of reward probabilities. Both in

human and rodent studies, probabilistic decision making relies on the medial prefrontal cortex (mPFC) and mesocortical dopamine transmission. However, it is unclear whether findings using probabilistic discounting assays are comparable to those obtained using cued tasks. Our group has recently developed a rodent operant assay which requires the use of explicit cues signaling the "odds" associated with various choices. In each trial of this "Blackjack task", rats choose between a small/certain option (1 pellet delivered with 100% probability) and a large/risky option (4 pellets) delivered in a probabilistic manner. On each trial, the odds of obtaining the large /risky reward (good - 50% or poor -12.5% odds) are signaled by distinct auditory cues. Previously, our group has revealed that the dorsal mPFC facilitates risky choice on good odds trials, whereas the ventral mPFC suppresses risky choice on poor odds trials. However, how PFC dopamine receptors modulate cue-guided probabilistic decision making is unknown. Here, we assessed the effect of blockade of dopamine D1, D2 and D4 receptors in the prelimbic cortex in rats well trained on the Blackjack task. Previous work by our group using probabilistic discounting tasks showed that dopamine D1 receptor blockade in the mPFC decreases risky choice whereas D2 blockade impairs adjustments in choice in response to changes in reward probabilities. In the present study, we show that blockade of D2 (but surprisingly, not D_1) receptors decreased risky choice on good odds trials - similar to the effect of prelimbic PFC inactivation. These data demonstrate a role for prefrontal dopamine receptors in cue guided risk/reward decision making that is distinct from their role in other types of risk/reward decision making.

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Poster

599. Decision Making and Action Selection

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Support: CIHR

Title: Increased corticotropin releasing factor signaling increases ventral tegmental area dopamine neuron activity

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Abstract: The neuropeptide corticotropin-releasing factor (CRF) is increased following episodes of acute stress and in patients with stress-related disorders, such as depression. Both stress and CRF alter motivational and effort-related decision making functions mediated by dopamine (DA)

function, which may be mediated by CRF-induced alterations in DA neural activity. However CRF/DA interactions are complex, with *in vitro* experiments reveal that CRF can increase or decrease excitatory and/or inhibitory transmission on DA neurons in the ventral tegmental area (VTA). Intracerebroventrical (ICV) CRF antagonism increases VTA DA neuron population activity, suggesting that CRF tonically inhibits spontaneous DA activity. However, intra-VTA CRF infusion reduces afferent input from the pedunculopontine tegmentum (PPTg), reducing motivation by blunting phasic DA release to reward. On the other hand, both ICV CRF and nucleus accumbens D_2 receptor stimulation reduce choice of larger rewards associated with greater effort costs (Bryce and Floresco, 2016, 2019), suggesting that increased central CRF reduces motivation by increasing mesoaccumbens DA release. Given these complex findings, we sought to clarify how excessive central CRF affects activity of VTA DA neuron physiology *in vivo*. Male rats received behaviorally-relevant doses of vehicle or CRF (1-3υg, ICV). Recording electrodes were lowered in the VTA to measure DA and GABA neuron activity, assessing overall population activity, basal firing rate, and burst firing. Both doses of CRF increased VTA DA and GABA firing rates, and 3υg CRF increased population activity, with no effects on burst firing. Together these findings suggest that excessive central CRF signaling increases tonic, but not phasic, DA neuron activity, serving to potentiate mesocorticolimbic DA release. Future experiments will investigate how excessive central CRF signaling alters afferent input to the VTA from the PPTg and prefrontal cortex. Understanding how CRF interacts with VTA DA signaling will help us elucidate how CRF hyperactivity may underlie symptom clusters common to various stress-related disorders characterized by altered DA function, such as depression.

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Poster

599. Decision Making and Action Selection

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Title: Oscillatory phase-locking within the primate anterior cingulate gyrus and basolateral amygdala in social decision-making

Authors: *C. C. J. CHU, O. DAL MONTE, N. A. FAGAN, S. W. CHANG;
Dept. of Psychology, Yale Univ., New Haven, CT

Abstract: In social decision-making, different decisions linked to preference and agency need to be accurately differentiated. Currently, we understand little about the neural mechanisms underlying this process. Although we are beginning to comprehend fundamental spike-based codes used by multiple brain areas in social decision-making, our knowledge on other neural mechanisms is lacking. Phase-locking of local field potential activity (LFP) has been found to facilitate various cognitive functions. Oscillatory properties of LFP may become entrained to a particular stimulus or behavioral event and may help reset the communication between different frequency channels to enhance signal processing (e.g.,. see Taub, Perets, Kahana, Paz, 2018 for phase-locking in the anterior cingulate cortex with the amygdala spiking activity in theta frequency during conditional learning). It remains unknown whether LFP phase-locking is also implicated in social decision-making. Here, we investigated this question by examining LFP signals within the rostral ACC gyrus (ACCg) and the basolateral amygdala (BLA) during a social reward allocation task involving pairs of rhesus macaques. Behaviorally, actor monkeys preferred to deliver a juice reward to a conspecific (*Other*) over a juice collection bottle (*Bottle*), displaying a prosocial decision preference, but preferred to consume a juice reward alone (*Self*) over simultaneously with the conspecific (*Both*), displaying an antisocial decision preference. During these behaviors, we examined phase-locking of LFPs across trials within ACCg and BLA by computing the mean resultant vector length. We observed two types of phase-locking differences in the LFPs encompassing theta (4-8Hz) and beta (15-25) ranges. First, both ACCg and BLA exhibited more sustained phase-locking for choosing an option resulting in actor's received juice reward (*Self* or *Both*) compared to choosing an option resulting in no juice reward to the actors (*Other* or *Bottle*). Second, in ACCg, phase-locking patterns were further differentiated between *Other* and *Bottle* choices such that the phase-locking for *Other* emerged earlier prior to the time of decision and was more temporally widespread. These results suggest that phase-locking in both ACCg and BLA may differentiate one's received and forgone rewards during social decision-making. Moreover, phase-locking in ACCg may be further used to distinguish between prosocial and antisocial decisions. LFP phase-locking in these brain areas may thus contribute to social decision-making by selectively promoting neural communications among different choices.

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Poster

599. Decision Making and Action Selection

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Title: Exploring shared neural codes across social gaze and reward value in the primate brain

Authors: *O. DAL MONTE, S. FAN, N. FAGAN, C. C. J. CHU, S. W. CHANG;
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Abstract: Social gaze interaction plays a dominant role in communicating information between individuals both in human and non-human primates. When we direct our attention to someone's eyes, for example, this decision is likely driven by the value associated with acquiring information from the eyes. However, it remains unclear whether neural codes used during social gaze interaction and non-social reward valuation are linked in any way within overlapping neurons in the primate brain. Previous single-neuron recording studies have found that neurons from several cortical and subcortical regions encode juice reward value as well as social value derived from various social information and social contexts (Azzi et al., 2012; Watson et al., 2012; Chang et al., 2013; Klein et al., 2013; Báez-Mendoza et al., 2013; Noritake et al., 2018). Particularly strong evidence for such relations came from the primate amygdala where identical subsets of neurons are found to encode juice value as well as social value such as conspecific's social status (Munuera et al., 2018). Here, we extend this line of work by examining neural codes used between social gaze interaction and non-social reward valuation in three distinct prefrontal areas and the amygdala. Across spontaneous social gaze interaction between pairs of macaques (Dal Monte et al., 2016, 2017) and non-social reward value association task, single-unit activity was recorded from a large number of neurons in the basolateral amygdala (BLA, n=564) and medial and orbital prefrontal structures - the rostral anterior cingulate gyrus (ACCg, n=249), the dorsomedial prefrontal cortex (dmPFC, n=236), and the orbitofrontal cortex (OFC, n=244). Based on a linear decoding analysis, neurons in all these areas discriminated juice value (small vs. large size) and social gaze region (e.g., eyes vs. non-eye region of the face) above chance. Upon applying cross-decoding analyses to directly test if overlapping neurons use generalizable neural codes for differentiating social gaze variables and juice reward value, we found that this generalizability depends on brain regions and specific social gaze variables. Overall, our findings indicate that reward valuation mechanism might be shared with computing social gaze variables in some but not all areas where reward value and social gaze signals are encountered.

Disclosures: O. Dal Monte: None. **S. Fan:** None. **N. Fagan:** None. **C.C.J. Chu:** None. **S.W. Chang:** None.

Poster

599. Decision Making and Action Selection

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 599.25/X40

Topic: H.01. Animal Cognition and Behavior

Support: National Institute of Mental Health (R01MH110750)

Yale Teresa Seessel Postdoctoral Fellowship

Title: Neuronal coordination across primate prefrontal regions and the amygdala in spontaneous social gaze interaction

Authors: *S. FAN, O. DAL MONTE, N. A. FAGAN, C. C. J. CHU, S. W. CHANG;
Dept. of Psychology, Yale Univ., New Haven, CT

Abstract: In primates, social gaze interaction serves an important function in communicating social information. Electrophysiological recording studies in non-human primates and neuroimaging studies in humans have shown that regions in the prefrontal cortex, the superior temporal sulcus, as well as the amygdala are implicated in social gaze processing. Yet, how different brain regions coordinate their neuronal activity during social gaze interaction remains elusive. We recorded single-unit and local field potential (LFP) activity from a large number of cells in three prefrontal regions—the rostral anterior cingulate gyrus (ACCg, n=249), orbitofrontal cortex (OFC, n=244), and dorsomedial prefrontal cortex (dmPFC, n=236)—and the basolateral amygdala (BLA, n=564) to examine the coordination of spiking and LFP between BLA and each of these prefrontal areas while pairs of rhesus macaques spontaneously interacted using gaze. We observed distinct spike-field coherence patterns across these three pairs of regions with respect to looking at the eyes of a conspecific compared to a non-social object. These coherence patterns were also frequency-specific depending on the spike contributor in a given pair. Specifically, spikes from BLA cells and LFP activity from ACCg (BLA[spikes]-ACCg[field]) showed enhanced synchrony in the beta frequency range (15-25Hz) immediately after looking at the eyes compared to an object. By contrast, ACCg[spikes]-BLA[field] coherence was enhanced in the gamma frequency band (45-70Hz) for the same comparison. Intriguingly, we recently observed enhanced spike-field coordination in the same two frequency bands across ACCg and BLA when monkeys expressed prosocial decision preference compared to antisocial decision preference in a social decision-making task (Dal Monte et al, 2019, BioRxiv). Moreover, while ACCg[spikes]-BLA[field] coherence was increased around and after looking at the eyes relative to an object in the gamma band, dmPFC[spikes]-BLA[field] coherence was enhanced mostly prior to looking at eyes in the gamma band, suggesting a possible role of dmPFC[spikes]-BLA[field] synchrony in social gaze planning. By contrast, we did not observe consistent coordination across OFC and BLA in either frequency band. These results demonstrate that social gaze is facilitated by specialized coordination of spiking and LFP activity in the primate prefrontal-amygdala network. Finally, the shared frequency channels utilized across ACCg and BLA between social gaze interaction and social decision-making imply that these coordination dynamics may be generalized across distinct social behaviors.

Disclosures: S. Fan: None. **O. Dal Monte:** None. **N.A. Fagan:** None. **C.C.J. Chu:** None. **S.W. Chang:** None.

Poster

600. Working Memory, Aging, and the Hippocampus

Location: Hall A

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Program #/Poster #: 600.01/X41

Topic: H.01. Animal Cognition and Behavior

Support: BMBF GERONTOSYS 0315581

Title: Enriched environment restores cognition and reverses aging-associated transcriptional changes in the hippocampus of old c57bl/6 mice

Authors: *C. FRAHM[1], M. GÜNTHER[1], S. SCHMIDT[1], C. KALETA[2], O. W. WITTE[1]; [1]Hans Berger Dept. of Neurol., Univ. Hosp. Jena, Jena, Germany; [2]Inst. of Exptl. Medicine, Res. Group Med. Systems Biol., Christian-Albrechts-University Kiel (UKSH Campus), Kiel, Germany

Abstract: BACKGROUND: The decline of cognitive functions is currently among the greatest health threats of old age. Therefore, measures to maintain cognitive ability and prevent dementia are of substantial importance. An active lifestyle with social interactions and physical activity - even when initiated at old age - can increase brain plasticity and improve cognition. However, the underlying mechanisms are still largely unknown, so that targeted therapies are not available yet. Here we examined to what extent exposure of old mice to an enriched environment (EE) promotes cognition and whether aging-associated transcriptional changes in the hippocampus can be slowed or even reversed. METHODS: Mice at the age of 22 months were transferred to an EE. In parallel, a group of old mice was maintained in standard conditions. After 2 months mice were subjected to the Barnes Maze Test or the hippocampus was isolated for RNAseq. Differentially expressed genes were identified using DESeq and edgeR from the R package. In parallel, we assessed changes in the activity of individual molecular processes through mapping of gene expression data onto processes annotated in Gene Ontology and determining differentially active processes directly. RESULTS: After 2 months of EE, 24-month-old mice exhibited an improved cognition which was undistinguishable from that of five months old controls. On the transcript level, we identified 503 significantly age-regulated genes (DEGs, 24 vs. 5 months) and 551 DEGs in response to EE in 24-month-old mice compared to 24-month-old controls. 124 differentially expressed genes overlapped between aging and in response to EE. Genes induced during aging were down-regulated by EE and vice versa suggesting that EE led to a reversal of age-related changes on the molecular level. Similar changes could be observed on process level. We identified 851 processes that showed significant changes in activity with aging while 332 processes changed activity in response to EE. Of the 32 commonly regulated processes between aging and EE, 13 processes changed activity in the same direction while 19 showed opposing directions of regulation between aging and EE. CONCLUSION: An

intervention in the form of an EE with already aged mice improves cognition and leads to a reversal or slowing down of aging-associated transcriptional changes in the hippocampus on gene and functional Level.

Disclosures: C. Frahm: None. **M. Günther:** None. **S. Schmidt:** None. **C. Kaleta:** None. **O.W. Witte:** None.

Poster

600. Working Memory, Aging, and the Hippocampus

Location: Hall A

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Program #/Poster #: 600.02/X42

Topic: H.01. Animal Cognition and Behavior

Support: NSF Grant IOS 08-4317
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Startup funds for Lori A. Newman from Vassar College

Title: Shifts in lactate during learning and memory with age from the hippocampus to the striatum: A focus on within trial extracellular lactate levels

Authors: *N. SHUKLA[1], D. ELENDU[2], C. GAHN[3], L. A. NEWMAN[4], P. E. GOLD[5], D. L. KOROL[5];
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Abstract: Alterations in glucose and energy metabolism have been associated with normal aging and the etiology of neurodegenerative diseases. Extracellular lactate, shuttled from astrocytes to neurons, has been shown to support spatial working memory in the hippocampus. Past studies have shown that glucose levels are diminished in the hippocampus in response to memory loads while lactate levels are increased. Additionally, inhibition of astrocytic glycogenolysis, which leads to lactate production, within the hippocampus has been associated with impaired performance on tasks of spatial memory. According to the multiple memory system theory, the striatum and the hippocampus have been shown to mediate dissociable types of learning. Response learning is correlated with physiological measures of activity in the striatum and place learning is correlated with physiological activation of the hippocampus. Additionally, prior research has suggested response learning improves with age while place learning declines. In the

current experiment, sensitive bioprobes (Pinnacle Technology) were used to measure extracellular brain lactate levels in the dorsolateral striatum or the dorsal hippocampus of young (age 3 months, n=15) or aged (age 24 months, n=11) male Fischer 344 rats in 1-sec intervals during spontaneous alternation, place learning, and response learning. Our prior data found lactate levels during learning and memory tasks were lower in aged rats compared to young rats. In this study, we explored the changes in lactate associated with discrete behaviors within the tasks. We observed brain region differences in extracellular lactate levels between old and young rats at the point of arm entries in the tasks. Increasing cognitive demands are correlated with greater declines in extracellular lactate in the hippocampus of young animals but not aged animals. Notably, we observed decreases in extracellular lactate levels in the striatum of aged rats after arm entries during tasks of spatial working memory and spatial learning, which are traditionally associated with the hippocampus. Our findings thus fit with the previous literature suggesting a shift in engagement and activity from the hippocampus to the striatum with age.

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Poster

600. Working Memory, Aging, and the Hippocampus

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

Support: Intramural Research Program of the NIA
Support was received from BBSRC grant BB/P004806/1

Title: Retinoic acid signalling differences in the hippocampus of aged rats with and without memory impairment

Authors: *M. U. WOLOSZYNOWSKA-FRASER[1], S. L. ROSSI[1], J. M. LONG[1], P. J. MCCAFFERY[2], P. R. RAPP[1];
[1]Lab. of Behavioral Neurosci., Natl. Inst. on Aging, Baltimore, MD; [2]Univ. of Aberdeen, Aberdeen, United Kingdom

Abstract: Retinoic acid (RA), a metabolite of vitamin A (retinol), has many key physiological functions, including roles in neuronal plasticity and homeostatic synaptic scaling in the hippocampus. Through binding to its receptor (RARα) and increasing dendritic synthesis of ionotropic glutamate receptors (GluR1), RA modulates synaptic efficacy in response to learning-induced changes. Retinol deficiency during adolescence causes memory impairments, and vitamin A supplementation can reverse these deficits. Although recent studies have expanded the understanding of RA function in memory processes, its role in neurocognitive aging has received

limited attention. Therefore, we asked if changes in RA signalling contributes to neurocognitive aging. Emphasising hippocampal dependent spatial memory, we used a well-established Morris water maze protocol and 24 male Long-Evans rats were characterized according to age and cognitive status, as either young (Y), aged unimpaired (AU) or aged impaired (AI). We measured serum levels of retinol binding protein (RBP4) and hippocampal protein levels of RA synthesizing (RALDH1; RALDH3) and catabolizing (CYP26A1; CYP26B1) enzymes. Additionally, RARα and GluR1 levels were measured in whole hippocampus lysates. We found significantly lower serum RBP4 in AU animals and decreased hippocampal protein expression of RALDH1 in aged rats, relative to Y ($p<0.05$), consistent with reports of decreased RA metabolism with age. However, serum RBP4, and protein expression of CYP26B1, and GluR1 in the whole hippocampus lysates were significantly increased in AI animals when compared with AU rats ($p<0.05$). Moreover, RARα expression was significantly increased in AI animals compared to Y ($p<0.05$). RALDH3 and CYP26A1 levels were unchanged. These results are indicative of increased RA metabolism in impaired aged rats, and overall, that altered hippocampal RA signalling is positioned to influence individual differences in the cognitive outcome of aging. Ultimately, our aim is to test whether exogenous manipulation of RA signalling in the hippocampus (stimulation or inhibition) affects the neurocognitive impairment in aging.
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Poster

600. Working Memory, Aging, and the Hippocampus

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Support: Luis Miguel Rodríguez-Serrano (CVU:237130), was supported by CONACyT postdoctoral grand, Mexico.
Financiamiento de la dirección de investigación de la Universidad Iberoamericana

Title: Sexual behavior can improve memory consolidation in young and adult male rats

Authors: *L. RODRIGUEZ-SERRANO[1], L. HERNÁNDEZ-GONZÁLEZ[1], A. RAMÍREZ-MAZÓN[3], M. MATA ESQUIVIAZ[1], A. TAPIA[1], P. ESPINOSA MIRELES DE VILLAFRANCA[1], O. GALICIA-CASTILLO[1], M. H. BUENROSTRO-JAUREGUI[2];
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Abstract: Recent experiments have shown that sexual interactions can induce neurogenesis, particularly in the hippocampus, and thus enhance the memory process. Some studies suggest that sexual interactions prevented a reduction in neurogenesis caused by exposure to chronic stress. Also, sexual activity enhanced the expression of BDNF, TrkB and CREB in the adult hippocampus (Kim, 2013). On the other hand, in both humans and rodents, aging is associated with decreased memory and neurogenesis in the hippocampus. We hypothesized that adult-male rats with sexual interaction will show higher memory retention compared to control groups. Thus, the aim of the present study is to determine if sexual interaction facilitates the consolidation of memory in young and adult male rats. We used young (12 weeks of age) and adult (36 weeks of age) male Wistar rats. Experimental groups (young and adult) were exposed to sexual interaction with receptive females for four trials (each session for 30 min) to gain sexual experience, while control groups were kept undisturbed in their home cage. Once sexual interaction was concluded, rats were trained in an inhibitory avoidance task using a foot-shock of 0.6 mA. Results show that, compared to control groups, those exposed to sexual interaction enhanced consolidation of memory. Also, adult sexual interaction groups showed better retention in the memory task when compared to young sexual interaction groups. Overall, these results indicate that sexual interaction can revert the effects of aging, such as cognitive decline.

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Poster

600. Working Memory, Aging, and the Hippocampus

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 600.05/X45

Topic: H.01. Animal Cognition and Behavior

Support: MRC CASE award

Title: Age-dependent changes in innate neuroimmunity affect hippocampal function

Authors: A. F. SMITH[1], A. ROT[2], *M. A. WHITTINGTON[1];
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Abstract: It is increasingly evident that the brain’s immune system is essential for normal cognitive function. When activated to excess, immune modulators are linked to pathology in

neurodegenerative disorders[1,2]. However, we know little of how baseline levels of these immune modulators shape normal neuronal function, nor how changes in neuroimmunity with age[3] relate to cognitive decline with normal senescence. Here we examine the effects of a subset of chemokine neuroimmune mediators on the activity of the hippocampus.
We took local field potential (LFP) recordings from subregions of hippocampal slices maintained *in vitro* following entorhinal cortex stimulation. Slices were prepared from mice at two age-points: Young adult (9-15 weeks old) and middle aged (25-35 weeks old). 3 genetic backgrounds were used: Wild-type controls (WT); mice lacking the chemokine receptor CCR5 ($CCR5^{-/-}$); mice lacking the atypical chemokine receptor ACKR1 ($ACKR1^{-/-}$). Enhanced chemokine signalling associated with neuroinflammation was, in part, modelled by bath application of the chemokine receptor ligand CCL5.
Slices from WT and $CCR5^{-/-}$ showed increased mean LFP response magnitude (area under stimulus-response curve) with age (WT young 13.8±1.9 vs aged WT 29.0±6.6, $P \leq 0.03$, and $CCR5^{-/-}$ young 12.2±4.7 vs aged $CCR5^{-/-}$ 31.0±6.2, $P \leq 0.03$) in dentate gyrus (DG, the main input subregion of the hippocampus) but not downstream area CA3. In contrast, slices from $ACKR1^{-/-}$ mice showed a decrease in mean LFP magnitude in the s*uprapyramidal* subregion of dentate gyrus (WT 1.1±0.5 vs $ACKR1^{-/-}$ -0.5±0.2, $P \leq 0.006$ and $ACKR1^{-/-}$ vs $CCR5^{-/-}$ 1.5±0.5, $P \leq 0.003$). This change was not affected by elevated CCL5 chemokine levels (10µg/ml) in young or older WT mice.
The data indicated a subregion-specific role for chemokine signalling for both age-related changes in DG function, and response to chemokine level increases associated with neuroinflammation. In both cases the age-related effects were profoundly altered in the absence of ACKR1, suggesting that changes in ACKR1-dependent chemokine signalling may play a pivotal role in normal cognitive decline and elevated susceptibility to neuroinflammation in senescence.
1. Mendiola, A. S. and Cardona, A. E. (2018) *J Neural Transm (Vienna)*, 125(5), pp. 781-795. 2. Taylor, J. M., Moore, Z., Minter, M. R. and Crack, P. J. (2018) *Journal of Neural Transmission*, 125(5), pp. 797-807. 3. Lynch, M. A. (2010) *Frontiers in Aging Neuroscience*, 1, pp. 8.

Disclosures: **A.F. Smith:** None. **A. Rot:** None. **M.A. Whittington:** None.

Poster

600. Working Memory, Aging, and the Hippocampus

Location: Hall A

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Program #/Poster #: 600.06/X46

Topic: H.01. Animal Cognition and Behavior

Support: Ministerio de Economía y Competitividad (PSI2017-84290-R)

Title: Effects of age, diet and histone deacetylase inhibition on hippocampal memories

Authors: *G. GUILLAZO-BLANCH, A. VALE-MARTÍNEZ, M. PORTERO-TRESSERRA, M. MARTÍ-NICOLOVIUS;
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Abstract: Variability in the trajectory of cognitive aging is due to genetic and environmental factors that affect our susceptibility or resilience to aging effects. Age-related cognitive decline correlates with decreased expression of hippocampal genes linked to synaptic plasticity and altered expression of immediate early genes. These transcription-signaling pathways interact with epigenetic mechanisms that may be modulated by environmental factors such as diet. For instance, a caloric restriction (CR) diet increases neurogenesis, improves memory, and protects from age-associated neurological disorders. The anti-aging value of CR has been proposed to act on epigenetic mechanisms, being histone acetylation and deacetylation two of the main players in these mechanisms. Since changes in histone acetylation have been linked to age-associated hippocampal memory decline, a recovery of their activity through histone deacetylase inhibitors -such as sodium butyrate (NaBu)- might delay the age-related hippocampal dysfunction. We assessed adult (3-month-old) and aged (24-month-old) male Wistar rats, with the goal to study the effects of both a life-long CR diet (25-30% of food intake reduction from 4-months-old) and administration of NaBu (1.2gr/Kg). The effects of both treatments were evaluated on two hippocampal-dependent learning tasks, the Morris water maze (MWM) and the object recognition task (ORT). The MWM task consisted of four daily acquisition trials for five days and a memory test conducted 72 h after the last acquisition session. The ORT entailed a 10-min acquisition session and two memory tests (24h and 72h). Immediately after each MWM and ORT acquisition session, rats received an intraperitoneal injection of saline or NaBu. The results revealed that both, post-training infusions of NaBu and CR diet prevented the deleterious effects of age on hippocampal memories. Animals fed ad libitum exhibited a lower performance when compared to old animals under CR, and aged NaBu-treated rats under CR did not differ from adult rats in the performance displayed in both tasks. These results cannot be attributed to alterations in sensory discrimination or locomotor activity. Our findings suggest that modulation of epigenetic factors may be a suitable strategy for the study of the mechanisms responsible for age-related cognitive decline and provide an effective approach to test new treatments aimed to alleviate memory deficits.

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Poster

600. Working Memory, Aging, and the Hippocampus

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 600.07/Y1

Topic: H.01. Animal Cognition and Behavior

Title: Neuroprotective effects of thymoquinone on the learning and memory mechanisms and hippocampal neurogenesis in aged rats

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Abstract: Thymoquinone (TQ) is the main active constituent of volatile oil from *Nigella sativa* seeds which has exhibited various beneficial properties in modern pharmacology including anti-inflammatory actions, suppression of oxidative stress-induced neuropathy, and neuroprotection. In this study, we aimed to investigate the effect of TQ on hippocampal neurogenesis of aged-rats both in functional and molecular perspectives. After determining blood-brain permeability of TQ by analyzing the presence of it in BOS by HPLC, TQ (10 mg/kg and 20 mg/kg, i.p.) was given to 15-month-old aged Long-Evans rats for 15 days. At the end of 15 days, the animals were subjected to some behavioral tests in terms of cognitive functions. There was no difference in the fear-conditioned memory determined by passive avoidance and the spatial memory determined by Morris water maze. On the second day of the spatial learning test, older rats receiving TQ showed better performance than their age-matched control group. From a molecular perspective, TQ increased the oxidative stress in elderly animals. In the high dose of TQ (20 mg/kg), the amount of IFNγ increased with no change in the levels of Ilα, Ilβ, and TNFα. However, low dose TQ decreased IFNγ level in the old animals. In parallel, an increase in the level of CORT and ACTH, which are stress indicators, was also detected. While there was no significant change in the level of DCX in old animals, it has been found that the expression of some neuroprotective proteins which are also related with synaptic plasticity (Klotho, prealbumin, clic6, BDNF, GDNF and NeuN) altered in elderly animals with TQ treatment. These results show that TQ administration in the elderly increases some neuroprotective properties by increasing synaptic plasticity, even if it made animals more stressed.

Disclosures: **B. Elibol:** None. **S. Terzioglu-Usak:** None. **M. Beker:** None. **S. Eyuboglu:** None.

Poster

600. Working Memory, Aging, and the Hippocampus

Location: Hall A

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Program #/Poster #: 600.08/Y2

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation
RO1 AG050548

Title: Role of prefrontal-hippocampal interactions in age-related deficits in spatial working memory

Authors: *S. V. SRIVATHSA[1,2], S. O. KHATTAB[1,2], A. W. LESTER[1,2], C. A. BARNES[1,2,3]; [1]Evelyn F. McKnight Brain Inst., [2]Div. of Neural Systems, Memory and Aging, [3]Departments of Psychology, Neurol. and Neurosci., Univ. of Arizona, Tucson, AZ

Abstract: Neural ensembles in hippocampus and mPFC play a crucial role in memory-guided navigation and decision making, a process susceptible to decline with age in mammals. These regions are connected via a unidirectional projection from the ventral hippocampus to the mPFC and damage or inhibition of this circuit leads to impairments in spatial alternation tasks (Wang et al, 2006). Rats with mPFC lesions show an impairment on spatial working memory tasks (Kim et al., 2009). On the other hand, rats with hippocampal lesions are impaired in both the spatial localization and spatial working memory components (Sapiurka et al., 2016). One task that was developed to test the interactions between these regions is a continuous spatial alternation task (Frank et al., 2000), which consists of two interleaved components: an "outbound" component (working memory) and an "inbound" component (spatial memory). Behavioral data from young (9-15 mo) and old (23-30 mo) rats tested on this task reveals that aged rats are slower in learning the inbound component and are unable to learn the outbound component (Kapellusch et al., 2018). The outbound component of the task requires coordination between the hippocampus and mPFC, suggesting that these interactions are impaired in aged rats. Here, we report data from an ongoing experiment studying the age-associated changes in the hippocampal-mPFC circuit that underlie the behavioral decline in spatial alternation in aged rats through simultaneous electrophysiological recordings in the ventral CA1 region of the hippocampus and in the dorsal ACC region of the mPFC. As disruption of hippocampal SWRs during awake rest leads to impairment of working memory performance (Jadhav et al., 2012) and CA1-mPFC synchronization is stronger during awake SWRs and enhanced in early stages of learning (Tang et al., 2017), several predictions of impact of age on these circuits can be offered. First, there may be a decrease in the synchronization between CA1 and mPFC unit activity during behavior in aged rats compared to young rats. This is likely to show a strong correlation with the age-related impairments in learning the outbound component. Second, since co-occurrence of hippocampal SWRs and spindles in the mPFC during sleep has been implicated in memory consolidation (Maingret et al., 2016), examining this relationship may provide insights into changes in memory consolidation with age. Furthermore, as increased coupling of the hippocampus and mPFC to the theta and gamma bands is correlated with spatial working memory (Jones et al., 2005; Tamura et al., 2017), we will study the disparities in this coupling during the working memory epochs of the task, between the age groups.

Disclosures: S.V. Srivathsa: None. **S.O. Khattab:** None. **A.W. Lester:** None. **C.A. Barnes:** None.

Poster

600. Working Memory, Aging, and the Hippocampus

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Program #/Poster #: 600.09/Y3

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation
R01 AG012609

Title: Spatial eye-blink learning but not age predicts theta-gamma coupling in the CA1 region of the hippocampus

Authors: *L. CROWN[1,2,3], D. T. GRAY[2,3], L. A. SCHIMANSKI[6], C. A. BARNES[2,3,4], S. L. COWEN[5,2,3];
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Abstract: Cross-frequency coupling (CFC) between theta- and gamma-band activity in the hippocampus has been linked to memory encoding and retrieval. Recent data suggest that the frequency of the gamma-band component of theta-gamma CFC differs as the relative contribution of entorhinal or hippocampal CA3 drive to mnemonic circuits within CA1 changes. While there are differing interpretations with respect to the generation of low gamma (25 - 50 Hz), one hypothesis is that it reflects drive from CA3 to CA1 while high gamma (75 - 90 Hz) denotes drive from medial entorhinal cortex (MEC) to CA1 (Colgin et al., 2009). Little is known about how activity in these frequency bands and their coupling changes with age; however, there are fewer functional Schaffer collateral synapses onto CA1 pyramidal cells and CA3 pyramidal cells show increased excitability. Given such alterations in these network properties, we hypothesized that high-gamma CFC associated with entorhinal input would be greater in aged animals. To examine this question, local field potential activity of 12 rats (n = 6 young, 9-12 mo, n = 6 old, 25-28 mo) was analyzed as they performed a spatial eye-blink conditioning task (Schimanski et al., 2013). We measured low-gamma power, high-gamma power, and theta-gamma phase-amplitude coupling (PAC) as animals approached and departed from the region of the maze associated with a brief eyelid stimulation. We observed no difference between young and old animals in 1) peak gamma frequency, 2) in CFC, or 3) the ratio of low- to high-gamma power. Interestingly, we observed that animals that did not develop reliable eye blink conditioning (n = 5), regardless of their age, showed greater low-gamma relative to high-gamma power than those (n = 7) that did consistently show conditioning (two-sample t-test, p = 0.01). This effect was apparent after 5 days of training, suggesting that eye blink training altered the

relative contribution of entorhinal drive to CA1. In addition, low-gamma PAC, but not high-gamma PAC, recorded as animals approached the eye-shock zone, was positively correlated with eye-blink learning in those animals that learned the task (one-sample t-test, $p < 0.01$), but not in animals that did not display learning, regardless of age. Taken together, these results suggest that age is a less important predictor of CA1 theta/gamma dynamics than is performance.

Disclosures: L. Crown: None. **D.T. Gray:** None. **L.A. Schimanski:** None. **C.A. Barnes:** None. **S.L. Cowen:** None.

Poster

600. Working Memory, Aging, and the Hippocampus

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 600.10/Y4

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation
RO1 AG003376
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Title: Quantification of neuronal and astrocytic cells in the locus coeruleus of cognitively assessed, young and aged nonhuman primates

Authors: *W. PYON[1,2], D. T. GRAY[1,2], W. SCHNAPP[1], R. SCHWYHART[1,2], S. KHATTAB[1,2], N. M. DE LA PENA[1,2], C. A. BARNES[1,2,3];
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Abstract: The locus coeruleus is a small brainstem nucleus that is known for its role in supplying noradrenaline to various regions in the brain. The locus coeruleus is especially susceptible to age-related neurodegeneration and is one of the first regions to display Alzheimer's and Parkinson's pathologies (Mather and Harley, 2016), in part due to its high bioenergetic need. Whether differences in number of tyrosine hydroxylase (TH)-expressing neurons significantly contribute to age-related cognitive decline remains less clear. To investigate this, coronal brainstem sections from cognitively assessed rhesus macaques (N = 3 aged, mean 28 years; N = 3 adult, mean 11 years) were immunohistochemically labelled to visualize neuronal nuclei (NeuN), catecholaminergic neurons (TH), astrocytes (glial fibrillary acidic protein - GFAP) and vasculature (Solanum tuberosum lectin - STL). For this study, unbiased stereological techniques are used to quantify neuronal numbers. Astrocyte and vascular characteristics are also investigated. The preliminary results suggest a trend towards lower TH neuron density within the locus coeruleus of aged monkeys. There was also a trend for a

relationship between higher TH density and better object recognition memory (delayed nonmatching-to-sample) performance. This trend was not observed with performance on spatial short-term memory (delayed response) or object discrimination tasks. We are currently examining whether the volume of vasculature within the sampled region, or if properties of astrocytes within the region differ with age. Additionally, we are expanding the number of animals, assessing other neuronal cell types, and evaluating stereological estimates of volume to more thoroughly characterize age-related changes in the locus coeruleus.

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Poster

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Topic: H.01. Animal Cognition and Behavior

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Title: Perineuronal nets in the cerebral cortex of cognitively-assessed aged macaque monkeys

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Abstract: Perineuronal nets (PNNs) are specialized extracellular matrix structures that envelop specific neurons in the central nervous system and play critical roles in controlling plasticity and maintaining synaptic function (Sorg et al., 2016, J Neurosci). Alterations in the expression of different components of the extracellular matrix have been shown to occur in normative brain aging, as well as in several nervous system disorders. No studies have investigated PNNs across the lifespan of behaviorally characterized, aged nonhuman primates. Furthermore, the impact that potentially altered PNNs have on the manifestation of different aspects of age-associated cognitive decline is not clear. To these ends, the present study used fluorescence labeling and unbiased quantification of perineuronal net markers [Wisteria floribunda agglutinin (WFA) and the chondroitin sulfate proteoglycan aggrecan] on the brains from a colony of 30 rhesus macaque monkeys ranging in age from 7 to 32 years. All of these monkeys also underwent tests of spatial

short-term memory (delayed response), object recognition memory (delayed nonmatching-to-sample), and object discrimination, which allowed relationships between PNNs and cognition to be investigated. While there are interesting trends with respect to age, PNNs and parvalbumin (PV)-immunoreactive neurons, our preliminary results (N = 3 aged, mean 28 years; N = 3 adult, mean 11 years) suggest no age effect. The data do suggest that the strongest associations are found between the proportion of PV-immunopositive neurons with nets and behavior. Specifically, animals with more perineuronal nets surrounding PV-immunoreactive neurons tended to show worse behavior on all of our cognitive tasks. Furthermore, animals that exhibited fewer PNNs associated with PV-immunopositive cells tended to show better behavioral performance on our tasks. We are currently expanding the sample size, PNN markers, and the brain regions analyzed to more thoroughly characterize these nets across aging.

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Poster

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Support: McKnight Brain Research Foundation
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Title: Estimation of non-rigid warps during 3D serial-section histology reconstruction optimization increases accuracy

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Abstract: 3D histology reconstruction brings cellular-level detail to 3D facilitating the ease of data analysis and enabling use of open-format brain atlases. These atlases facilitate automatic segmentation, 3D morphological analysis, and promote sharing across laboratories. Recently, a number of novel methods have been created to estimate the required spatial transformations that bring sections of histology into alignment with a 3D template without intermediate imaging steps such as block-face imaging. Although each section of tissue typically undergoes non-rigid

transformation when it is mounted, to date, no direct-to-template method has accounted for non-rigid terms during the optimization process. Instead, non-rigid transformations of each section of histology are estimated during a post-processing step after the sections have been localized to a specific plane of the template. Recently, we developed an artificial neural network-based 3D reconstruction method that utilizes "spatial transformer networks" to estimate non-rigid transformations thousands of times faster than traditional registration algorithms. The increase in computational speed allows us to include non-rigid transformations throughout the optimization process. Here, we compare a version of our method that uses rigid warps to the histology sections during optimization followed be a non-rigid post-processing step, to a version that includes non-rigid estimation throughout the optimization. We show that inclusion of the non-rigid estimation increases reconstruction accuracy as measured by target-registration error (TRE). Using the rigid version, we calculated a TRE of 1.7594 ± 1.3797 pixels (1.0996 ± 0.8623 mm), while using the non-rigid version we calculated a TRE of 2.1929 ± 1.6257 pixels (1.3706 ± 1.0161 mm). A paired t-test revealed that the rigid version had significantly higher TRE ($t(12) = 2.6879$ $p = 0.0197$) indicating lower (less accurate) reconstruction accuracy. Additionally, the non-rigid version of our algorithms produces the lowest TRE of any 3D histology reconstruction method that we are aware of, including block-face methods that utilize intermediate imaging to simplify 3D histology reconstruction. Thus, we show that direct-to-template methods are competitive with block-face methods without the added expense and effort involved in collecting and processing block-face images.

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Poster

600. Working Memory, Aging, and the Hippocampus

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Title: Effects of induced hypertension in middle aged CYP1A1-REN2 transgenic rats

Authors: *M. ZEMPARE[1,2], N. J. CAREY[1,2], A. DALMENDRAY[1,2], K. YOUNG[1,2], K. M. BOHNE[1,2], L. DO[3], T. TROUARD[1,3], K. D. MITCHELL[5], M. K. CHAWLA[1,2], M. J. HUENTELMAN[6,1], C. A. BARNES[1,2,4];
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of Arizona, Tucson, AZ; [5]Dept. of Physiol., Tulane Univ. Hlth. Sci. Ctr., New Orleans, LA; [6]The Translational Genomics Res. Inst., Phoenix, AZ

Abstract: Hypertension is associated with an increased risk of cardiovascular disease (CVD) and cognitive decline in aging humans (Keenan et al., 2011) with the onset occurring around middle-age (Wilkie et al., 1971). While prior research has suggested an association between CVD and cognitive decline in the elderly (Haring et al., 2013), it is also critical to investigate how this dynamic may evolve from middle to older age. In this study, Cyp1a1-Ren2 xenobiotic-inducible transgenic rats were used to model the gradual rate and age-of-onset observed in humans. In these transgenic rats, Ren2 expression in the kidney is driven by the Cyp1a1 promoter, which is activated by ingestion of indole-3-carbinol (I3C), causing elevated kidney angiotensin levels, increased arterial pressure, and reduced renal hemodynamics (Mitchell et al., 2006). Fifteen month old male rats were assigned to either control or treatment diet groups, and given a battery of behavior tests to establish baseline cognition measures. Following these tests the treatment group received a diet with 0.015% I3C while control rats received a global 18% protein rodent diet. Post-treatment, the same behavioral battery was given to assess the effect of hypertension on cognition. Gradual onset of hypertension was confirmed through systolic and diastolic blood pressure changes. Postmortem heart and kidney analysis replicated and expanded on recent studies (Willeman et al., 2019). The behavioral battery includes spatial and cued versions of the Morris watermaze, spontaneous object recognition (SOR) and a delayed matching- to-place working memory task. Analysis of the hippocampal-dependent spatial watermaze, the perirhinal cortex-dependent SOR, and the prefrontal cortex-dependent working memory task, suggest that these hypertensive rats maintain high performance levels on each behavioral task. While the treated group in this study did show significant cardiac and renal end organ damage as in the Willeman et al. (2019) study, we did not replicate the impairment observed in spatial memory in this larger cohort. Further studies, including those that assess vascular damage in relevant brain regions, are needed to determine if the molecular and cellular changes observed in these animals are similar to those seen in the peripheral vasculature. For example, the persistence of normal cognition after hypertension may be due to compensatory mechanisms such as local modulation of vascular tone and arteriole diameter by neurons and glial cells.

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Poster

600. Working Memory, Aging, and the Hippocampus

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Topic: H.01. Animal Cognition and Behavior

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Title: Effects of NPTX2 knockout on behavior, brain volume by MRI and CA1 hippocampal single unit properties

Authors: *A. TERRAZAS[1,2], W. PYON[1,2], M. ZEMPARE[1,2], K. F. YOUNG[1,2], A. DALMENDRAY[1,2], L. DO[3], B. DAVID[1,2], K. M. BOHNE[1,2], N. J. CAREY[1,2], M. K. CHAWLA[1,2], T. P. TROUARD[1,3], J. ZHOU[5], P. F. WORLEY[5], C. A. BARNES[1,2,4];
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Abstract: Long-term memory is dependent on rapid, de novo protein synthesis, and we have studied immediate early genes (IEG) that act at excitatory synapses to understand the molecular basis of memory. IEGs Arc, Homer1a, and NPTX2 each play a unique and essential role in homeostatic restoration of activity levels of pyramidal neuron-inhibitory interneuron circuits in culture (1) (2) (3). Here, we examine NPTX2, which is induced by patterned activity that induces synaptic plasticity (4), is trafficked along axons, secreted from presynaptic elements, and selectively accumulates at excitatory synapses on PV-interneurons (3). This synaptic NPTX2 binds postsynaptic AMPAR (GluA1 and GluA4) and strengthens excitatory drive of PV-interneurons. Sprague Dawley CRISPR-Cas9 NPTX2 knockout (KO) rats were compared to their wildtype (WT) littermates on 1) a battery of behavioral tasks (spatial and working memory on the watermaze, spontaneous object recognition memory and a test of anxiety), 2) MRI brain regional volumetric analysis, and 3) multiple single unit electrophysiological recordings in area CA1 of the hippocampus while rats traversed a 65 cm track for reward. The NPTX2 KO (n=7) rats exhibited similar performance to WT rats (n=5) on these tasks. Furthermore, regional brain volumes were not significantly different between KO and WT rats. Place-specific firing of CA1 single units, however, was strikingly different between groups. Compared to WT rats (n=2), KO rats (n=3) (8 to 15 mo) exhibited significantly lower spatial information content per spike and information per second (for KO and WT respectively, number of single units =142 and 63, mean information per spike +/- std = 0.66 +/- 0.52 and 1.10 +/- 0.72, $t=-4.30$, $p<0.0005$; mean information per second = 0.59 +/- .79 and 1.06 +/- 0.93, $t=-3.48$, $p< 0.005$.) Firing rates of pyramidal cells were assessed while rats were on the maze and during pre- and post-maze sleep periods. There was a trend for the firing rates of hippocampal place cells to be higher in KO rats for all behavioral conditions, and this reached statistical significance in post-behavior sleep sessions (mean rate in Hz 0.84 +/- 1.14 compared to 0.54 +/- 0.60 for WT, $t=2.40$, $p<0.05$). Surprisingly, the reduction of information content and spatial tuning of place cells is not manifest as deficits in the standard behavioral tasks used. NPTX2 is required for developmental plasticity in the visual cortex to refine tuning properties of excitatory neurons (5), and a similar role in the hippocampus might create circuits capable of optimal information processing. In fact it is possible that, during development, NPTX2 sets the spatial tuning parameter space for hippocampal networks.

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Poster

600. Working Memory, Aging, and the Hippocampus

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Topic: H.01. Animal Cognition and Behavior

Support: McKnight Brain Research Foundation
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Title: Age-related, specific changes in expression of several central melanocortin receptor subtypes in the rat

Authors: *M. K. CHAWLA[1,2], M. ZEMPARE[1,2], V. HRUBY[3], C. A. BARNES[1,2,4], M. CAI[3]; [1]Evelyn F. McKnight Brain Inst., [2]Div. of Neural Systems, Memory and Aging, [3]Dept. of Chem. & Biochem., [4]Departments of Psychology, Neurol. and Neurosci., Univ. of Arizona, Tucson, AZ

Abstract: The five melanocortin receptors cloned so far (MCR1-5) have been associated with control of inflammatory disorders, immunomodulation, antipyretic effect and prevention of brainstem ischemia and reperfusion injury (Schimolli et al. 2009). It has been reported that the human melanocortin 4 receptor (hMC4R) is involved in neurodegenerative disease (Shen et al., 2016). Melanotropins may protect against the progression of Alzheimer's disease (Giuliani et al., 2014). Furthermore, administration of α-MSH or its more stable analog [Nle4,D-Phe7]-α-MSH (NDP-α-MSH) has been observed to enhance learning and memory (Beckwith, et al. 1975). However, the impact of age with respect to melancortin receptor expression remains unexplored. Previously we have shown that the total expression of melanocortin receptor is reduced in the aged rats in four of the six brain regions studied. In the present study, we systematically investigated the expression of 5 different subtypes of melanocortin receptors in brain of young (9 months) and aged (23 months) rats that were assessed for their cognitive status in memory tasks. Spatial memory and visual discrimination ability were assessed using the Morris watermaze task. Six regions of the brain were extracted from each animal, including the frontal cortex + anterior midbrain, parietal cortex, cerebellum, posterior midbrain, hippocampus and occipital lobe. We collected the membrane fragments from each region of all animals in each age group, then ran a specific binding assay using iodine labelled NDP-α-hMCHR1-5 on a high throughput Micro Beta II radiation counter. Six samples were measured from each animal for each region, and then averaged to produce a single count for each animal in each region. All measurements were collected in a blind fashion. We then ran a linear regression analysis with spatial learning

behavior and specific receptor binding for hMCHR1-5 receptors using Graph-pad Prizm software. A significant correlation was found between spatial memory and two receptor subtypes MCH-1R ($p = 0.048$) and MCH-3R ($p = 0.049$) in old animals. This finding potentially opens a new window of discovery for exploring and developing new treatments for cognitive changes that arise in normative aging and in neurodegenerative disease.

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Poster

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Title: A computational model of aged head direction network updating in the presence of sudden spatial cue mismatch

Authors: *A. W. LESTER[1,2], A. J. KAPELLUSCH[1,2], C. A. BARNES[1,2,3];
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Abstract: As with older adults, aged rats show pronounced impairments on a number of different spatial navigation tasks as well as a bias toward relying on self-motion (i.e., idiothetic) over environmental (i.e., allothetic) cue-based navigation strategies (Lester et al., 2017). Rosenzweig et al. (2003) found that, when exposed to conflicting allothetic and idiothetic feedback, aged rats were impaired in navigating to an allothetic cue-aligned goal location and the place cell networks of aged rats were delayed in realigning their firing fields to match the spatial information relayed by the allothetic cues. The Instantaneous Cue Rotation (ICR) task used here requires animals to navigate to a reward location that is always aligned to the projected visual cues in the environment (Lester et al., 2018). We previously reported that, when young and aged rats were tested on the ICR task, allothetic cues were found to exert a less pronounced influence on the running behavior of aged rats following sudden cue rotation. The overall pattern for young rats, in contrast, suggested a reliable although incomplete control by allothetic cues, which may reflect a greater tendency for young animals to resolve conflicting allothetic-idiothetic feedback by integrating information from both. A continuous attractor neural network model was created to assess how a sudden rotation of visual cues may affect the spatial tuning of head direction cell networks and how the behavior of these networks may be altered in the presence of erroneous

self-motion feedback (i.e., idiothetic error). The model incorporates a head direction (HD) and angular head velocity (AHV) network, the tuning of which depend on both angular movement and visual cue inputs. In the absence of any idiothetic error, the HD and AHV networks collectively undergo a gradual but reliable realignment of their directional firing after visual cue rotation. In contrast, the introduction of idiothetic errors either amplifies or diminishes visual cue control over HD-AHV alignment depending on the degree and direction of drift these errors induce in the network's directional firing. As a consequence, visual cues exert less reliable control over directional tuning and often lose control over the networks directional tuning following visual cue rotation. Considered in the context of known age-related changes in vestibular function as well as deficits in self-motion perception and path integration, the findings from this computational model suggest a plausible mechanism that could contribute to impaired integration of conflicting spatial signals in aged spatial networks.

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Poster

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Title: Rna stress granule components are dynamically expressed during aging and stress conditions in rats and fruit flies

Authors: R. ECK[1], M. K. CHAWLA[2,3], B. BAGEVALU SIDDEGOWDA[1], N. J. CAREY[2,3], M. ZEMPARE[2,3], C. NGUYEN[2,3], D. BILLHEIMER[4], *C. A. BARNES[2,3,5], D. C. ZARNESCU[6,1];
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Abstract: During times of cellular insult, non-membrane bound organelles called RNA stress granules form to sequester mRNAs, translation initiation factors and proteins into dense cytoplasmic structures, halting translation. Dysfunction in the dynamic assembly and disassembly of RNA SGs has been linked mechanistically to age-related neurodegenerative

diseases. It is not known, however, how these mechanisms are affected during aging. To understand the molecular mechanisms that underly these links, we profiled the dynamic changes of RNA SGs during aging and their relationship to stress resiliency through examining the expression of genes critical to translation initiation and RNA SGs formation in behaviorally characterized young (6-10 mo, n=11), middle-aged (15-19 mo, n=11), and old rats (23-25 mo, n=13). These rats were assessed for their spatial memory, working memory, and motor function using the Morris water maze. Some of the genes profiled were G3BP1, necessary for RNA SGs formation, FMRP, a modulator of mRNA association with RNA SGs, EIF2alpha, a translation initiation factor whose phosphorylation indicates RNA SG formation, and PABP and TIAR among others. Western blots and real-time PCR found region-specific expression of these critical genes in the hippocampus, pre-frontal cortex, and cerebellum throughout aging. Using regression models, we sought to determine if these region-specific expression changes can account for variation among rats in behavioral performance, when taking age into account. We used Principle Component Analysis to determine if the variations among critical protein and transcript expression levels reveal differences or similarities between rats that relate to age or behavioral performance. The levels of key proteins and transcripts, along with other analysis trends, will be compared between young and old rats who received maximum electro-convulsive shock treatment (shock duration = 1 second, current intensity = 85mA, 1 hour recovery) and those who did not. In fruit flies, the dynamic response of RNA SGs under stress conditions appears to vary with age compared to the non-stressed control condition. Future investigation will focus on isolating RNA SGs from fruit flies to examine how components associated with RNA/protein structures change during aging and in response to multiple stress conditions.

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Poster

600. Working Memory, Aging, and the Hippocampus

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Title: Sex differences in exercise-induced extracellular vesicle release and cognitive enhancement

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Abstract: Aging is characterized by a substantial loss of muscle mass and strength, which is associated with higher mortality. Exercise can not only mitigate age-related frailty and muscle weakness but also improve metabolic, cardiovascular, and cognitive function. The mechanism by which exercise exerts these effects remains to be elucidated. Thus, this study examines age- and sex-related differences in exercise-induced intercellular signaling, specifically extracellular vesicles (EV) and their miRNA content, and how this relates to changes in muscle, cognition, inflammation, and redox state in multiple organs with exercise. One cohort of young and aged (6 & 24 mo) male and female Fischer-344 rats (N=4/group) underwent treadmill running for a single bout of exercise at 70% VO_{2max} to determine maximal plasma EV release post-exercise (<15, 90, 180min after). A second cohort ran on treadmills for two months on a progressive workload schedule to elicit 70% VO_{2max}. Following exercise rats were evaluated for physical and cognitive changes compared to sedentary controls. After a final bout of exercise, rats were euthanized, and blood, muscle, liver, kidney, brain, and fat were collected to examine the impact of age, sex, and exercise on EV-derived miRNA expression, redox levels, and inflammatory markers. For the first cohort, CD-63+ EVs displayed a relative increase 90min after acute treadmill running (z-score; control: -0.24±0.22; <15min: 0.04±0.28; 90min: 0.30±0.29; 180min: -0.10±0.20). This timepoint was utilized for euthanizing the second cohort. Interestingly, young females released significantly more EVs after exercise than young and aged males (p<0.02) and aged females released more than young males (p=0.01). For behavioral measures, repeated exercise elicited sex-specific effects in open field measures ($F_{1,20}$=5.21, p=0.03), where female runners moved more than other rats (p<0.05). They also froze less during contextual fear conditioning (p<0.05) and throughout cued extinction (p<0.01) compared to controls. Exercise enhanced cognitive performance on a hippocampal task (context-object discrimination; $F_{1,19}$=4.69, p=0.04), with all runners exploring a context-incongruent object more than controls. Next-generation sequencing of EV miRNA and inflammatory quantification are currently being conducted. It is predicted that continued exercise will shift the aging secretome to resemble a younger profile. Overall, these data are the first to demonstrate a sex-specific effect of exercise on EV release and physical and cognitive measures, which may allude to differential exercise-induced EV content in males and females.

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Poster

600. Working Memory, Aging, and the Hippocampus

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Title: Impaired pattern separation during aging is associated with altered hippocampal gene transcription

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Abstract: Previous studies of age-related transcriptional changes indicate that cognitive impairments are associated with differentially expressed genes (DEGs) linked to defined neural systems (e.g. episodic memory-CA1, executive function-prefrontal cortex). These findings provide information on possible molecular mechanisms for age-related cognitive decline. Aging is also associated with a deficit in pattern separation (PS), the generation of distinct mnemonic representations from overlapping experiences. The dentate gyrus (DG) is implicated in PS and exhibits several age-related changes (e.g. decrease in neurogenesis, impaired synaptic plasticity, and loss of afferent input) that could impair PS performance. We hypothesize that aged animals with impaired PS ability will express a distinct transcriptional profile relative to unimpaired animals, specifically within the DG and not in other hippocampal subregions. We used a modified water maze beacon discrimination task to characterize PS in young (5 mo, n=12) and middle-age (12 mo, n=16) F344 male rats. This was followed by a reference memory task. Middle-age rats showed deficits in discriminating two identical beacons compared to young, when trials began with the rat positioned equidistant between the two beacons (p=0.005). Reference memory performance between these two age groups was not significantly different (p=0.2); however, older animals appeared to compensate for impaired for PS though greater reliance on reference memory. Following behavioral testing, mRNA sequencing was performed on hippocampal subregions DG, CA1, and CA3. The DG exhibited more age-related DEGs compared to CA1 and CA3. Likewise, middle-age rats impaired on the PS task showed more DEGs in the DG than in CA1 or CA3, compared to age-matched unimpaired rats. Functional

annotation clustering of impaired animals highlighted dysregulation of genes related to RNA processing and protein folding in the DG, downregulation of inflammation-related genes in CA1, and no significant cognition-related gene dysregulation in CA3. These results suggest: 1) the beacon task is sensitive to age-related PS impairment, 2) the three hippocampal regions age independently, and 3) regional differences are reflected in differential use of strategies to solve the task.

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Poster

600. Working Memory, Aging, and the Hippocampus

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Title: Age and sex influence the hippocampal response and recovery following sepsis

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Abstract: Although in-hospital mortality rates for sepsis have decreased, survivors often experience lasting physical and cognitive deficits. Sex and age are major factors contributing to variability in the response to sepsis. Many studies in humans and rodents have demonstrated decreased mortality following sepsis for females and the incidence of sepsis and associated complications increase with advancing age. We employed a murine model to examine the influence of age and sex on the brain's response and recovery following sepsis. Young (~4 months) and old (~20 months) mice (C57BL/6) of both sexes underwent cecal ligation and puncture (CLP) with restraint stress. The hippocampal transcriptome was examined in age and sex-matched controls at 1 and 4 days post-CLP. A considerable number of hippocampal genes were altered in a similar manner across all sex and age groups on day 1. In general, immune and

stress-related genes increased while neuronal, synaptic, and glial genes decreased one day after CLP-induced sepsis. However, specific age and sex differences were observed for the initial responsiveness to sepsis as well as the rate of recovery examined on day 4. Young males differentially expressed a substantial number of genes 1 day after sepsis, but recovered normal gene expression profile 4 days after sepsis. Young females were the least responsive group across the four days of sepsis, exhibiting the fewest number of altered genes and gene ontology clusters. Old females exhibited a robust shift in gene transcription on day 1 and, while most genes recovered, genes linked to neurogenesis and myelination continued to be downregulated by day 4. In contrast, old males exhibited a more delayed or prolonged response to sepsis, such that neuronal and synaptic genes continued to decrease while immune response genes continued to increase on day 4. The genes that were altered on day 4 in older animals may shed light on the mechanism for sepsis-induced cognitive impairment, which is particularly evident in older individuals. These results suggest that aging is associated with delayed recovery from sepsis, which is particularly evident in males.

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Poster

600. Working Memory, Aging, and the Hippocampus

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Evelyn F. McKnight Brain Research Foundation

Title: Longitudinal characterization of sex differences in functional and cognitive decline during aging

Authors: *A. RANI[1], B. YEGLA[1], J. BARTER[1], A. KUMAR[1], M. FEBO[2], K. ESSER[3], T. C. FOSTER[4];
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Abstract: Variability in cognitive decline during aging is related to biological factors (e.g. sex) and the history of experience (e.g. environmental enrichment, previous testing) and lifestyle factors (diet, exercise). In order to understand the contribution of these factors and underlying mechanisms, longitudinal studies are required to define when cognitive decline first emerges. An important caveat for longitudinal studies is the need to control for practice and carry-over effects, associated with multiple testing, which could mask the effects of aging. The current longitudinal study was designed to examine the role of biological and behavioral factors that might predict the variability in age-related cognitive decline. Fischer-344 male (n = 10) and female (n = 10) rats were first characterized at 6 months. Behavioral tests included physical ability (grip strength, Rotarod, and activity wheel), anxiety (neophobia and open field activity), episodic memory (water maze delayed match to place and novel object recognition), and a circadian stress test of resiliency. These measurements were repeated at 12 and 18 months. Sex differences were observed as increased grip strength for males (6 mon: $p < 0.01$, 12 mon: $p < 0.005$, 18 mon: $p < 0.005$). Females exhibited increased activity (6 mon: $p < 0.001$, 12 mon: $p < 0.0001$, 18 mon: $p < 0.0001$). Females also exhibited better Rotarod performance ($p < 0.01$) at 12 mon. In general, neophobia and open field activity declined across testing sessions in the absence of a consistent sex difference. A decline in episodic memory for longer delays (30 and 120 min) emerged at 12 month, particularly for males. Within sex comparisons confirmed that males exhibited a decline in episodic memory during aging. Functional magnetic resonance imaging measures indicated impaired memory was associated with changes in functional connectivity, which suggest compensatory mechanisms. Currently, analysis is focused on the circadian stress test of resiliency and other biological measures. The results of the current study demonstrate sexual dimorphism in the onset and trajectory of cognitive decline.

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Poster

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Title: Does systemic inflammation contribute to the senescent synapse?

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Abstract: Low-grade chronic systemic inflammation during aging is associated with poorer cognitive performance. The current study was design to address the question of whether systemic inflammation contributes to a decrease in hippocampal synaptic transmission and redox mediated decline in NMDA receptor function, which are characteristic of aged-memory impaired animals. Young (5-6 months) Fischer 344 X Brown Norway hybrid rats were injected once a week, for six weeks, with either lipopolysaccharide (LPS) (1 mg/kg, i.p.) or vehicle. Starting 72 hr after the final LPS/vehicle injection, we performed *in vitro* slice electrophysiological recording from CA3-CA1 hippocampal synapses. An input-output curve was generated for total synaptic response across different stimulation intensities for vehicle (n=7/4 slices/animals) and LPS (n=8/4 slices/animals) treated animals. A repeated-measures ANOVA across stimulation intensities indicated an interaction of treatment by stimulation intensity [$F(8,104)=4.029$, $p<0.001$] due to a decrease total synaptic response in slices from LPS animals. Following assessment of total synaptic responses, the NMDA receptor mediated synaptic component was pharmacologically isolated, and input-output curves were generated from vehicle (n=7/4 slices/animals) or LPS (n=7/4 slices/animals) treated animals. A repeated-measures ANOVA across stimulation intensities indicated an interaction of treatment by stimulation intensity [$F(8,96)=3.3$, $p<0.01$], due to a decrease in the NMDA receptor response for LPS-treated animals. The role of redox stress in the decline of the NMDA receptor mediated synaptic component was also tested. After collection of baseline responses, the reducing agent, dithiothreitol (DTT) was added to the bath and responses were measured for 60 minutes. No group differences were observed following addition of DTT, which increased the NMDA receptor synaptic response by 127±10% (3/6 animals/slices) in the vehicle control group and 123±3% (4/7 animals/slices) in the LPS group, indicating no redox effects at this time point. We suggest that synapse elimination underlies LPS-mediated decrease the total and NMDA receptor synaptic transmission. However, transcriptional evidence indicates that younger animals exhibit considerable recovery at the 72 hr time point. Preliminary results suggest that a redox mediated NMDA receptor hypofunction may be present within 24 hr after LPS treatment.

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Poster

600. Working Memory, Aging, and the Hippocampus

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Title: Effect of age and estrogen on whole genome DNA methylome profiling of CpGs in CA1 region of the hippocampus

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Abstract: The ability of estradiol (E2) to improve hippocampal-dependent memory declines with advanced age and prolonged E2 deprivation, indicating a closing of the E2 therapeutic window. Similarly, the ability of E2 to induce transcription of synaptic plasticity genes in the hippocampus deteriorates with advanced age. We hypothesize that during aging, epigenetic modification through DNA methylation renders these genes unresponsive to E2. Estrus cycle was checked by vaginal lavage before and after ovariectomy (OVX) to confirm the loss of E2. Young and middle aged (MA) rats were cycling at regular intervals while two out of six aged animals had an irregular estrus cycle prior to OVX. Six weeks following OVX, two injections of E2 (10 µg: young, n = 4; MA, n = 3; aged, n = 4) or oil (young, n = 2; MA, n =2; aged, n = 2) were given 24 hours apart. The hippocampal CA1 region was collected 6 hours following the second E2/Oil injection and flash frozen. Genomic DNA was isolated. Following sodium bisulfite conversion of genomic DNA, whole genome bisulfite sequencing (WGBS) was performed. WGBS libraries were constructed with the Illumina Truseq DNA Methylation kit, and libraries were paired-end sequenced with the Illumina HiSeq3000 (2X150 cycles). Data analysis was performed using the differential methylation analysis pipeline to detect differentially methylated regions (DMRs) as well as the differential CpG methylation in promoters and gene bodies. The majority of identified CpG sites (> 90%) were found in gene body regions. Methylation analysis of E2-treated relative to age matched oil-controls indicated decreasing effect of E2 on differential CpG methylation with advancing age, particularly for hypomethylation following E2 treatment: young (hyper/hypo-653/660 sites), MA (hyper/hypo-555/485 sites), and aged (hyper/hypo-553/291 sites). Similarly, DMRs for E2 treatment were 113, 59 and 45 in young, MA, and aged treated groups, respectively. The results support a decrease in E2 induced differential methylation with advanced age. Gene ontology (GO) was used to examine gene clustering for hypermethylated and hypomentylated genes in E2 treated versus controls within each age group. A treatment associated enrichment was observed for MA hypomethylated genes (cAMP signaling pathway) and hypermethylated genes for aged animals (calcium-dependent membrane targeting). Comparisons between control groups indicated hypermethylation of synaptic signaling genes in MA relative to young control. The results are consistent with hypermentylation contributing to an age-related **1)** decreased expression of synaptic genes and **2)** decreased E2-responsive transcription.

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Poster

600. Working Memory, Aging, and the Hippocampus

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 600.24/Y18

Topic: H.01. Animal Cognition and Behavior

Title: Low dose of THC improves age-related cognitive impairments

Authors: *R. DORON[1], R. TOLEDANO[1], L. RACHMANY[2], E. SASSON[2], Y. SARNE[2];
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Abstract: The world's population is ageing. Population ageing is poised to become one of the most significant social transformations of the twenty-first century. a variety of insults In the present study we evaluated the effect of the same ultra-low dose of THC on reversing age-related cognitive decline in mice. As was expected, the cognitive prefomance of Old (18-24 months) mice were found to be weaker then the performance young ones (3-4 months). The important finding was that we showed that a single injection of an ultra-low dose of THC (0.002mg/kg) ameliorated cognitive functioning of old (but not of young) mice, as was evaluated by six different assays that measured various aspects of memory and learning. The assays that were used were: Morris Water Maze, Active and Passive Avoidance, Y maze, Object Recognition and Place Recognition tests. The old mice were found to preform the tasks similarly to young mice. The behavioral results were consistent with Magnetic Resonance Imaging (MRI) findings that demonstrated a larger volume and higher tissue of entorhinal cortex, prefrontal cortex and posterior hippocampus. In addition higher density in various regions of the brain (including the entorhinal cortex, amygdala, cingulate cortex and caudate/putamen) following ultra-low-THC treatment Sirtuin 1 (SIRT1) is an NAD-dependent protein deacetylase that has been previously shown to be involved in neuroprotection and neuroplasticity. It was found to mediate the protective effects of resveratrol, of melatonin and of caloric restriction, and was suggested to take part in the pathology of various neurodegenerative diseases. In the current study we showed that the same treatment elevated the level in the brain of SIRT1 at least for 7 weeks. These behavioral, biochemical and structural effects lasted for at least seven weeks following a single injection of ultra-low-THC. The harmful effect of THC on young brains has long been known, but the present study suggests that a minimal dose of THC can be an effective pharmaceutical treatment for age related cognitive impairment.

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Poster

601. Neural Circuits for Learning and Memory

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Title: Steady stream of complex traveling waves underlying cortical up-down states in sedated mice

Authors: *Y. LIANG[1], C. SONG[2], L. MIANXIN[4], T. KNOPFEL[3], P. GONG[6], C. ZHOU[5]; [1]Hong Kong Baptist Univ., Hong Kong, Hong Kong; [2]Med., [3]Imperial Col. London, London, United Kingdom; [4]HKBU, Hong Kong, China; [5]HKBU, Hong Kong, Hong Kong; [6]The Univ. of Sydney, Sydney, Australia

Abstract: Up (high neuronal firing probability) and Down (low firing probability) states have been widely observed in the cerebral cortex, which play important functional roles such as memory consolidations. However, the dynamical mechanism of Up-Down transitions and their spatiotemporal organization properties and principles remain unclear. We investigated the dynamical properties of various waves and their interactions using high spatiotemporal resolution optical voltage imaging of the upper cortical layers in sedated mice.
Our analysis based on phase velocity fields revealed that there are only a small number of large-scale, cortex wide plane wave and synchrony (standing wave) patterns during Up-Down states. During transition of Up to Down state, a large plane wave swept across the whole cortex. Interactions of local sources and sinks can generate saddles and interactions of local wave patterns with large plane waves can induce a change of their wave propagating direction. Local wave patterns emerge at preferred spatial locations. Specifically, sources are predominantly found in cortical regions with high cumulative input through the underlying connectome. Our findings reveal the principled spatiotemporal dynamics of Up-Down states and associate them with the large-scale cortical connectome.

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Poster

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NIH grant MH057440-11

Title: The medial septum enhances cognitive flexibility via actions on ventral tegmental area and substantia nigra dopamine neurons

Authors: *D. M. BORTZ, K. L. GAZO, A. A. GRACE;
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Abstract: Cognitive flexibility deficits are one of the most pervasive symptoms across psychiatric disorders, making continued investigation of the circuitry underlying this function a top priority. One brain area that has emerged is a sub region of the basal forebrain called the medial septum (MS). The MS has a well-established role in learning and memory processes, specifically in behaviors that require inhibition of prior learned information in order to learn a new rule. Furthermore, the MS potently regulates dopamine (DA) neuron activity in both the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), which are known to be involved in reward learning, both in general and in the context of cognitive flexibility tasks. Despite this, a role for the MS in cognitive flexibility circuitry has never been examined. To test this hypothesis, we activated the MS of male and female Sprague-Dawley rats with designer receptors exclusively activated by designer drugs (DREADDs) and measured their performance on a T-maze spatial reversal-learning task, an operant-based strategy shifting task, and an operant-based non-spatial reversal learning task. Next, we determined if the effects of MS activation on both cognitive flexibility and midbrain DA activity were mediated via the same pathway. Finally, we determined whether DA transmission at D1 receptors was necessary to produce the MS's effects on cognitive flexibility. DREADD activation of the MS via systemic and intra-ventral subiculum (vSub) CNO improved performance on the cognitive flexibility tasks compared to the control groups. Intra-vSub CNO also increased (78%) the number of spontaneously active DA neurons in the VTA, and decreased (31%) the number of active DA neurons in the SNc, revealing that the MS's regulation of cognitive flexibility and DA activity both occur via the specific MS to vSub pathway. Finally, co-injection of the D1 antagonist SCH23390 completely prevented the enhancement in cognitive flexibility performance seen in the DREADD/CNO rats, suggesting the MS's effect on DA transmission is necessary for its enhancement of cognitive flexibility. In conclusion, these data add substantially to the known circuitry involved in cognitive flexibility, demonstrating a key role for the MS to vSub pathway.

They also provide evidence to suggest that this pathway's regulation of VTA and SNc DA activity could be the mechanism by which strategy-switch signals, precipitated during cognitive flexibility tasks, could be enacted downstream. Taken together, these data provide a first step towards developing novel, more effective therapies to treat cognitive flexibility deficits.

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Poster

601. Neural Circuits for Learning and Memory

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Topic: H.01. Animal Cognition and Behavior

Support: MH108837
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Title: Mechanisms of stress-induced memory generalization

Authors: *L. Y. REN[1], J. M. RADULOVIC[2];
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Abstract: Episodic memories must be encoded and maintained with specificity so that information about different situations is not generalized to unrelated novel situations. Stress is known to promote generalization of memories, and this effect likely relies on stress-induced neurobiological changes that bias memory systems towards increased generalization. A promising locus for these stress-induced changes is the dorsal hippocampus given that (1) excitatory neurotransmission in the dorsal hippocampus is crucial for associative learning, contextual memory, and episodic memory and (2) abnormal hippocampal function contributes to generalization of memories in rodents and humans. Thus, we sought to explore the role of the dorsal hippocampus in stress-induced generalization of memories. As dorsal hippocampal excitatory efferents contain either vesicular glutamate transporter 1 (vGlut1) or 2 (vGlut2), we used vGlut1- and vGlut2-Cre mice to investigate their roles in stress-induced generalization of context memories. After training mice to associate a context with a fear-provoking stimulus, we exposed mice to social defeat stress. Under these conditions, mice that normally acquired fear responses began to show generalization during testing in a novel context, thus providing a model

of stress-induced generalization of fear memory. Using this model, we found that chemogenetic inhibition of vGlut1-expressing dorsal hippocampal neurons before memory tests prevented generalization of the context fear memory, whereas inhibition of vGlut2-expressing dorsal hippocampus neurons did not have this effect. Additionally, inhibition of muscarinic acetylcholine receptors in the dorsal hippocampus before memory tests also prevented stress-induced generalization of the context fear memory. Next, we sought to explore the role of vGlut1-expressing dorsal hippocampal projections to the retrosplenial cortex in stress-induced generalization of memories, as these projections play a role in processing of recent contextual memories. We found that chemogenetic inhibition of these outputs prevented generalization of context fear. These results suggest that fear memory generalization is promoted by social defeat stress, and this effect is mediated through cholinergic mechanisms in the hippocampus and a glutamatergic output from dorsal hippocampus to retrosplenial cortex.

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Poster

601. Neural Circuits for Learning and Memory

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Topic: H.01. Animal Cognition and Behavior

Support: NSFC 31650110468

Title: Mechanisms underlying sharpening of visual response dynamics with familiarity

Authors: *S. LIM;
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Abstract: Experience-dependent modifications of synaptic connections are thought to change patterns of network activities and stimulus tuning with learning. However, only a few studies explored how synaptic plasticity shapes the response dynamics of cortical circuits. Here, we investigated the mechanism underlying sharpening of both stimulus selectivity and response dynamics with familiarity observed in monkey inferotemporal cortex. Broadening the distribution of activities and stronger oscillations in the response dynamics after learning provide evidence for synaptic plasticity in recurrent connections modifying the strength of positive feedback. Its interplay with slow negative feedback via firing rate adaptation is critical in sharpening response dynamics. Analysis of changes in temporal patterns also enables us to disentangle recurrent and feedforward synaptic plasticity, and provides a measure for the strengths of recurrent synaptic plasticity. Overall, this work highlights the importance of analyzing changes in dynamics as well as network patterns to further reveal the mechanisms of visual learning.

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Poster

601. Neural Circuits for Learning and Memory

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Support: Welcome Trust Grant 206401/Z/17/Z

Title: There and back again: Identification of distinct neural circuits for associative recognition memory encoding and retrieval

Authors: *G. R. I. BARKER, Z. I. BASHIR, E. C. WARBURTON;
Physiology, Pharmacol. & Neurosci., Univ. of Bristol, Bristol, United Kingdom

Abstract: Associative recognition memory, the ability to associate an object with its location or position in a sequence, is critically dependent upon a neural network which includes the medial prefrontal cortex (mPFC), hippocampus (HPC) and nucleus reuniens (NRe) of thalamus (Barker & Warburton 2011, 2018) which are anatomically interconnected. While the key nodes for associative recognition memory have been identified, how these brain regions interact during the different stages of memory formation is poorly understood. This study aimed to investigate how information moves between these brain regions during the encoding and retrieval of associative recognition memory by deactivating specific anatomical projections between these brain regions. Projection specific deactivation was achieved using either optogenetic or chemogenetic approaches in male lister-hooded rats. The following projections were deactivated using an optogenetic approach intermediate CA1→mPFC, NRe→mPFC and mPFC→NRe. Thus an AAV vector expressing the inhibitory opsin ARCH3.0 was injected into the somatic site of the projection and optrodes were implanted into the axonal target, The NRe→HPC projections were investigated via chemogenetic manipulation through injection of an AAV vector expressing the inhibitory DREADD receptor (hMDi4) in NRe combined with guide cannula implantation into both the dorsal and intermediate HPC. Associative recognition memory was tested using a range of different spontaneous preferential exploration tasks with deactivation of the projections during either memory encoding or retrieval. Performance in associative recognition memory tasks was compared using a two-way or one-way ANOVA and post-hoc comparisons used a Bonferroni correction.
Deactivation of iCA1→mPFC and NRe→mPFC projections selectively impaired associative recognition memory encoding but not retrieval, in contrast deactivation of mPFC→NRe projections selectively impaired memory retrieval but not encoding. Deactivation of NRe→HPC projections impaired both the encoding and retrieval of associative recognition memory but with distinct anatomical loci in dHPC and iHPC between encoding and retrieval. Further when

animals were simultaneously encoding and retrieving object associations deactivation of NRe→mPFC projections selectively impaired encoding and deactivation of mPFC→NRe projections selectively impaired retrieval. Thus, this study has revealed distinct networks which are critical for associative recognition memory encoding and retrieval.

Disclosures: G.R.I. Barker: None. **Z.I. Bashir:** None. **E.C. Warburton:** None.

Poster

601. Neural Circuits for Learning and Memory

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 601.06/Y24

Topic: H.01. Animal Cognition and Behavior

Support: ONR MURI N00014-16-1-2832

Title: Cortical and subcortical information processing during a context-association task

Authors: *M. MOAZAMI GOUDARZI, E. K. MILLER;
MIT, Cambridge, MA

Abstract: Learning associations based on context is a fundamental hallmark of intelligence. Multiple cortical and subcortical brain regions have been implicated in context-association behavior, but the flow of information between these areas for underlying neuronal computations remains unclear. To address this question, we simultaneously recorded spiking and local field potential (LFP) activity from up to 104 electrodes in the prefrontal cortex (PFC), hippocampus (Hpc), and caudate (Cd) of monkeys. During recording, monkeys performed a context-specific rule-switching task. In each trial, one of four object cues was shown in one of four locations. Two of the objects mandated a leftward saccadic response following a brief delay when presented in the upper right or bottom left quadrants of the screen, and a rightward saccadic response when in the other two quadrants. This mapping was reversed for the other two objects. Thus, this task required monkeys to adjust their decisions based on the integration of both object identity and its spatial context. We investigated how information about the object identity, spatial context, and behavioral response was represented in multiunit spiking activity (MUA) within each area. First, we found strong information about object identity and spatial context in PFC and Cd in MUA during the sample period, with shorter latency in the Cd. This information decayed more slowly during the delay period in PFC. Interestingly, information about the behavioral response was only manifested in PFC. In contrast, the Hpc represents object identity, spatial context, and behavioral response only in its LFPs. Second, we examined the LFP Granger causality between Cd, Hpc, and PFC. We found that during the sample period the Cd and Hpc influence PFC in beta frequency bands. These results suggest that the Cd processes object

identity and spatial context and passes them to PFC to integrate them and guide the behavioral response.

Disclosures: M. Moazami Goudarzi: None. **E.K. Miller:** None.

Poster

601. Neural Circuits for Learning and Memory

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Program #/Poster #: 601.07/Y25

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Grant 2T32MH067564
Northwestern University Nicholson Fellowship
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Title: Tracing of glutamatergic afferents and efferents of dorsal hippocampus and retrosplenial cortex

Authors: *P. GAO[1], M. MEYER[3], L. Y. REN[3], J. M. RADULOVIC[2];
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Abstract: The dorsal hippocampus (DH) and retrosplenial cortex (RSC) play important roles in contextual memory processing. In particular, glutamatergic neurotransmission in these regions is crucial for these functions. DH and RSC glutamatergic neurons express either vesicular glutamate transporter 1 (vGlut1) or 2 (vGlut2), and these contribute differentially to processing of contextual fear memories. Given this, a map of vGlut1-expressing and vGlut2- expressing DH and RSC afferents and efferents would help further our understanding of memory circuits. We performed cre-dependent AAV-mediated tracing to identify brain areas projecting to and receiving innervation from DH and RSC. Analyses were performed separately for vGlut1-expressing and vGlut2-expressing projections, and for males and females. The identified brain areas will improve our understanding of memory networks and their interactions during contextual memory processing.

Disclosures: P. Gao: None. **M. Meyer:** None. **L.Y. Ren:** None. **J.M. Radulovic:** None.

Poster

601. Neural Circuits for Learning and Memory

Location: Hall A

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Program #/Poster #: 601.08/Y26

Topic: H.01. Animal Cognition and Behavior

Support: FG20621

Title: New non-canonical circuit connections between the subicular complex and hippocampal CA3

Authors: *X. LIN[1], R. TAFLA[1], C. BLANTON[1], Y. WU[1], D. A. NITZ[2], X. XU[1];
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Abstract: The hippocampal formation is traditionally viewed as having a feedforward, unidirectional circuit organization. However, recent studies (Sun et al., 2014; 2018) using genetically targeted rabies tracing show a significant backprojection pathway from the subiculum (SUB) and other parts of the subicular complex to hippocampal CA1 in the mouse as previously suggested in other mammalian species using less strict mapping methods. We refer to this circuit as 'non-canonical' in that it runs opposite the prominent pathway leading from CA1 to SUB. Furthermore, theta rhythms generated in the rat subiculum are reported to flow backward to actively modulate spike timing and local network rhythms in CA1 and CA3 (Jackson et al., 2014). This suggests an even larger, non-canonical circuit networks involving the subicular complex and hippocampal CA3. Thus we address whether hippocampal CA3 participates in these non-canonical circuit connections and investigate if CA3 excitatory neurons receive significant direct synaptic inputs from SUB and its associated structures including presubiculum (PrS), poststubiculum (PoS) and parasububium (PaS). We used our established monosynaptic rabies tracing approach to map brain-wide inputs to CA3 excitatory neurons in the mouse. As expected, the rabies-mediated input mapped regions include the dentate gyrus, medial septum, entorhinal cortex and contralateral CA3. Interestingly we also find that a significant number of rabies labeled neurons are present in the PrS, PoS and PaS, following rabies tracing from excitatory neurons in CA3 subregions. Reciprocally, we confirmed a direct projection of the subicular complex to hippocampal CA3 using anterograde directed herpes simplex virus (H129) mapping. Together, our data demonstrate the existence of new non-canonical circuit connections between the subicular complex and hippocampal CA3, which offers the anatomical circuit basis to consider the largely unexplored role of the subicular backprojection to the hippocampus.

Disclosures: X. Lin: None. **R. tafla:** None. **C. Blanton:** None. **Y. Wu:** None. **D.A. Nitz:** None. **X. Xu:** None.

Poster

601. Neural Circuits for Learning and Memory

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Program #/Poster #: 601.09/Y27

Topic: H.01. Animal Cognition and Behavior

Title: The lateral septum drives sex differences in fear memory encoding

Authors: *S. BASU, E. K. LUCAS;
North Carolina State University, Col. of Vet. Med., Raleigh, NC

Abstract: Fear-based psychiatric conditions, such as post-traumatic stress and anxiety disorders, are the most prevalent mental illnesses worldwide, affecting 18% of the population annually. These illnesses are thought to arise from enhanced encoding of cues associated with aversive outcomes, leading to maladaptive fear responses that persist in the absence of threat. Women are twice as likely as men to be diagnosed with fear-based mental illness, suggesting that the mechanisms underlying associative fear memory differs between the sexes. One possibility is that females encode fear memories through different neural networks than males. To explore this possibility, we quantified expression of the neural activity marker c-fos throughout selected forebrain regions in auditory fear conditioned and naïve male and female littermates. While both sexes equally engaged canonical regions of cued fear circuit, such as basolateral and central amygdala, we found a robust female-specific increase of c-fos expression in the lateral septum (LS). We next used designer receptors exclusively activated by designer drugs (DREADDs) to determine if sex-specific LS activation is causally related to sex-specific memory encoding. We bilaterally infused adeno-associated viruses encoding $hM3D_{Gq}$ (excitatory DREADD), $hM4D_{Gi}$ (inhibitory DREADD), or eYFP (empty-vector control) into the LS of male and female mice, injected clozapine-*N*-oxide 30 minutes prior to auditory fear conditioning, and assessed fear memory encoding and persistence. LS activation enhanced fear memory in females but impaired memory formation in males. Conversely, LS inhibition enhanced fear memory in males but rendered female fear memory more pervious to degradation. To reveal the neurons of the LS memory ensemble, we employed a viral vector approach for permanent eYFP labeling of neurons active during fear memory acquisition. Consistent with our c-fos data, we observed more tagged neurons in fear-conditioned females than fear-conditioned males or naïve animals of either sex. Analyses of eYFP-positive terminals revealed that female LS ensemble neurons mainly project to the lateral hypothalamic area, periaqueductal gray, and ventral hippocampus. Taken together, these data suggest that sex-specific engagement of the lateral septum during associative fear learning enhances fear memory in females through canonical mediators of fear-evoked responses. This in turn might be a contributing factor for the increased prevalence of fear-based psychiatric disorders observed in women.

Disclosures: **S. Basu:** None. **E.K. Lucas:** None.

Poster

601. Neural Circuits for Learning and Memory

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Title: The primate subthalamic nucleus encodes both current and historical values of visual objects in the experience-based learning

Authors: *H. JIANG, H. F. KIM;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: The basal ganglia play a crucial role in value-guided decision making through three pathways: Direct, indirect and hyperdirect pathway. The hyperdirect pathway transmits the cortical signal to motor output structures in the basal ganglia through the subthalamic nucleus (STN), contributing fast inhibition of motor responses. Neurons in the STN showed responses for behavioral switching and canceling in instructive cue-driven choice tasks. In real life, however, the cue is often not clear, and animals have to discriminate the object values and recognize their changes to choose the best one by trials and errors. The STN in hyperdirect pathway may have a role to suppress the unnecessary movement based on the experience of object values.
To test the value process in the STN neurons during the experience-based learning, we recorded the STN neurons while a monkey learned value changes of visual objects without an instructive cue. The object-reward value contingency was reversed across the blocks, and the monkey made quicker saccades to rewarded objects in current blocks than no rewarded ones. Among 125 visually responsive neurons, 14 neurons (11.2%) showed discrimination activity to flexibly changed values of objects (current value-coding neurons). These neurons negatively encoded the current values: higher activity to no rewarded objects than rewarded ones. Next, the STN neurons were tested during stable-value learning task, where the object-value contingency was sustained across whole sessions. During the first day of learning, the STN neurons gradually developed the value discrimination activity: higher response to no rewarded objects.
We further tested whether the STN neurons memorize previously learned object values. Behaviorally, the monkey showed a gaze preference to the previously rewarded objects in free viewing task after long-term value learning. The STN neurons encoded learned object values: 15 of 125 visual neurons (12%) responded higher to previously no rewarded objects than rewarded

ones (historical value-coding). 12 of 15 (80 %) stable value-coding neurons also encoded flexible value, indicating that most of value-coding neurons in the STN encoded both historical and current values.
Our data indicate that the STN neurons negatively encoded object values in trials and error-based learning. The neural excitation to no rewarded objects in the STN can directly increase the neural activity in the substantia nigra pars reticulata (SNr). Consequently, the superior colliculus neurons are inhibited by no rewarded objects, leading to the gaze suppression on no rewarded objects.

Disclosures: H. Jiang: None. **H.F. Kim:** None.

Poster

601. Neural Circuits for Learning and Memory

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Topic: H.01. Animal Cognition and Behavior

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Wellcome (202805/Z/16/Z)
785907 Human Brain Project SGA2

Title: A two-stage model of landmark processing in retrosplenial cortex

Authors: Y. YAN, *A. BICANSKI, N. BURGESS;
UCL, London, United Kingdom

Abstract: Electrophysiology studies in rodents and imaging studies in humans suggest a role for the retrosplenial cortex (RSC) in spatial memory and navigation. In particular, the existence of head direction coding in RSC is well established. However, theoretical models have only recently begun to address the functional role of this head direction signal (Bicanski and Burgess 2016; Page and Jeffrey 2018), with RSC hypothesized to be a key gateway for visual landmark information that can stabilize head direction signals against drift. Recent empirical data suggest separate populations of landmark and head-direction dominated neurons in RSC. In addition, the role of theta modulation in a subset of head direction cells along Papez' Circuit is so far unaccounted for. Here, we propose a two stage model of visual processing in RSC to account for these phenomena within a single theoretical framework. In the first stage, combinations of visual inputs generate a stable unimodal landmark bearing signal even in complex environments composed of multiple landmarks with differing directional specificity and stability. In the second stage, this representation is associated with the retrosplenial head direction signal (inherited from thalamic head direction cells), in order to convey feedback to the generative circuitry of the head direction system. We explore different algorithmic solutions, investigate the capacity of the

system to map distinct environments, and suggest a neural implementation which may account for the difference between head direction cells with and without theta-modulation. In summary, this theoretical framework integrates numerous empirical findings to provide a coherent account of the role of RSC in spatial cognition, and makes predictions for future experimental studies.

Disclosures: Y. Yan: None. **A. Bicanski:** None. **N. Burgess:** None.

Poster

601. Neural Circuits for Learning and Memory

Location: Hall A

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Program #/Poster #: 601.12/Y30

Topic: H.01. Animal Cognition and Behavior

Title: The role of VTA-infralimbic circuits in mediating estrous-dependent fear extinction learning

Authors: *P. RUBIO ARZOLA[1], N. SHEPARD[2], R. SHANSKY[3];
[1]Psychology, Northeastern Univ., Boston, MA; [2]Psychology, Northeastern Univ., Bostonq, MA; [3]Behavioral Neurosci., Northeastern Univ., Boston, MA

Abstract: Post-traumatic stress disorder (PTSD) is characterized by excessive fear to stimuli that no longer predict an aversive situation and is more than twice as likely to occur in women than in men. Extensive research has been done to understand fear extinction in rodents, yet most of these studies have only used male rodents. The few relevant studies that do include female subjects have revealed that there are clear sex differences in fear extinction. Considering that PTSD is more prevalent in women, it is imperative to investigate the neural circuits underlying fear extinction in females. Several studies have revealed that estrogen has an effect on learning. Specifically, estradiol has been shown to facilitate extinction through estrogen receptor ER-β activation and elicits an increase of c-fos in the infralimbic cortex (IL). However, whether estrogen affects extinction through direct actions in the IL or through upstream brain regions that target the IL has not been investigated. One intriguing possibility is that estrogen might have a modulatory effect on the IL through its interactions with dopamine (DA). Previous studies in our lab have shown that administering a D1 receptor agonist improved the extinction of females with low estrogen. Furthermore, it has been noted that DA VTA cells projecting to the prelimbic cortex (PL) contain estrogen receptors ER-β but not ER- α, yet no one has looked at estrogen receptor expression in VTA projections to IL. We hypothesize that estrogen promotes fear extinction by selectively activating dopaminergic VTA neurons that project to the IL (VTA-IL). We further predict that this activation occurs via actions at ER-β. To test this, we first injected CTB-555 bilaterally into IL and, after 2 weeks, began a 2-day fear conditioning and extinction paradigm. After fear extinction, rats were sacrificed and VTA slices were collected and used immunofluorescence to co-labeled for c-fos and tyrosine hydroxylase (TH) to identify activated

dopaminergic neurons. We then used fluorescent microscopy to examine overlap between these markers and CTB-555 and quantified the relative recruitment of VTA-IL neurons. Additionally, we assessed which estrogen receptor was necessary for this by implanting bilateral cannulae into VTA and infusing with an ER-β antagonist before undergoing fear extinction. The following day, rats were tested on an extinction retrieval paradigm to assess the effects of the antagonist on extinction recall. Taken together, these data will help elucidate how estrogen and dopamine interact to improve fear extinction in females.

Disclosures: P. Rubio Arzola: None. **N. Shepard:** None. **R. Shansky:** None.

Poster

601. Neural Circuits for Learning and Memory

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 601.13/Y31

Topic: H.01. Animal Cognition and Behavior

Title: Functional connectivity between the nucleus basalis and the dorsolateral prefrontal cortex during visual-motor associative learning

Authors: *N. J. KILLIAN, E. N. ESKANDAR;
Leo M. Davidoff Dept. of Neurolog. Surgery, Albert Einstein Col. of Med., Bronx, NY

Abstract: The nucleus basalis of Meynert (NBM) and dorsolateral prefrontal cortex (dlPFC) have a multimodal involvement in associative learning, dynamically encoding novelty, reward, and learning state. The NBM is known to degenerate in Parkinson's disease dementia (PDD) and Alzheimer's disease (AD), contributing to impaired learning. However, manipulations of the NBM with deep brain stimulation (DBS) in PDD and AD patients have had mixed results (Kuhn et al., 2015). A better understanding of the functional circuitry of the NBM may improve attempts to compensate for impaired learning in pathological states. The NBM provides the primary source of cholinergic efferents to the dlPFC, which does not reciprocate these connections. The NBM has reciprocal connections with limbic and paralimbic areas, which are also reciprocally-connected with the dlPFC. To examine how this circuitry influences learning, we inferred functional connectivity from simultaneous single-electrode recordings of the NBM and dlPFC (N = 25) in two monkeys (*Macaca mulatta*) as they performed an associative learning task. In this task, the animal learns visual-motor associations between specific novel visual images and a saccade to one of four target locations. In a given trial, an image is first viewed (*viewing phase*), and then the animal is forced to make a saccade to a target (*choice phase*). Saccades to the correct location are rewarded, and visual feedback is given to indicate whether the decision was correct or incorrect. We analyzed connectivity by applying Granger causality (GC) statistics to the local field potentials. Consistent with anatomical connectivity, we observed no GC influence of the dlPFC on the NBM. The GC influence of the NBM on the dlPFC

occurred in two distinct bands, theta-alpha (5 to 15 Hz) and high-gamma (100 to 170 Hz). The NBM drove theta-alpha power in the dlPFC during both the viewing phase and the choice phase. Additionally, during the choice phase, the NBM drove high-gamma power (100 to 170 Hz) in the dlPFC ($p < 0.025$, cluster-based permutation test). These results suggest that the NBM modulates cortical activity using separate frequency bands for different stages of learning, consistent with recent findings (Martinez-Rubio et al., 2018). Strategies for DBS of the NBM might be improved by differentially stimulating to induce distinct oscillations based on learning state estimates.

Disclosures: N.J. Killian: None. **E.N. Eskandar:** None.

Poster

601. Neural Circuits for Learning and Memory

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 601.14/Y32

Topic: H.01. Animal Cognition and Behavior

Title: Transformation of motor memory

Authors: *G. SULLENS[1], K. GILLEY[2], M. J. SEKERES[3];
[2]Psychology, [3]Psychology & Neurosci., [1]Baylor Univ., Waco, TX

Abstract: In both humans and rodents, episodic and episodic-like memories may undergo a process of transformation, in which a memory that is initially context-specific strongly engages the hippocampus. Over time, hippocampal activity may decline as the memory trace reorganizes and becomes represented in prefrontal cortical regions. The hippocampus is not critical for the acquisition of motor memory, but if intact, the hippocampus may participate in the episodic-like encoding of the task event. Over time, as the task becomes highly familiarized, and less bound to the context in which the task was acquired, we predict that hippocampal engagement will decrease, and increasingly engage regions within the prefrontal cortex and striatum. To test this idea, three-month-old male C57BL6 x 129 hybrid mice learned a straight alley motor task. Mice were assigned to one of six conditions: homecage control; 1 training day in Context-A; 1 training day in CXT-B; 20 training days in CXT-A; 19 training days in CXT-A with 1 additional day in a novel Context-B; and 1 training day in CXT-A prior to 18 days of homecage control rearing followed by one final training day in CXT-A. Latency to mount the hidden platform revealed decrease time across training exposure, which is indicative of motor learning. Immediate early gene expression (IEG) of c-Fos is being used to assess the neural activation at the time of the last training session, which will identify how motor memory networks reorganize over time, exposure, and across contexts in the intact mouse brain. We predict that motor memories will engage an altered network as the task becomes highly familiarized.

Disclosures: G. Sullens: None. **K. Gilley:** None. **M.J. Sekeres:** None.

Poster

601. Neural Circuits for Learning and Memory

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Program #/Poster #: 601.15/Y33

Topic: H.01. Animal Cognition and Behavior

Title: Effects of amygdala lesions on stimulus vs. action based learning

Authors: *B. H. HARRIS[1], N. MANEM[2], C. A. TASWELL[2], E. A. MURRAY[2], B. B. AVERBECK[2];
[1]Natl. Instituteof Hlth., Bethesda, MD; [2]NIH/NIMH, Bethesda, MD

Abstract: Reinforcement learning (RL), is the process of associating values with objects and actions. Work in our lab has been dissecting the neural circuitry that underlies visual stimulus-based vs. action based RL. We have developed a task that interleaves blocks of trials in which animals have to learn to associate rewards with actions or with visual stimuli. In previous work, we found evidence that animals with lesions of the ventral striatum were impaired on visual stimulus based, but not action based learning (Rothenhoefer, K, et al., 2017). In the present study we examined the effects of lesions of the amygdala on the same task. Specifically, we trained unoperated control monkeys (n = 6) and monkeys with bilateral excitotoxic amygdala lesions (n=4) on a probabilistic two-arm bandit reversal learning task. The task had two conditions, which were run in randomly interleaved blocks of 80 trials. In the What condition, the monkeys had to learn which of two images was more frequently rewarded. In the Where condition, they had to learn which of two saccade directions was most frequently rewarded. At the beginning of each block of 80 trials, two new images were introduced. In a What block, a high reward probability was assigned to one image and a low reward probability was assigned to the other. In a Where block, a high reward probability was assigned to one of the saccade directions (left or right) and a low reward probability was assigned to the other. In each trial the animals made a saccade to one of the images to indicate their choice. Following their choice, they were stochastically rewarded. In addition, on a randomly chosen trial between 30 and 50, the choice-outcome mappings were reversed, so the opposite choice within the same condition became more frequently rewarded. Compared with controls, amygdala lesioned monkeys showed deficits in both stimulus-based and action-based learning.

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Poster

601. Neural Circuits for Learning and Memory

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Program #/Poster #: 601.16/Y34

Topic: H.01. Animal Cognition and Behavior

Support: R01 NS088661
NARSAD Young Investigator Award

Title: Fast cholinergic prediction errors track conditioned behavior during reversal learning

Authors: *J. F. STURGILL[1], A. SIEBELS[1], S.-J. LI[1], B. HANGYA[2], A. KEPECS[1];
[1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Dept. of Cell. and Network Neurosci., Inst. of Exptl. Med., Budapest, Hungary

Abstract: The cholinergic basal forebrain (CBF) projects throughout pallium-derived structures such as cortex, and, by modulating plasticity, may support learning. Yet the principles governing CBF activation, and the precise relationships of CBF signals to learning have remained unclear. Recent work from our lab revealed that CBF neurons respond rapidly to reinforcers (reward, punishment) and are modulated by reinforcement expectation or surprise, similar to dopaminergic reward prediction error (RPE). Therefore we hypothesized that the CBF provides a valence-free counterpart to dopaminergic RPE. Confirming this hypothesis we show that: 1) the CBF encodes a quantitative prediction error signal that is conveyed to cholinergic terminal fields 2) CBF predictions adapt as quickly with learning as their dopaminergic counterpart 3) overlapping afferent circuitry and correlated activities indicate a global, distributed circuit for computing reinforcement prediction errors.
To relate CBF signals to reinforcement expectation, we used fiber photometry to record CBF activity in a cued, probabilistic outcome task to manipulate reinforcement expectations. Consistent with an unsigned signal, our data confirm that the CBF responds alike to reward and punishment. With learning, the CBF acquires responses to outcome predictive stimuli. These responses precede and predict the degree of anticipatory licking, as well as are modulated by expected outcome value. Furthermore, CBF neurons show diminished responses to expected outcomes, a hallmark of a prediction error signal.
A key, outstanding question is how the activities of neuromodulatory systems, including the CBF, are coordinated during learning. Using dual fiber recordings we simultaneously recorded dopaminergic and cholinergic signals in a serial reversal learning paradigm. We found that cholinergic responses to positive valence cues emerge at least as quickly following reversals as dopaminergic responses and track the acquisition of conditioned behavior. At a finer timescale, noise correlations to cue and reinforcement delivery and coherent activity even in spontaneously behaving mice suggest that the CBF and dopaminergic systems are driven in part by common

upstream circuits. These data indicate the CBF's involvement in reinforcement learning in parallel to dopamine and are consistent with emerging evidence that the prediction error circuits governing learning are more distributed and diverse than originally appreciated.

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Poster

601. Neural Circuits for Learning and Memory

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH118339
NIH Grant MH113894

Title: Synaptic correlates of contextual fear memory consolidation in prefrontal neocortical circuit

Authors: W. KIM, E. PARK, ***J.-H. CHO**;
Univ. of California, Riverside, Riverside, CA

Abstract: In contextual fear learning, experimental subjects learn to associate a neutral context with an aversive stimulus and display fear responses to a context that predicts danger. Exposure to a context activates a subset of hippocampal neurons, which convey contextual representations to the amygdala and medial prefrontal cortex (mPFC). The contextual information is then integrated with aversive signals for fear memory formation. Once encoded, contextual memories progressively mature to a stabilized form during systems consolidation. Although it has long been proposed that permanent storage of contextual memories involves strengthening of neocortical circuits, this hypothesis has not been thoroughly tested. To test the hypothesis, we employed a combined approach of neural activity-dependent labeling, optogenetics, and electrophysiology in a mouse model of contextual fear conditioning. With this approach, we labeled mPFC neurons active during contextual fear learning and found that they were reactivated during the recall of a remote contextual fear memory. Moreover, consolidation of a contextual fear memory was associated with selective strengthening of excitatory connections between mPFC engram cells active during fear learning. Our study suggests that strengthening of connections between memory engram cells plays pivotal roles in permanent storage of contextual fear memories in prefrontal neocortical circuits.

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Poster

601. Neural Circuits for Learning and Memory

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Support: NeuroCog
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NeuroGlia

Title: Specific reorganization of striatal network dynamics during habit formation

Authors: *N. BADREDDINE[1,2], G. ZALCMAN[1,2], F. APPAIX[1,2], G. BECQ[3], N. TREMBLAY[3], F. SAUDOU[1,4], S. ACHARD[3], E. FINO[1,5];
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Abstract: Procedural memory, the memory of habits, is formed by the repetition of a given action. The neural substrates underlying this memory are the basal ganglia, long known to be critical for normal motor control, but now also recognized as influencing cognitive and motivational aspects of behavior. The striatum, the input stage of basal ganglia, relays information between the cortex and other subcortical structures, thus ensuring the selection and integration of cortical information by forming functional parallel loops (associative, sensory-motor and limbic). The associative loops include the dorsomedial striatum (DMS) and mediate the first phase of procedural learning (goal-directed behavior). The sensorimotor loops include the dorsolateral striatum (DLS) and mediate habit formation. Although the anatomy of the circuits involved in procedural learning has been well described, little is known about the dynamics of the striatal networks responsible for the engram of procedural memory. The goal of our study is to characterize the dynamics of the striatal networks involved in the different phases of procedural learning. For this purpose we are using a behavioral paradigm to form procedural memory and anatomical and functional approaches (ie. tracing and two-photon calcium imaging). This will allow us to characterize the networks' activity and properties in relation to memory formation.

Disclosures: **N. Badreddine:** None. **G. Zalcman:** None. **F. Appaix:** None. **G. Becq:** None. **N. Tremblay:** None. **F. Saudou:** None. **S. Achard:** None. **E. Fino:** None.

Poster

601. Neural Circuits for Learning and Memory

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 601.19/Y37

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant F31 DK116558

Title: Medial septum cholinergic signaling regulates gastrointestinal-derived vagus sensory nerve communication to the hippocampus

Authors: *A. N. SUAREZ[1], C. M. LIU[2], A. M. CORTELLA[1], E. N. NOBLE[1], S. E. KANOSKI[1];
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Abstract: The vagus nerve delivers bi-directional communication between feeding-relevant gastrointestinal (GI) signals and the brain. Vagal sensory-mediated GI satiation signals, including gastric distension and intra-gastric nutrient infusion, activate neurons in the hippocampus (HPC). Recent work from our lab revealed that selective GI-derived vagal sensory signaling is required for HPC-dependent episodic and visuospatial memory, effects accompanied by reduced dorsal HPC (dHPC) expression of neurotrophic and neurogenic markers. To investigate the neural pathways mediating gut regulation of hippocampal-dependent memory, here we investigate the hypothesis that GI-derived signals communicate to dHPC neurons via cholinergic input from the medial septum, a memory-promoting pathway that is vulnerable to disruption in various degenerative dementia diseases. To explore this putative gut-to-brain pathway, we administered 192IgG-saporin, a neurotoxin that selectively kills cholinergic neurons via apoptosis, in the medial septum to determine whether septal cholinergic neurons regulate vagally-mediated neuronal activation in dHPC. Results revealed that elimination of cholinergic neurons in the MS reduced peripherally-administered cholecystokinin (CCK)-induced c-Fos expression in the dHPC, suggesting that cholinergic inputs from the MS transmit GI-derived signaling to the dHPC. Consistent with this interpretation, dHPC protein expression of vesicular acetylcholine transporter (VAChT), which promotes memory function and acetylcholine release without disrupting other co-released molecules, was significantly reduced in rats with GI-specific vagal sensory ablation via nodose ganglion injections of CCK conjugated to saporin. Collectively these results suggest that GI-derived vagal sensory signaling influences memory function via enhancement of MS cholinergic signaling to the dPHC.

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Poster

601. Neural Circuits for Learning and Memory

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Title: The role of coordinated activation between insular cortex and basolateral amygdala during taste-aversion association learning to recruit a memory trace

Authors: *K. ABE[1], M. KURODA[1], Y. NARUMI[1], Y. KOBAYASHI[2], S. ITOHARA[2], T. FURUICHI[1], Y. SANO[1];
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Abstract: Memory is thought to be stored in a subset of neurons activated during learning. These neurons are reactivated during memory retrieval. In the amygdala and hippocampus, it has been shown that the selection of this subset of neurons is regulated by neural excitability and CREB (cAMP response element binding protein) activity during learning. We previously showed that insular cortical neurons with virally transduced CREB are preferentially activated after taste memory retrieval and memory retrieval was impaired by selectively silencing those neurons. However, it is not well known about cellular mechanisms of memory allocation in the cortex. Conditioned taste aversion (CTA) is associative learning in which a taste (such as saccharine; conditioned stimulus [CS]) with the experience of malaise (in this experiment, it was induced by i.p. of LiCl; unconditioned stimulus [US]). It is believed that the insular cortex (IC) and basolateral amygdala (BLA) are required for formation and retrieval of CTA memory. First, we tested whether it is possible to recruit the encoding of an taste memory to a subset of IC neurons with increased excitability. We manipulated neural excitability using Gq-DREADD (hM3Dq receptor). Contrary to previous findings about mechanism of fear memory allocation in the amygdala, increased neural excitability during learning did not bias c-fos expression following retrieval in IC when neural activity was only manipulated in IC. While highly excitable neurons during conditioning were preferentially expressed c-fos following CTA memory retrieval in BLA. Interestingly, IC neurons with higher excitability during learning were preferentially expressed c-fos following memory retrieval when both of IC and BLA was manipulated during

learning. These findings probably suggest that coordinated activation of IC and BLA determines which subset of neurons recruits a taste memory trace in the insular cortex.

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Poster

601. Neural Circuits for Learning and Memory

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Program #/Poster #: 601.21/Y39

Topic: H.01. Animal Cognition and Behavior

Support: CIHR Operating Grant MOP-133693
NSERC Discovery Grant RGPIN-2015-05458
CFI Leaders Opportunity Fund 25026

Title: Prefrontal neural ensembles develop selective code for event associations within minutes of novel experiences

Authors: *K. TAKEHARA-NISHIUCHI[1,2], M. D. MORRISSEY[1], M. PILKIW[2];
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Abstract: Prevailing theories posit that the hippocampus rapidly learns stimulus conjunctions during novel experiences, whereas the neocortex learns slowly through subsequent, off-line interaction with the hippocampus. Recent studies, however, show that at the time of encoding, the medial prefrontal cortex (mPFC, a critical node of the neocortical network supporting long-term memory storage) undergoes rapid modifications of synaptic structure and physiology (Bero et al., 2014) as well as tagging of memory-bearing “engram” cells (Kitamura et al., 2017; see also Lesburgueres et al., 2011). These observations, along with impaired learning with disrupted mPFC (Weible et al., 2000; Takehara-Nishiuchi et al., 2005; Barker and Warburton, 2008; Gilmartin et al., 2010; Bero et al., 2014), suggest that mPFC neurons may exhibit rapid neural plasticity during novel experiences; however, direct empirical evidence is lacking. With chronically implanted an array of tetrodes, we recorded spike activity of cells in the prelimbic region of the mPFC while four naïve, male Long-Evans rats received a sequence of neutral sensory stimuli and aversive eyelid shock for the first time. Moment-to-moment tracking of neural ensemble firing patterns revealed that prefrontal network exhibited an abrupt transition upon the first presentation of an aversive, but not neutral, stimulus. This network-level change was driven by ~20% of putative excitatory neurons that acquired firing responses to the aversive and the preceding neutral stimulus within a few instances of their pairings. When a new sensory stimulus was paired with the same aversive event, these neurons immediately generalized firing responses to the new stimulus association. These results suggest that mPFC neurons are capable

of developing firing selectivity for novel relevant events on the fly, which may facilitate selective gating of those events into long-term storage.

Disclosures: K. Takehara-Nishiuchi: None. **M.D. Morrissey:** None. **M. Pilkiw:** None.

Poster

601. Neural Circuits for Learning and Memory

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Support: CIHR Operating Grant MOP-133693
NSERC Discovery Grant RGPIN-2015-05458
CFI Leaders Opportunity Fund 25026

Title: Event-locked cholinergic signal in the medial prefrontal cortex has opposing effects on temporal associative learning depending on event types

Authors: *G. TU[1,2], S. GILLMAN[3], X. YU[3], A. HALAWA[4], K. TAKEHARA-NISHIUCHI[1,2,3]; [1]Psychology, [2]Collaborative Program in Neurosci., [3]Cell and Systems Biol., [4]Human Biol., Univ. of Toronto, Toronto, ON, Canada

Abstract: The basal forebrain (BF) cholinergic system plays an important role in higher cognitive function, including learning and memory, sleep-wake regulation and attention. Recent studies found that BF cholinergic neurons respond to reward and punishment with millisecond precision (Hangya et al., 2015). Additionally, the cholinergic activity increases in response to sensory cue (Parikh et al., 2007) and stimulating BF cholinergic neurons enhances cue detection (Gritton et al., 2016). These findings led us to hypothesize that the transient, event-locked cholinergic signal improves cortical neural responses to the events and in turn facilitates encoding of event memories. Among various targets of BF cholinergic innervation, the prelimbic subregion (PrL) of the medial prefrontal cortex (mPFC) plays a key role in associating temporally discontinuous events. We thus optogenetically manipulated cholinergic terminals in PrL in trace eyeblink conditioning task, where mice associate a neutral tone (conditioned stimulus; CS) with a mild eyelid shock (unconditioned stimulus; US) over a stimulus-free trace interval. Male ChAT-IRES-Cre mice (C57B6J) were injected with adeno-associated viral vectors carrying archaerhodopsin (Arch), or channelrhodopsin (ChR2), or green fluorescent protein (Control) in a Cre-recombinase-dependent manner. Over ten days of conditioning, photo-inhibition of cholinergic terminals in PrL during the CS impaired associative learning (Control, n=13; Arch n=11); while the same manipulation during the US facilitated the learning (Control, n=13; Arch n=11). Conversely, photo-stimulation of cholinergic terminals during the US impaired the learning (Control, n=8; ChR2 n=8). In parallel, cholinergic inhibition during the

US, but not the CS, increased the expression of neuronal activity marker, c-Fos in somatostatin-positive interneurons and excitatory neurons in PrL while cholinergic excitation during the US decreased c-Fos expression in these neuron types. These findings support the proposed role of transient cholinergic signal in cue detection (Parikh et al., 2007; Howe et al., 2013; Gritton et al., 2016) but contradict with its role in signaling reinforcement surprise (Hangya et al., 2015). Rather, the reinforcer-locked cholinergic signal may modulate the level of recurrent excitation in mPFC network, thereby controlling the degree to which the network integrates information across days.

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Poster

601. Neural Circuits for Learning and Memory

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Support: KAKENHI 15K21013
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The Ichiro Kanehara Foundation
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Title: Excitation of medial prefrontal cortex during conditioning enhances fear memory formation

Authors: N. SHIBANO[1], M. YAMAZAKI[1], M. KURODA[1], K. ABE[1], T. ARIMA[1], Y. KOBAYASHI[2], S. ITOHARA[2], T. FURUICHI[1], ***Y. SANO**[1];
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Abstract: Memories of fearful events can be remembered for a long time, which allow animals to predict danger and is important for their survival. While the formation of strong fear memory can drive neuropsychiatric disorders, such as posttraumatic stress disorder. Contextual fear memory is initially encoded and consolidated in the hippocampus and gradually consolidated in multiple brain regions over time including the medial prefrontal cortex (mPFC). In mPFC, a subset of neurons are tagged for a given memory at early phase of learning and become functionally mature as engram cells with time. However, it is not well known how mPFC neurons contribute to fear memory formation at early phase. Previously, we and other groups showed that neural excitability biases the allocation of fear memory. Here, we have tested

whether it is possible to recruit the encoding of fear memory to a subset of mPFC neurons with increased excitability at recent time point. We manipulated neural excitability in a small or large population of mPFC neurons using Gq-DREADD (hM3Dq receptor) during contextual fear learning. Next day, retrieval test was implemented and analyzed c-fos expressing neurons which were activated by memory retrieval. In both of manipulation in a small and large neural population, increased neural excitability during learning did not bias c-fos expression following fear memory retrieval. But contextual fear memory formation was significantly enhanced when neural excitability was manipulated in a large but not small subset of neurons. Interestingly, a size of cell assembly involved in memory retrieval was significantly increased in the basolateral amygdala (BLA) but not in mPFC. The number of c-fos expressing neurons was correlated with the amount of freezing behavior. We have also tested which neuromodulator is involved in fear memory formation. A weak fear memory was strengthened by increasing noradrenergic activity in mPFC. Taken together, our results suggest that neural excitability in mPFC during learning modulates fear memory formation via activation of BLA neurons, which could be independent of recruiting mPFC neurons into a memory trace. And strong input from noradrenergic neurons to mPFC could augments fear memory formation.

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Poster

601. Neural Circuits for Learning and Memory

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Program #/Poster #: 601.24/Y42

Topic: H.01. Animal Cognition and Behavior

Support: NSF BRAIN EAGER award IOS-1545885
NIH/NIMH 1 F31 NS100412-01
Sloan Fellowship

Title: *Danionella translucida:* A novel fish species for systems neuroscience

Authors: *A. PENALVA-TENA, A. D. DOUGLASS, J. BEDKE, J. P. BARRIOS, E. P. L. BERTRAM, W.-C. WANG, E. S. B. COOK;
Univ. of Utah, Salt Lake City, UT

Abstract: A central goal of systems neuroscience is to understand how the coordinated activities of many single neurons determine behavior. The small size and optical transparency of the larval zebrafish (*Danio rerio)* enable the recording and manipulation of neural activity throughout its brain, but larval zebrafish have a rudimentary behavioral repertoire, and complex social and learning behaviors do not appear until adulthood when they are no longer optically transparent.

Here we establish miniature fish species *Danionella translucida* as a laboratory model that overcomes these limitations, demonstrating the genetic, optical, and behavioral advantages of this novel fish model during its adult stages.
Adult *Danionella* retain a small size and optical transparency during adulthood, allowing for whole-brain imaging techniques. We demonstrate the use of two-photon microscopy to image deep within the brain of adult *Danionella* at a high optical resolution, a feat not achievable in adult zebrafish. The close phylogenetic relationship between *Danionella* and zebrafish has also allowed us to use zebrafish-derived enhancer elements to drive the expression of foreign transgenes in specific cells within *Danionella.*
We demonstrate the complex behavioral repertoire of *Danionella* by reliably developing a social preference and reinforcement assay for this fish species. We show *Danionella* exhibit an innate preference for social interaction, which acts as a behavioral reinforcer in a conditioned place preference paradigm. These innate social responses are species and gender-specific, and are mediated by visual and olfactory cues. In addition, the introduction of antagonists to the oxytocin receptor, a peptide implicated in social reward, diminishes these behaviors.
The optical, genetic, and behavioral tractability of *Danionella* provides a new model to interrogate the neural circuitry of complex social and learning behaviors.

Disclosures: A. Penalva-Tena: None. **A.D. Douglass:** None. **J. Bedke:** None. **J.P. Barrios:** None. **E.P.L. Bertram:** None. **W. Wang:** None. **E.S.B. Cook:** None.

Poster

601. Neural Circuits for Learning and Memory

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01-NS93909
DARPA

Title: Cognitive enhancement of perceptual decision making through vagus nerve stimulation

Authors: *N. SUBRAMANIAN[1], B. GOOLSBY[2], H. KIM[1], P. NAVARRO[1], M. BRODSKY[2], M. MANSY[2], K. OWEISS[1,2,3];
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Abstract: The vagus nerve innervates the Nucleus Tractus Solitarius (NTS), which in turn relays much of the information received to the reticular formation, the Locus Coeruleus (LC) and Basal forebrain (BF) which directly innervate the medial prefrontal cortex (mPFC). Previous studies from our group have demonstrated that reversible optogenetic suppression of mPFC neurons

degrades performance in a delayed response task requiring animals to perceive auditory cues for rewarded choice. Herein, we hypothesized that vagus nerve stimulation (VNS) would enhance perceptual decision making when the task required animals to accumulate evidence from a mix of salient and non-salient cloud of tones. We varied the task complexity by increasing the degree of tone overlap between the low and high frequency categories. We found significant improvement in behavioral performance in the VNS group compared to the sham and untrained control groups. Furthermore, VNS significantly shortened decision time and increased performance accuracy for complex task (20% tone overlap between tone categories) compared to the basic task (no tone overlap). Using fiber photometry, VNS stimulation increased the rate of Ca^{2+} transients in GCaMP6f+ mPFC neurons, suggesting that VNS might enhance attentional mechanisms through increased synchrony between neurons in the neuromodulatory pathways of both LC and BF that permits deciphering salient and non-salient cues.

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Poster

601. Neural Circuits for Learning and Memory

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 601.26/Y44

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant NS93909

Title: All-optical functional mapping of association cortex subserving working memory and perceptual decision making

Authors: B. GOOLSBY[1], H. J. KIM[2], J. CANZANO[3], *K. G. OWEISS[1,2,3];
[1]Biomed. Eng, [2]Electrical & Computer Eng, [3]Col. of Med., Univ. of Florida, Gainesville, FL

Abstract: The posterior parietal cortex (PPC) is part of association cortex that reciprocally projects to primary sensory areas, thalamus and striatum. It has been implicated in a number of higher order cognitive processes, including decision making (DM), working memory (WM) and motor planning (MP). The extent to which PPC neurons simultaneously contribute to these processes, however, remains elusive. Here we trained head fixed mice on a delayed response task that required animals to discriminate a sequentially presented 'cloud of tones' sampled randomly from high and low frequency bands to earn water reward through corresponding left or right lick ports after a delay period. Mice learned to perform the task at 90% correct at one second delay and maintained up to 70% performance through a five second delay. Two-photon Ca^{2+}imaging of the genetically encoded Ca^{2+} indicator GCaMP6f revealed differential engagement of GCaMP6f^{+} PPC neurons during multiple task epochs. Individual spikes from Ca^{2+}dynamics were inferred

and used to estimate the extent of temporal correlation with behavioral task variables using a generalized linear model, permitting individual neurons to be characterized by their weights in each behavioral epoch with high temporal precision. We found that neuronal population activity significantly encodes task variables with different degrees across time, suggesting dynamic contributions to DM, WM and MP. Within behavioral epochs, neurons were differentially tied to tone, delay, and behavioral response epochs, including choice outcome in each trial. Inferring functional connectivity between these task-dependent neurons using Bayesian graphical models allowed us to study the extent to which specific network states during each behavioral epoch are critical to maintain in the next epoch for correct choice, thereby contributing to a sequential - rather than a persistent - activity coding model of task variables. Furthermore, event-triggered targeted photostimulation of a subset of graph-derived influential neurons using the redshifted opsin C1V1 permits establishing causal contribution of subpopulations of PPC neurons to both network dynamics and choice behavior.

Disclosures: B. Goolsby: None. **H.J. Kim:** None. **J. Canzano:** None. **K.G. Oweiss:** None.

Poster

601. Neural Circuits for Learning and Memory

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 601.27/Z1

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant NS93909

Title: Simultaneous two-photon calcium imaging and cell-targeted optogenetic stimulation shapes somatosensory cortex plasticity

Authors: N. SUBRAMANIAN[1], ***J. S. CANZANO**[2], B. GOOLSBY[3], H. KIM[1], P. NAVARRO[1], R. CASTRO[1], K. G. OWEISS[1,3,2];
[1]Electrical & Computer Engin., [2]Col. of Med., [3]Biomed. Engin., Univ. of Florida, Gainesville, FL

Abstract: Somatosensory feedback is a fundamental component of motor learning. Subjects with disembodied limbs rely on artificially induced somatosensation to guide motor control, yet despite advances in stimulation strategies that measure perception in these subjects, successful integration into moment-to-moment movement trajectories remains largely unexplored. In the intact system, sensory-evoked population activity in primary somatosensory cortex (S1) could be viewed to arise from a low-dimensional latent dynamic system in which implicit latent variables drive the evoked high dimensional neural activity. Thus, neurons with the highest weight in this low dimensional space would theoretically be the most influential in driving local population activity towards desired states associated with ongoing motor encoding populations in primary

motor cortex (M1). Herein we developed a platform for interrogating S1 populations in head-fixed behaving mice via two-photon volumetric calcium imaging and simultaneous cell-targeted optogenetic stimulation. The platform benefits from close proximity of the M1 and S1 regions of the caudal forelimb area (CFA) and therefore simultaneous imaging and stimulation of both regions is possible. Mice chronically implanted with cranial windows and virally-induced to co-express the calcium indicator GCaMP6f and redshifted opsin C1V1 in the CFA are trained to perform a simple sensory-guided motor task. The apparatus consists of mice locomoting on a floating ball capable of delivering vibrotactile feedback during virtual navigation. M1 and S1 CFA responses to passive and active forepaw touch are first analyzed to functionally tag GCaMP6f+, C1V1+ neurons. Estimating latent variables to identify neurons with high weights in the low-dimensional latent space is then achieved through a Bayesian graphical model. These ensembles are then photostimulated conditioned on behavioral events in the virtual maze to achieve S1 activity dynamics that inform motor planning. Preliminary results show as little as 30 trials of timelocked vibrotactile + optogenetic stimuli delivered to an individual CFA neuron is sufficient to introduce a significant change in receptive field and a transient calcium response (crossing 3xSD threshold of baseline during post-stim period, n=10 trials). These results will help describe 1) cortico-cortical information transmission between S1 and M1 in response to natural tactile stimuli during ongoing movements 2) cortical responses to cell-targeted optogenetic stimulation and its capacity to inform motor output 3) the capacity for cell-targeted optogenetic stimulation to drive local circuit plasticity.

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Poster

601. Neural Circuits for Learning and Memory

Location: Hall A

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Program #/Poster #: 601.28/Z2

Topic: H.01. Animal Cognition and Behavior

Support: NIH/NIMH Grant 1R01MH102394 – 01A1

Title: Differential task coding between the prelimbic and rostral anterior cingulate cortices during spatial working memory

Authors: *J. J. STOUT, Jr[1], A. L. GRIFFIN[2];
[1]Psychological and Brain Sci., Grad. Student, Newark, DE; [2]Univ. Delaware, Newark, DE

Abstract: The medial prefrontal cortex (mPFC) is composed of distinct sub-regions defined by anatomical connectivity and behavioral correlates. The prelimbic sub-region (PrL) of the mPFC receives dense innervation from the hippocampus with converging findings of spatially

modulated neuronal firing-patterns during spatial working memory. Alternatively, the anterior cingulate sub-region (ACC) receives less input from hippocampus and has been shown to be more involved in attention and reward-related processes. To better understand how neuronal activity in these prefrontal sub-regions supports memory and decision-making, we conducted *in vivo* single-unit recordings as rats performed a delayed non-match to position task (DNMP) on a T-maze. This paradigm teases apart encoding, maintenance, and decision-making processes via the distinct sample, delay, and choice-phases of the task. We sought to understand how neurons represent and integrate goal-relevant spatial information within the context of DNMP task-phase. First, by comparing the correlation-coefficients between firing-rates from each maze-location, we find spatially-influenced firing-patterns such that neurons increase, or decrease, their activity while traversing locations of the maze. Next, we report that a task-phase code is integrated into this spatially-influenced activity, with both sub-regions exhibiting a decision-accuracy-dependent increase in firing-rate at the sample-phase T-junction. Lastly, training a linear classifier to distinguish population firing-patterns during the sample and choice-phases of the task, we find that both sub-regions were predictive of task-phase at the T-junction. However, ACC showed selective prediction of task-phase at stem and goal-zone, while PrL showed selective prediction of task-phase on the goal-arms. Given the overlap of sample-phase preference among the sub-regions, it is likely that stronger limbic connections support PrL's shared importance with infralimbic for DNMP performance. Finally, our classification findings support ACC's roles in attentional and reward-related processes, while suggesting that PrL continues to exhibit a representation linked to decision-making after T-junction occupancy. These results establish a multiplexed code for location and task-phase, while supporting a subtle heterogeneity among the sub-regions.

Disclosures: **J.J. Stout:** None. **A.L. Griffin:** None.

Poster

602. Learning and Memory: Genes and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 602.01/Z3

Topic: H.01. Animal Cognition and Behavior

Support: CIHR Grant MOP-53761

Title: Odor preference training in week-old rat pups is associated with changes in protein and non-protein coding messenger ribonucleic acids in odor-encoding mitral cells

Authors: *C. W. HARLEY[1], M. N. NARTEY[2], L. PEÑA-CASTILLO[3], M. LEGROW[2], J. DORÉ[2], A. DARBY-KING[2], S. J. CAREW[2], Q. YUAN[2], J. H. MCLEAN[2];
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Abstract: Odor preference learning in the week-old rat pup captures the main features of associative mammalian learning. Odor learning requires the cAMP/PKA/CREB cascade. NMDA receptors are needed for its initiation, and memory is supported by AMPA receptor insertion. A ten-minute pairing of odor with stroking produces a 24-hour long-term memory. Protein translation and transcription within the first hour post-training are required for 24-hour memory. Here pups were trained with peppermint odor and stroking for 10 min, tested for associative learning at 30 min and sacrificed at 50 min for laser micro-dissection of the dorsal olfactory bulb peppermint-encoding mitral cells. Control tissue was taken from rat pups not given stroking during the 10 min odor exposure. Microarray analysis revealed changes in 11 protein-coding mRNAs and 13 non-protein coding mRNAs. Among the protein-coding mRNAs, Sec23b, Clic2, Rpp14, Dcbld1, Magee2, Mstn, Fam229b, RGD1566265, and Mgst2 were up-regulated, while Gng12 and Srcg1 were down-regulated. MicroRNA23b was also down-regulated. Sec23b, Clic2, and Dcbld1 proteins were confirmed, using immunocytochemistry, to be increased in the mitral cell layer 50 min post training using odor and stroking with single naris occlusion. Thus, neither odor nor stroking alone is responsible for increases in these pathways. The protein-coding changes are consistent with extracellular matrix remodeling and ryanodine receptor mediation in odor preference memory, and with a role for CREB and AP1 in regulating memory-related mRNA changes. The majority of the mRNA changes (13) were in nucleolar and nuclear non-coding RNAs. The non-coding changes suggest splicing alterations in early olfactory memory and are consistent with evidence that changes in t-mRNA fragments occur with olfactory learning. While a number of the mRNA changes identified correlate well to models of learning and memory that depend on circuitry change, the roles of others are unknown and may point to novel supporting elements. The relatively small number of gene changes in the input/output link for learning in this model, the mitral cells, offers an opportunity to thoroughly characterize learning's remodeling and structural support after training.

Disclosures: C.W. Harley: None. **M.N. Nartey:** None. **L. Peña-Castillo:** None. **M. LeGrow:** None. **J. Doré:** None. **A. Darby-King:** None. **S.J. Carew:** None. **Q. Yuan:** None. **J.H. McLean:** None.

Poster

602. Learning and Memory: Genes and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 602.02/Z4

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R33 DA041883

NIH Grant T32 GM008151

Title: Cornichon homolog-3 (CNIH3) modulates hippocampal synapses and memory in female mice

Authors: *H. E. FRYE[1], C. TROUSDALE[1], J. D. DOUGHERTY[2], E. C. NELSON[3], J. MORON-CONCEPCION[1];
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Abstract: Cornichon homolog-3 (CNIH3) is an AMPA receptor (AMPAR) auxiliary protein highly expressed in the hippocampus. While AMPARs are critical actors for hippocampal synaptic plasticity and memory formation and maintenance, little is known about the role of CNIH3 in these processes. We hypothesize that CNIH3 modulates learning and memory through regulation of AMPAR activity and synapse stability in the hippocampus. Using C57BL/6 *CNIH3* knockdown (KD) mice obtained from the Knockout Mouse Project, we generated *CNIH3* full knockout (KO) male and female mice for use in this study. Western blot analysis in sub-cellular fractions demonstrate that female *CNIH3* KD mice have reduced PSD-95 expression, an excitatory post-synaptic scaffolding protein, at hippocampal post-synaptic densities (PSD). As synaptic stability plays a critical role in learning and memory, we utilize the Barnes Maze assay to assess the impact of *CNIH3* expression on AMPAR-mediated spatial memory. In this task, *CNIH3* KO females show impaired learning processes compared to wild-type (WT) controls, as observed through increased primary errors, reduced path efficiency, and higher latency to locate the target. Interestingly, no deficits are observed in *CNIH3* KO male mice. To determine if increased *CNIH3* expression in the dorsal hippocampus (dHPC) improves spatial memory, we injected an AAV5-CAMKII-myc-CNIH3-t2A-GFP virus into the dHPC of WT mice to induce local *CNIH3* overexpression (OE). *CNIH3* OE in the dHPC significantly improves spatial memory compared to sham injected controls in female mice, but not in male mice. We hypothesize that we can rescue the spatial memory deficits in *CNIH3* KO females with *CNIH3* OE in the dHPC. This study establishes CNIH3 as a key component in the maintaince of hippocampal synaptic structure and spatial memory in female mice. Future studies will assess the role of CNIH3 on hippocampal synapse formation and density within the dHPC of *CNIH3* KO mice, and investigate how sex impacts the role of CNIH3 in these processes.

Disclosures: H.E. Frye: None. **C. Trousdale:** None. **J.D. Dougherty:** None. **E.C. Nelson:** None. **J. Moron-Concepcion:** None.

Poster

602. Learning and Memory: Genes and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 602.03/Z5

Topic: H.01. Animal Cognition and Behavior

Support: NHRI-EX106-10613NI

Title: Conditional deletion of CC2D1A impairs hippocampal synaptic plasticity and cognitive function through Rac1 hyperactivation

Authors: *C.-Y. YANG[1], T.-H. YU[1], W.-L. WEN[2], P. LING[3], K.-S. HSU[1,2];
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Abstract: Coiled-coil and C2 domain containing 1A (CC2D1A) is a protein recently identified as nuclear factor-κB activator. Human studies have shown that, Mutation of CC2D1A result in nonsyndromic intellectual disability. However, it remains unclear how *cc2d1a* mutation alters brain functions. We used Cre/loxp recombinase-based strategy to conditional delete CC2D1A in excitatory neurons to explore its role in hippocampal synaptic plasticity and cognitive function. We have confirmed the expression pattern of CC2D1A in hippocampus from embryonic stage to adulthood and it expresses in both excitatory and inhibitory neurons. Conditional deletion of CC2D1A (cKO) in excitatory neurons leads to spatial memory impairment and anxiety-like behavior. Consistently, cKO mice exhibited impaired long-term potentiation (LTP) maintenance in hippocampal CA1 region. We also discovered that, cKO mice have decreased complexity in apical and basal dendritic arbors of CA1 pyramidal neurons. An enhanced basal Rac1 activity was observed in cKO mice. This enhancement was mediated by reduced SUMO-specific protease 1 (SENP1) and SENP3 expression, thus increasing the amount of Rac1 SUMOylation. Partial blockade of Rac1 activity by NSC23766 rescued the impairment of cognitive function and LTP maintenance in cKO mice. Altogether, our results implicate Rac1 hyperactivity in synaptic plasticity and cognitive deficits observed in *Cc2d1a* cKO mice and reveal a novel role for CC2D1A in regulating hippocampal synaptic function. Such insights may have implications for the utility of Rac1 inhibitors in the treatment of intellectual disability caused by Cc2d1a mutations in human patients.

Disclosures: C. Yang: None. **T. Yu:** None. **W. Wen:** None. **P. Ling:** None. **K. Hsu:** None.

Poster

602. Learning and Memory: Genes and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 602.04/Z6

Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI 16K13054
KAKENHI 16H05443

Title: Pin1 gene deficient mice impair spatial memory and show small brain volume

Authors: *H. OHTAKI[1], Y. TANAKA[1], T. UCHIDA[3], K. KIRIYAMA[1], K. ONO[2], K. HONDA[4];
[1]Anat., [2]Neurol., Showa Univ. Sch. of Med., Tokyo, Japan; [3]Mol. Cell Sci., Tohoku Univ., Sendai, Japan; [4]Anat., Showa Univ., Tokyo, Japan

Abstract: Pin1 is a ubiquitous peptidyl-prolyl cis/trans isomerase (PPIase) and has been shown to be necessary for cell growth and apoptosis. While pin1 deficient (-/-) mice are suggested the contribution of the age-dependent neurodegeneration, the relation between behavior and pin1 deficient has not been clarified in detail. The purpose of study is to determine the relationship between pin1 gene and spatial memory. Pin1 homozygous gene deficient (-/-) and the wild-type mice were obtained as a littermate by breeding from the heterozygous gene deficient (+/-) mice. Battery of behavioral tests were performed age-matched Pin1 (-/-) and wild mice at 12 month old. The tests were involved in Y-maze, open-field spontaneously motor activity, new objective recognition and Morris water maze to examine the recognition, learning and memory function. Another group of animals was examined light/dark transition to determine the anxiety-like behavior at 13 month. To determine morphology of the brain, the animals were also measured T2-weight MRI (ICON 1T, Burker) coronal images in the brain every 3 month for 15 month, and semi-quantified the area of coronal plate by manually tracing with Osirix software. No significantly differences were recognized in the body weight during the experiment. Y-maze score, and open-field spontaneously motor activity between Pin1 (-/-) mice and the wild-type (+/+) mice also recognized no difference between the littermate. However, the Pin1 (-/-) mice impaired the score in the new objective recognition and Morris water maze. Although there were no differences to the total sojourn time in light/dark room for 3 days (6-trials), the Pin1 (-/-) mice significantly frequent passing number of gate after 3rd trial, suggesting the mice was restless. The brain volume in the Pin1 (-/-) KO mice was significantly smaller than the wild-type mice, especially in the frontotemporal plane. These results suggest that Pin1 (-/-) mice impaired spatial cognitive function with frontotemporal atrophy.

Disclosures: H. Ohtaki: None. **Y. Tanaka:** None. **T. Uchida:** None. **K. Kiriyama:** None. **K. Ono:** None. **K. Honda:** None.

Poster

602. Learning and Memory: Genes and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 602.05/Z7

Topic: H.01. Animal Cognition and Behavior

Support: MOST 107-2511-H-003-010-MY3
MOST 107-2634-F-008-003

National Taiwan Normal University Subsidy for Talent Promotion Program

Title: Synaptogenesis and neuronal activation dependent on MeCP2/CaMK2A phosphorylation signaling pathway

Authors: *L.-C. LEE[1], M.-T. SU[2], H.-Y. HUANG[1], Y.-C. CHO[3], T.-K. YEH[1], C.-Y. CHANG[1]; [1]Sci. Educ. Center, Natl. Taiwan Normal Univ., Taiper, Taiwan; [2]Dept. of Life Sci., [3]Grad. Inst. of Sci. Educ., Natl. Taiwan Normal Univ., Taiper, Taiwan

Abstract: Calcium/Calmodulin-dependent protein kinase II (CaMKII) plays fundamental roles in synaptic plasticity that underlies learning and memory. The auto-phosphorylation of CaMK2A (CaMKII alpha) works as a 'molecular memory' for a transient calcium activation, thereby accelerating learning. From previous study, we proposed and evidenced that microRNAs and MeCP2 homeostatic regulation are involved in the same molecular signaling pathways as disease development and normal synaptic plasticity in learning. Bridging perception and cognition, we decide to investigate the synaptogenesis and neuronal activation. How it dependent on MeCP/CaMK2A phosphorylation and de novo variants in CaMK2A cause impairment perception or cognitive ability. Neuronal human derived neuroblastoma cell line (SH-SY5Y) cells with inducible MeCP2 overexpression gain-on-function will dramatically increase phosphorylated MeCP2 (phosphor Ser80). Then it positivity affected phosphorylated CaMK2A (phosphor Thr286) and CaMKII-PP1 signaling pathway, which CaMK2A is simultaneously bound by Ca^{2+}/CaM following a Ca^{2+} influx initial phosphorylation and neuronal activation. Furthermore, the negative regulation CaMK2A phosphorylation by microRNA will be investigated either. De novo variants in CaMK2A predict perception or cognitive ability in human adolescent. CaMK2A-rs2241694 was significantly associated with perceptual speed and accuracy in this 832 tenth-grade Taiwanese volunteers' cognitive ability study. The others de novo variants has been assay by a cell- and single molecule-based methods to monitor conformational signaling required for synaptic plasticity. Our data established the importance of CaMK2A and its auto-phosphorylation in human cell based model for neuronal plasticity and this molecular memory mechanism was associated with human adolescent's perception or cognitive ability.

Disclosures: L. Lee: None. **M. Su:** None. **H. Huang:** None. **Y. Cho:** None. **T. Yeh:** None. **C. Chang:** None.

Poster

602. Learning and Memory: Genes and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 602.06/Z8

Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI Grant 17H06051
KAKENHI Grant 16H06276

Title: Mice deficient in Akain1, a novel protein kinase A-binding protein, exhibit decreased pain sensitivity and impaired context discrimination

Authors: K. FUJII[1,2], Y. KOSHIDAKA[2], M. ADACHI[2], Y. YANAGIBASHI[2], M. MATSUO[2], H. NISHIZONO[2], Y. AIZAWA[3], *K. TAKAO[1,2];
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Abstract: Cyclic AMP (cAMP) -dependent protein kinase (PKA) is a ubiquitous serine/threonine kinase. PKA plays a key role in the signaling of many G protein-coupled receptors through the consequent production of cAMP. The specificity of PKA actions is achieved by controlling its cellular localization through a family of A-kinase anchoring proteins (AKAPs). AKAPs localize PKA to specific intracellular sites and spatially restrict intracellular signaling events. AKAP-PKA interactions control various cellular processes, including the regulation of neuroplasticity. A-kinase anchor inhibitor 1 (Akain1) is a novel PKA-binding protein with a unique function in PKA signaling. Akain1 competes with other AKAPs (e.g., AKAP1 and MAP2) for PKA binding and seems to cancel intracellular localization of PKA. In particular, Akain1 is preferentially expressed in neural tissues. How Akain1 affects brain function and behavioral characteristics, however, is unclear. To elucidate the function of Akain1, we generated Akain1 knockout (KO) mice on the C57BL/6J background using the CRISPR/Cas9 genome editing system. Akain1 KO mice were subjected to a comprehensive battery of behavioral tests. In the hot plate test, the latency to the first hind paw response on the hot plate was significantly longer in Akain1 KO mice than in their wild-type (WT) litter mates, suggesting that Akain1 KO mice have decreased pain sensitivity compared with WT mice. In the pattern separation test, Akain1 KO mice exhibited impaired performance in distinguishing between two similar contexts. In the Barnes maze test, Akain1 KO mice and WT mice learned the fixed escape box position at the same rate. For reversal learning, in which the target was moved to the opposite side of the maze, the Akain1 KO mice and WT mice learned the new escape box position at similar rates. While the time spent investigating the new target was significantly longer than the original target, there was no significant difference in Akain1 KO mice, suggesting that Akain1 KO mice had deficits in behavioral flexibility. These findings suggest that Akain1 has a critical role in pain sensitivity and discrimination of similar contexts.

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Poster

602. Learning and Memory: Genes and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 602.07/Z9

Topic: H.01. Animal Cognition and Behavior

Support: MOST 107-2314-B-182A-002

Title: miR-195 affects cognitive function in the aging-associated changes by targeting semaphorin 3A

Authors: *Y.-M. CHAO, J. Y. H. CHAN;
Inst. for Translational Res. in Biomedicine, Kaohsiung Chang Gung Mem. Hosp., Kaohsiung, Taiwan

Abstract: MicroRNA-195 (miR-195), a member of the miR-16/15/195/424/497 family, is abundantly expressed in normal tissue, including the brain. Recently, an anti-aging role of miR-195 was reported. However, its significance in the change of cognitive function, in particular in the whole animal system, has not been properly characterized. Using a tamoxifen-inducible miR-195 knockout (miR-195 /- KO) mice based on the *Cre-loxP* system, we compared in this study temporal profiling of cognitive functions in the KO mice at age of 3, 6, 12, 18 or 24 months to their wild-type (WT) control. The Morris water maze was performed for the evaluation of cognitive function. In both WT and miR-195 /- KO mice, the learning ability was age-dependent but there was no significant difference between the two groups to learn the location of a hidden platform in the water maze for 5 consecutive days. After training, both groups of mice were subjected to probe trials at 24 h, or in 1 and 2 weeks after the last training session, in which the hidden platform was removed from the water maze. At age of 3, 6 and 12 months, not an only preference in the target quadrant was less but also the time spending in the target quadrant was shorter in miR-195 /- KO mice, compared to the WT mice. Semaphorin 3A (Sema 3A) as a potential target gene downregulated by miR-195. So, we overexpressed Sema 3A by lentivirus microinjection into hippocampus and Rapamycin intervention by microinjection into the dorsal third ventricle, the mice which administrated rapamycin reversed the disrupted learning and memory induced by overexpressed Sema 3A. Taken together, these data indicated that while miR-195 targeting gene Sema 3A may play a permissive role in consolidating the spatial working memory, its role in age-associated memory impairment.

Disclosures: Y. Chao: None. **J.Y.H. Chan:** None.

Poster

602. Learning and Memory: Genes and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 602.08/Z10

Topic: H.01. Animal Cognition and Behavior

Title: Neuronal cannabinoid receptor 2 plays a role in anxiety and memory

Authors: J. KOMOROWSKA, A. BILKEI-GORZO, A. ZIMMER, *B. SCHURMANN; Univ. of Bonn, Bonn, Germany

Abstract: The Endocannabinoid system is a neuromodulatory system that influences a majority of vital physiological functions. It consists of endocannabinoids, their synthesizing and degrading enzymes and receptors. The main receptors are CB1 (cannabinoid receptor 1, localized primarily on neurons) and CB2 (cannabinoid receptor 2, localized primarily on glial and immune cells). Contrary to the common believe, recent publications showed the presence of the CB2 receptor on hippocampal neurons and its functional relevance specifically in the CA2/3 area (Stempel et al., 2016). A long-lasting activity driven hyperpolarization depends on neuronal CB2 in CA2/3 pyramidal neurons. CB2 signaling in turn alters the input/output function of CA3 PCs and changes gamma oscillations *in vivo*.
To assess the behavioral consequences of the CB2 deletion we tested constitutive (*Cnr2* d/d) and neuron-specific (*Cnr2* fl/fl Syn-Cre wt/tg) knock-out mice in two sets of behavioral paradigms. We analyzed social (Partner Recognition test) and spatial (Novel Object Location Recognition and Morris Water Maze) memory as well as anxiety (Light-Dark test and O-maze test) in 3 months old male mice. Constitutive deletion of the receptor affects social memory and memory retrieval in the Probe trial of Morris Water Maze. For the most part these phenotypes depend on neuronal Cnr2 as we observed similar behavioural phenotypes in neuron specific conditional knock out animals. Both constitutive and conditional knock-out mice display alterations in anxiety-related behaviours. Altogether our results clearly show that the neuronal cannabinoid receptor 2, despite its low expression, has an impact on mice behaviour playing a role in memory and anxiety.

Disclosures: J. Komorowska: None. **A. Bilkei-Gorzo:** None. **A. Zimmer:** None. **B. Schurmann:** None.

Poster

602. Learning and Memory: Genes and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 602.09/Z11

Topic: H.01. Animal Cognition and Behavior

Support: NIH DA039658
TRDRP 26IP-0043

Title: Subregion-specific expression of the endogenous nicotinic receptor modulator Lynx1 and relation to cognitive function in mice

Authors: *Y. SHERAFAT[1], M. BAUTISTA[2], J. FOWLER[2], C. D. FOWLER[3];
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Abstract: Nicotinic acetylcholine receptors (nAChRs) have been implicated in various aspects of cognitive function, including learning, memory and sensory processing. However, little is known about the endogenous modulators that alter the function of nAChRs and the resulting impact on behavior. Here, we examined the role of the nAChR endogenous protein modulator, Lynx1, in a knockout mouse model. The expression of Lynx1 was first assessed in various brain regions, and interestingly, we found subregion specific expression of the gene within relevant brain regions, such as the hippocampus and cortex. Thus, we then probed for differences in nAChR-mediated neuronal activation patterns between Lynx1 knockout and wildtype mice. Thereafter, to test the effects of Lynx1 on sensory processing, Lynx1 knockout mice and their wildtype littermates were examined in the prepulse inhibition test. To examine the effects on learning and cognitive flexibility, Lynx1 knockout and wildtype mice were trained to press a lever to receive food reward under a fixed ratio schedule of reinforcement. After acquisition, mice were then assessed in a lever reversal task. Together, these findings further define the function of Lynx1 proteins in cholinergic signaling mechanisms in the brain.

Disclosures: Y. Sherafat: None. **M. Bautista:** None. **J. Fowler:** None. **C.D. Fowler:** None.

Poster

602. Learning and Memory: Genes and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 602.10/Z12

Topic: H.01. Animal Cognition and Behavior

Support: NSFC

Title: The E3 ubiquitin ligase ITCH is critical for learning and memory

Authors: *Y. DU[1], R. ZHENG[2], J. XU[2], J. LUO[2];
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Abstract: It is wildly accepted that memory formation and consolidation needs protein synthesis which is required for synaptic plasticity changes in neurons, while whether memory requires protein degradation is not well known. ITCH, an E3 ubiquitin ligase, is involved in the controlling of many aspects of immune responses, tumorigenesis, development, and stress responses. However, few findings indicated the role of ITCH in nervous system. Here, we reported that nestin-cre induced conditional knockout of ITCH in brain impaired multiple forms of memory but had no influence on the anxiety level or the social ability of mice. It suggested that ITCH maybe specifically important for memory through mediating the degradation of related proteins. ITCH might be crucial elements of memory modulation and therefore also of intervention.

Disclosures: Y. Du: None. **R. Zheng:** None. **J. Xu:** None. **J. Luo:** None.

Poster

603. Memory and Cognition

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 603.01/Z13

Topic: H.01. Animal Cognition and Behavior

Support: Otsuka Toshimi Scholarship Foundation

Title: Acute administration of methamphetamine impairs higher cognitive functions in C57BL/6J mice through cortico-striatal circuits

Authors: *J. LIAO[1], T. NAGAI[2], B. WULAER[2], T. NABESHIMA[3], K. YAMADA[2];
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Abstract: Touchscreen-based cognitive tasks have been developed for rodents to provide a better translational approach across species for further understanding of the cognitive impairments observed in various neuropsychiatric disorders. METH is one kind of highly addictive drugs, and METH-treated animals have been widely used as a pharmacological animal model of schizophrenia for the screening of compounds with antipsychotic properties. In the

present study, we aimed to explore the effect of methamphetamine (METH) on higher cognitive functions by a touchscreen-based visual discrimination task. Mice were initially trained to discriminate between a pair of stimuli. On the testing day, mice were treated saline or METH (0.3 or 1 mg/kg, i.p.). METH significantly reduced the accuracy in the visual discrimination task. To clarify the mechanism underlying the METH-induced cognitive deficits, we also analyzed the changes in neuronal activity by METH treatment using c-Fos immunostaining. METH treatment markedly increased the number of c-Fos-positive cells in the medial prefrontal cortex, dorsomedial striatum and thalamus. We demonstrated that acute METH treatment induces cognitive dysfunction by using the translatable visual discrimination task, possibly through the activation of cortico-striatal-thalamic circuits.

Disclosures: J. Liao: None. **T. Nagai:** None. **B. Wulaer:** None. **T. Nabeshima:** None. **K. Yamada:** None.

Poster

603. Memory and Cognition

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 603.02/Z14

Topic: H.01. Animal Cognition and Behavior

Title: Alpha lipoic acid and metformin alleviates experimentally induced insulin resistance and cognitive deficit by modulation of TLR2 signalling

Authors: *A. UNIYAL[1], S. P. SAH[2];
[1]Dept. of Pharmaceut. engineering and Technol., Indian Inst. of Technol., Varanasi, India; [2]Univ. Inst. of Pharmaceut. Sci., Panjab Univ., Chandigarh, India

Abstract: Background: Obesity is commonly found to be co-morbid with type 2 Diabetes Mellitus. In obese diabetic patients, TLR-2 receptor induced inflammation leads to the development of insulin resistance (IR). Furthermore, the IR is considered to be the most important cause for promoting cognitive decline which is evident in brain of patients with Alzheimer's disease related dementia (ADRD). **Methods:** In this study, the effect of α-lipoic acid (ALA) has been examined in rodent model of zymosan induced insulin resistance and cognitive deficits, targeting at TLR-2 signalling. TLR-2 agonist, Zymosan initiates inflammatory cascade, resulting in IR and cognitive dysfunction. Zymosan (50 mg/kg *ip*) was given to mice on 1st, 8th, 15th and 22nd day to induce IR which was confirmed by hyperglycaemia, hyperinsulinemia, hyperlipidimea, increased glycated haemoglobin and HOMA-IR. Further the cognitive performance was assessed in Morris water maze revealing cognitive deficit in zymosan treated mice. **Results:** Daily treatment with ALA for 28 days (50, 100, 200 mg/kg *ip*) significantly improved insulin sensitivity and cognitive performance in mice by decreasing insulin resistance, corticosterone, IL-6 levels, acetylcholinesterase enzyme activity and oxidative

stress in liver, cortex and hippocampus. ALA also increased adiponectin level and reduced body weight. Combination of ALA (100 mg/kg, *ip*) with metformin (100 mg/kg, *ip*) exhibited a potentiating effect in improving cognitive performance and insulin signalling.

Disclosures: A. Uniyal: None. **S.P. Sah:** None.

Poster

603. Memory and Cognition

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 603.03/Z15

Topic: H.01. Animal Cognition and Behavior

Title: Centrally administered scopolamine impairs spatial memory retrieval and alters hippocampal matrix metalloproteinase levels

Authors: *M. L. OLSON, A. BENSON, C. BUCHING, H. GLEWWE;
Concordia Col., Moorhead, MN

Abstract: The accurate formation and retrieval of memories is an important function of the brain, and the forebrain cholinergic system has been widely studied for its role in spatial memory formation. Morphologically, the structural alteration of synaptic connections that underlies spatial memory appears to also require reorganization of the extracellular matrix (ECM). A family of enzymes known as matrix metalloproteinases (MMPs) are known to play an important role in restructuring the ECM. Our study sought to determine whether the cholinergic antagonist scopolamine affects spatial memory retrieval in a standard circular water maze paradigm. We also tested whether scopolamine affects learning-induced changes in hippocampal MMP-3 and MMP-9. Male Sprague-Dawley rats were trained in the circular water maze for 5 days and then underwent cannulation surgery. Scopolamine was administered prior to retrieval testing and hippocampi were dissected and analyzed for levels of MMP-3 and MMP-9. Our results indicate that scopolamine impairs spatial memory performance on testing trials and on post-test probe trials. Our results also indicate a relationship between hippocampal MMP-3 and MMP-9 levels and spatial memory formation, and suggest that regulation of these proteins may be important in mediating the activity-induced neuronal plasticity which is thought to underlie memory formation.

Disclosures: M.L. Olson: None. **A. Benson:** None. **C. Buching:** None. **H. Glewwe:** None.

Poster

603. Memory and Cognition

Location: Hall A

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Program #/Poster #: 603.04/Z16

Topic: H.01. Animal Cognition and Behavior

Support: CONACYT 251634
CONACYT 419800
PAPIIT-UNAM IN204118

Title: GR receptor activation in dorsolateral striatum enhanced extinction of a response memory

Authors: A. FUENTES-IBAÑEZ, N. SERAFÍN, R. A. PRADO-ALCALÁ, *G. L. QUIRARTE;
Dept. de Neurobiología Conductual y Cognitiva, Inst. de Neurobiología-UNAM, Querétaro, Qro., Mexico

Abstract: Extinction has been used as therapeutic method to treat neuropsychiatric disorders such as posttraumatic stress disorder and addictions. These kinds of disorders have been associated with deficiencies in the mnemonic functions of several brain structures, including the dorsolateral striatum (DLS). DLS is a cerebral region involved in acquisition, consolidation and extinction of tasks acquired through operant conditioning procedures such as stimulus-response associations, skills, and habits. On the other hand, glucocorticoids (GCs), such as corticosterone (CORT) in rodents, are hormones that modulate the acquisition and use of response strategies and could modulate extinction as well. In this context, we wondered if the administration of CORT to EDL could facilitate extinction when activating the GCs receptor. To study this issue male Wistar rats were trained in a DLS-dependent response task using the Tolman maze. Once this behavior had been acquired, three extinction sessions were given. Immediately after the first extinction session, CORT (5, 10 or 30 ng/0.5 μL) or vehicle was bilaterally administered to the DLS. The second and third extinction sessions took place 24 and 48 h after the first one, respectively. The latencies to reach the reinforcer and the number of conditioned responses were recorded. The statistical analysis showed no differences between groups regarding the number of conditioned responses or latencies in the first extinction session. In the second and third extinction sessions, the CORT 30 ng group exhibited more efficient extinction. Administration of RU486, a selective antagonist to GR receptor, before the administration of CORT blocked this effect. Importantly, CORT (30 ng) administered 90 min after of the first extinction session had no effect on the parameters measured. These results suggest that striatal glucocorticoids enhance extinction; this effect may be attributed to an effect on consolidation of the extinction memory which may be mediated by GCs receptor activation. We thank Cristina Medina, Martin García, Alejandra Castilla, Deisy Gasca, Nuri Aranda, Lourdes Lara, Ramón Martínez and Omar

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Poster

603. Memory and Cognition

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 603.05/Z17

Topic: H.01. Animal Cognition and Behavior

Title: 5-HT_6 receptor and forgetting process

Authors: *A. MENESES[1], I. PAZ[2,3], K. GRYCHOWSKA[3], V. CANALE[3], P. ZAJDEL[3]; [1]Cinvestav - IPN, Mexico City, Mexico; [2]Cinvestav - IPN, Mexico, Mexico; [3]Medicinal Chem. Dep, Jagiellonian Univ. Med. Col., Krakow, Poland

Abstract: Forgetting is a physiological process seldom investigated as a therapeutic target for memory disorders. In a decay forgetting paradigm there are two-time points to study this process, when forgetting is forming (e.g., 48-h following the interruption period) and/or before the retrieval of memory (e.g., 168-h). We know that forgetting occurs one week of interruption following autoshaping training/testing sessions, showing decreased conditioned responses (CR%). In this work, the partial 5-HT_6 receptor agonist EMD-386088 (5.0 mg/kg, *ip*) partially reversed forgetting or facilitated retrieval (administration -168-h); however, when this compound was administered before forgetting formation and retrieval, the latter process was even more importantly facilitated. The 5-HT_6 receptor inverse agonist PZ-1444 (3.0 mg/kg, *ip*) had an anti-forgetting effect and facilitated retrieval. When PZ-1444 was injected at 48- and 168-h from the interruption, it produced minor facilitation of retrieval. However, a higher dose of PZ-1444 (5 mg/kg, *ip*) produced a minor anti-forgetting effect or less retrieval. Moreover, the 5-HT_6 receptor antagonists SB-399885 (5.0 mg/kg, *ip*) and CPPQ (3.0 mg/kg, *ip*) partially prevented forgetting and retrieval when were injected previously to forgetting formation or retrieval; however, these effects disappeared when injected at 48- and 168-h from the interruption period. In the case of CPPQ, its anti-forgetting effects are in line with evidence reported by Grychowska *et al* (2016), finding that CPPQ administration facilitated performance in the novel object recognition task. In contrast, a higher dose of CPPQ (5 mg/kg, *ip*) had no effect in any time of administration in our model. Summing up, these findings suggest that the pharmacological manipulation of the 5-HT_6 receptor represents an important therapeutic target in the treatment of forgetting alterations (e.g., PTSD), and further studies with inverse agonists as well as agonists and antagonists are warrant.

Disclosures: **A. Meneses:** None. **I. Paz:** None. **K. Grychowska:** None. **V. Canale:** None. **P. Zajdel:** None.

Poster

603. Memory and Cognition

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 603.06/Z18

Topic: H.01. Animal Cognition and Behavior

Support: Department of Science & Technology Grant INT/RUS/RFBR/P-244
Russian Foundation for Basic Research Grant 16-54-45016

Title: Bradykinin B2 receptor, a novel drug target for vascular dementia: *In-silico* and *in-vivo* evidence

Authors: *S. KUMAR[1], S. IVANOV[3], A. LAGUNIN[3], R. K. GOEL[2];
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Abstract: Vascular dementia is attributable to several risk factors such as hypertension, diabetes, hyperlipidemia, atherosclerosis, obesity, and hyperhomocysteinemia, etc. A network pharmacology approach was adopted for collective analysis of genetic interactome of these risk factors with an aim to find a new drug target for the development of specific therapy because available drugs such as cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine are symptomatic in nature i.e. do not alter the underlying disease trajectory. Bradykinin B2 receptor evolved as a new drug target and its antagonism may trigger several downstream pathways that are relevant for the treatment of vascular dementia (viz. protection against atherosclerosis, blood-brain barrier dysfunction, oxidative stress, neuronal death along with cognitive enhancement by acetylcholine synthesis and neurogenesis). Experimental validation of bradykinin B2 receptor antagonism involved a total of six animal groups (n=7) i.e. naïve, control, donepezil 5mg/Kg, and icatibant (bradykinin B2 receptor antagonist) treated 5,10,20 nmol/Kg. Vascular dementia was induced through mild chronic cerebral hypoperfusion in adult Swiss albino mice of either sex. The discrimination, recognition, emotion, spatial and fear-motivated learning, and memory impairments were assessed by object recognition task, step-through, water maze task and elevated plus maze task, respectively. These learning and memory impairments were significantly ($P < 0.05$) attenuated by icatibant treatment, along with significant ($P < 0.05$) attenuation of oxidative stress, cholinergic dysfunction and glutamate-induced excitotoxicity in critical brain areas (viz. cerebral cortex and hippocampus) than available standard drug donepezil. All these behavioral, biochemical and histological evidence agreed well with the pre-experimental in-silico predictions. Collectively, these findings infer that antagonism of the bradykinin B2 receptor may ameliorate learning and memory impairment

associated with mild chronic cerebral hypoperfusion that mimics the core features of vascular dementia.

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Poster

603. Memory and Cognition

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 603.07/Z19

Topic: H.01. Animal Cognition and Behavior

Support: grant number: 232/2014, from the Deanship of Research at the Jordan University of Science and Technology to KA.

Title: Vitamin E prevents the cognitive impairments in post-traumatic stress disorder rat model: Behavioral and molecular study

Authors: *K. H. ALZOUBI[1], M. AHMED[2], O. F. KHABOUR[3];
[1]Jordan Univ. of Sci. & Technol., Irbid, Jordan; [2]Sorbonne Univ., Paris, France; [3]Jordan Univ. of Sci. and Technol., Irbid, Jordan

Abstract: Post-traumatic stress disorder (PTSD) is a psychiatric disorder developed after an exposure to severe traumatic events. Patients with PTSD suffer from different symptoms including memory impairment. In addition, PTSD is associated with oxidative stress. Vitamin E. A fat-soluble vitamin, possesses cognition protective effects via its antioxidative properties. In this study, the impact of vitamin E on memory impairment induced by PTSD was tested using rat model and the radial arm water maize (RAWM) learning and memory paradigm. Rats were divided into 4 groups: control, vitamin E, PTSD and Vitamin E + PTSD. In the learning phase, results showed no significant differences among all groups, indicating that PTSD did not impair learning ability. However, memory tests in RAWM showed that PTSD impairs both short-term and long-term memories. Vitamin E, on the other hand, prevented these impairments of memory. With respect to oxidative stress, significant decreases were detected in GSH/GSSG ratio, GPx and catalase enzyme activities, global histone 3 acetylations, and BDNF levels in the PTSD group compared with other groups ($P<0.05$). Vitamin E prevented these oxidateve stress biomarkers, global histone 3 acetylations, and BDNF. In conclusion, vitamin E prevents memory impairments associated with PTSD, probably via its antioxidative properties, and preservation of epigenetic changes induced during PTSD.

Disclosures: **K.H. Alzoubi:** None. **M. Ahmed:** None. **O.F. Khabour:** None.

Poster

603. Memory and Cognition

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 603.08/Z20

Topic: H.01. Animal Cognition and Behavior

Title: Exploring the persistence of learned sexual behavior in male Japanese quail conditioned on a Pavlovian partial schedule: Behavioral and opioid antagonist effects

Authors: T. K. BAK, R. L. FISHER, J. M. GRANATO, D. R. C. HAGOOD, L. M. PRICE, B. A. SULAMAN, ***K. S. HOLLOWAY**;
Vassar Col., Poughkeepsie, NY

Abstract: Male Japanese quail will approach and remain near an arbitrary conditional stimulus (CS) that predicts the arrival of a quail hen. This behavior has been demonstrated to be remarkably persistent. We explored the persistence of this behavior in two experiments, one utilizing a behavioral manipulation and one utilizing a pharmacological manipulation. In the first experiment, subjects acquired approach to a CS paired with a quail hen on either a continuous or partial schedule in a Pavlovian conditioning procedure. In a subsequent extinction phase, during which the CS was presented by itself, the approach behavior of subjects trained under a continuous schedule of reinforcement extinguished more rapidly than that of subjects trained under a partial schedule. In the second experiment, we explored the effect of naloxone administration during extinction trials following Pavlovian sexual approach conditioning under both continuous and partial schedules of reinforcement. Confirming earlier findings, naloxone injections (30 mg/kg, i.m.), administered 15 minutes prior to each extinction trial, facilitated the extinction of approach responses of subjects trained under a continuous schedule of reinforcement as compared to subjects that received saline vehicle injections. Extending these findings, naloxone administration also facilitated extinction of responses of subjects conditioned under a partial schedule. The results of these two experiments are discussed as factors contributing to the persistence of learned behaviors.

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Poster

603. Memory and Cognition

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 603.09/Z21

Topic: H.01. Animal Cognition and Behavior

Title: The serotonin 1A1B receptor agonist RU24969 on behavioral flexibility in mice

Authors: B. OLIVER, A. PAHUA, S. PETERSON, S. SANCHEZ, R. POSADAS, *D. A. AMODEO;
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Abstract: Obsessive compulsive disorder (OCD) is defined as insistent urges, persistent thoughts, and/or repetitive behaviors that are difficult to inhibit (DSM-5, 2013). Pharmacological alterations to the serotonergic system have shown to induce OCD-like behaviors in mouse models (Shanahan et al., 2009; Ho et al., 2015). Moreover, the serotonin-1B/1A receptor (5-HT1B/1A) agonist RU24969 has been shown to induce OCD-like behavior in rodents (Ho et al., 2015; Shanahan et al., 2009; Woehrle et al., 2013), and induce deficits in working memory as evidenced by impaired performance on the delayed alternation task (Woehrle et al., 2013). Much of the current literature has modulated other serotonergic receptor cites in attempts at rescuing OCD-like behaviors induced by RU24969 treatment such as increased locomotor stereotypy (Ho et al., 2015; Shanahan et al., 2009) and deficits in pre-pulse inhibition (Shanahan et al., 2009; Thompson & Dulawa, 2019). Many studies examining increased 5-HT1B/1A activation use relatively high dosages of RU24969 anywhere from 1 to 10 mg/kg (Ho et al., 2015; Shanahan et al., 2009; Thompson & Dulawa, 2019; Woehrle et al., 2013). OCD's symptomology includes excessive habit formation that can impact goal-directed learning (Gillan & Robbins, 2014) and cognitive flexibility (Grutter & Pitteger, 2017). The current study examines the effects of systemic 5-HT1B/1A receptor agonist RU24969 (0.01 or 0.1 mg/kg) treatment on behavioral flexibility testing C57BL/6 mice in the spatial 80:20 probabilistic reinforcement reversal learning task. Before acquisition, all mice were treated with vehicle. Before the reversal phase, mice were injected with RU24969 (0 mg/kg, 0.01 mg/kg, or 0.1 mg/kg) and the reinforcement contingencies were reversed to examine how many trials were required for mice to reach learning criterion. Learning criterion was met when mice made six consecutive correct choices. As we have previously demonstrated, all groups performed similarly on acquisition of the initial spatial discrimination. On reversal, mice treated with 1.0 mg/kg RU4969 required significantly more trials to reach criterion. This impairment was driven by a specific increase in regressive type errors, suggesting RU24969 treatment impaired the ability to maintain a new choice pattern during reversal. Further analysis show that neither dose of RU24969 increased trials per minute demonstrating that RU24969 was not sedative. In sum, these findings indicate that acute systemic 5-HT1B/1A receptor activation significantly impaired reversal learning performance.

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Poster

603. Memory and Cognition

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 603.10/Z22

Topic: H.01. Animal Cognition and Behavior

Title: Investigating the effects of methylphenidate on cue salience and strategy set-shifting: Role of D_2 receptors

Authors: *M. MCWATERS[1], A. L. BLAKER[2], S. B. FLORESCO[3], B. K. YAMAMOTO[2], L. MATUSZEWICH[1];
[1]Northern Illinois Univ., Dekalb, IL; [2]Pharmacol. and Toxicology, Indiana Univ. Sch. of Med., Indianapolis, IN; [3]Dept. of Psychology, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Healthy individuals worldwide are using cognitive enhancing drugs in an attempt to remain competitive in society for education, careers, and athletics. Commonly, these individuals are using prescription stimulants, such as methylphenidate (MPH), due to their known acute neuroenhancing effects. While these neuroenhancing effects have been established using a variety of learning, memory, and attention tasks in ADHD-diagnosed humans and rodents, little research has investigated the effects of MPH on set-shifting, which is a higher-level cognitive function with many clinical implications. Previous research indicates that MPH enhances set-shifting task performance in ADHD-diagnosed individuals (Cao et al., 2012; Mehta, Goodyer, & Sahakian, 2004), however, the effect of MPH in healthy individuals and potential mechanisms underlying its cognitive enhancing effects on strategy set shifting remain elusive. Recent evidence suggests that association learning and set-shifting are dopamine-dependent (Flagel et al., 2011; Floresco, Magyar, Ghods-Sharifi, Vexelman, & Tse, 2006). Cue salience, one type of association learning, is related to D_2 function. Therefore, the purpose of the current study was to investigate: 1) MPH's influence on cue salience in rats using the Pavlovian Conditioned Approach (PCA) Index; 2) whether cue salience affected the set-shifting task in healthy rats and 3) whether D_2 receptor function affects set-shifting. Rats received MPH or saline daily 20 minutes prior to each autoshaping session for 5 days to measure PCA Index (Meyer et al., 2012). Rats were then trained on a strategy set-shifting paradigm (Brady & Floresco, 2015) and administered either the D_2 antagonist raclopride (0.2 mg/kg i.p.) or vehicle 30 minutes prior to the set-shift test. MPH decreased PCA Index Scores, however PCA Index was not a significant covariate on the set-shifting task. There was no effect of MPH exposure on the set-shift. When administered raclopride, rats in the MPH condition had poorer performance on the set-shift compared to saline rats. However, raclopride alone did not affect set-shifting. Western blot

analysis showed D_2 receptor immunoreactivity in the striatum was increased following MPH treatment compared to rats injected with saline. Future research will further explore the effects of MPH on the dopaminergic system and assess the impact of this alteration in other learning tasks, as this may have clinical implications for cognitive enhancement use in healthy individuals.

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Poster

603. Memory and Cognition

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 603.11/Z23

Topic: H.01. Animal Cognition and Behavior

Support: NIH DA R01 027222

Title: Addiction potential in methylphenidate treated rats after chronic drug exposure

Authors: S. D. GEORGE, P. B. YANG, *D. J. FELLEMAN, N. DAFNY;
McGovern Med. Sch. -UTHealth, Houston, TX

Abstract: Methylphenidate, commonly known as Ritalin, is a psychostimulant prescribed for behavioral disorders. Its use is widely accepted to treat young children and adults exhibiting attention-deficit/hyperactivity disorder (ADHD) symptoms. Methylphenidate (MPD) consumption has increased in popularity as a cognitive enhancer and recreational drug among multiple age groups. Due to the close chemical profile it shares with cocaine and amphetamines there is concern for the compound's potential to elicit dependence and abuse. The objective of this study was to test whether chronic MPD exposure in three different rat genetic strains, including an ADHD model, would express symptoms of drug dependence in young and adult, male and female rats. Three hundred and eighty-four rats composed of adult, adolescent, male, female, and three different genetic strains were used for this experiment. The three strains of rats studied in the experiment were Sprague Dawley (SD), Wistar-Kyoto (WKY), and Spontaneous Hyperactive (SHR). Forty-eight groups of rats were used, each with an N=8. Control groups were treated with saline, and experimental groups were treated with acute and chronic dose responses (0.6, 2.5, and/or 10 mg/kg i.p.) of MPD. An open field assay was used to record and monitor behavioral activity of the animal before and after acute and chronic psychostimulant exposure. Total distance traveled, horizontal activity, and the number of stereotypic repetitive purposeless activity were quantified with an Accusan analyzer to detect changes in locomotor

activity. Data was collected at baseline (Day 1), followed by daily MPD doses for 6 consecutive days (Day 2-7), 3 subsequent washout days (Day 8-10), and rechallenge doses of MPD at Days 11, 27, and 32. The chronic effect of MPD exposure in rats demonstrates behavioral tolerance in some animals while behavioral sensitivity in others. Differences between animals of different age, sex, and strain were observed. The changes in behavioral activity following chronic MPD use suggest its potential to cause drug dependence, in adolescent, adult, male, and female rats.

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Poster

603. Memory and Cognition

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Program #/Poster #: 603.12/Z24

Topic: H.01. Animal Cognition and Behavior

Support: CIHR Grant PJT159586
J & J Memorial Scholarship 2017

Title: Delta-9-tetrahydrocannabinol regulates memory, anxiety, and sensorimotor gating via dissociable modulation of the Wnt and mTOR signalling pathways in the nucleus accumbens shell

Authors: *C. NORRIS[1], R. M. HUDSON[2], H. J. SZKUDLAREK[3], D. KHAN[1], W. J. RUSHLOW[4], S. R. LAVIOLETTE[1];
[2]Neurosci., [3]Dept. of Anat. & Cell Biol., [4]Dept of Anat. and Cell Biol., [1]Univ. of Western Ontario, London, ON, Canada

Abstract: Exposure to Δ^9-tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis, is associated with psychotomimetic side-effects and an increased risk of serious neuropsychiatric disorders, such as schizophrenia. The nucleus accumbens shell (NASh) is involved in the neuropathological phenotypes associated with schizophrenia and anxiety-related disorders. Given previous evidence also indicating a functional division between the anterior NASh (aNASh) and posterior NASh (pNASh), we evaluated the effects of direct infusions of THC in the NASh on the levels of signaling proteins associated with psychiatric illness, the formation of associative fear memory, pre-pulse inhibition (PPI) and facilitation (PPF) of the acoustic startle response, object recognition memory, and anxiety in the elevated-plus maze (EPM). Our results indicated that THC infused in the pNASh decreased levels of phosphorylated GSK3α and increased levels of β-catenin but had no significant effect on pGSK3β, or total GSK3. THC infused into the aNASh, however reduced levels of the Ser473 isoform of phosphorylated Akt and phosphorylated mTOR but not Thr308 phosphorylated Akt, total Akt, or total mTOR. Next, we examined the role these molecular signaling compounds played in the

behaviour effects of THC by co-administering THC into the pNASh with SB216763, a GSK3 inhibitor, and into the aNASh SC-79, an Akt promoter. We demonstrated that intra-pNASh infusions of THC produced GSK3 dependent potentiation of fear memory salience; induced anxiogenic effects and impaired PPI and PPF; and pNASh THC exposure induced object recognition memory deficits. In contrast, intra-aNASh THC blocked the encoding of normally supra-threshold associative fear memory and produced anxiolytic effects. When THC was co-administered with SC-79, the formation of associative fear memory was restored, time in the open arms during EPM increased, PPF was impaired and object recognition memory was reduced. Our findings provide several novel mechanisms for how THC differentially modulates CB_1 signalling pathways and provide new insight into the underlying molecular mechanisms of THC in distinct regions of the NASh and how they may underlie both the affective and cognitive side-effects of cannabis exposure.

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Poster

603. Memory and Cognition

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 603.13/Z25

Topic: H.01. Animal Cognition and Behavior

Support: CAPES Finance code 01
CNPq 446025/2014-3

Title: Influence of habituation and NMDA receptor antagonism on novel object recognition and object location tasks in zebrafish

Authors: K. V. GASPARY, G. K. REOLON, D. GUSSO, ***C. D. BONAN**;
Pontificia Univ. Catolica Rio Grande do Sul, Porto Alegre, Brazil

Abstract: This study aims to establish a protocol for evaluating the object recognition memory and object location tasks in zebrafish. We evaluated the novel object recognition memory and analyzed the exploration time of the objects during training and testing. Zebrafish explored more the new object in comparison to the familiar object (61% of exploration time during test session). We also tested the object location task and measured the exploration time of each object in the familiar and novel object location. There was a preference to explore the object in the novel location (63% of exploration time during test session). The effect of the non-competitive NMDA receptor antagonist MK-801 was investigated on the object recognition and object location memory. Control (water only) and treated animals (5 μM MK-801) presented a significant preference in exploring the familiar object in comparison to the new object (66 and 68% of

exploration time, respectively); however, 10 μM MK-801-treated animals did not show differences in the exploration time of the objects. In the object location task, the animals treated with the 5 or 10 μM MK-801 did not show a preference for the familiar or novel location whereas the control group had a higher preference in exploring the object in the familiar location (64% of exploration time during test session). Considering the different responses of the control group between original task and in the regimen treatment, we evaluated the impact of habituation on cortisol levels of animals in three different protocols: (1) habituated at the experiment apparatus for 3 days (C1 condition), (2) habituated at the experiment apparatus for 3 days plus treatment tank exposure at fourth day (C2 condition), (3) habituated at the treatment tank and experiment apparatus for 3 days and exposed to treatment tank again at fourth day (C3 condition). The results showed higher levels of cortisol in animals submitted to C2 and C3 conditions compared to animals submitted to C1. Treatment tank exposure induced a different performance in object recognition and object location memory due to stress responses. These tasks are prone to evaluate memory in physiological and pathological conditions, but its use is limited due to sensitivity to stress caused by manipulation.

Disclosures: K.V. Gaspary: None. **G.K. Reolon:** None. **D. Gusso:** None. **C.D. Bonan:** None.

Poster

603. Memory and Cognition

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 603.14/Z26

Topic: H.01. Animal Cognition and Behavior

Title: Potent, highly selective and brain penetrant adrenergic alpha 1a antagonists for improvement of cognition in neuropsychiatric disorders and Alzheimer's disease

Authors: *H. H. SCHIFFER[1], S. KIKUCHI[1], J. RUSSO[1], Y. CHEN[1], J. BLIESATH[1], B. LAM[1], S. OLSEN[1], K. MA[2], S. SAILLET[2], J. J. PALOP[2], J. RAY[1], H. MONENSCHEIN[1], S. HITCHCOCK[1];
[1]Takeda California Inc., San Diego, CA; [2]Gladstone Inst. and Univ. of California San Francisco, San Francisco, CA

Abstract: The role of adrenergic alpha 1a receptors in cognitive functions in health and disease is not fully understood due to the lack of brain penetrant highly selective alpha1a ligands. We have developed nM potent and highly selective (>1000x selective over adrenergic alpha 1b and d) adrenergic alpha1a receptor antagonists, which enabled us for the first time to study the biological role of antagonizing alpha 1a receptors in health and disease mouse models *in vivo*. BacTRAP data and *in situ* hybridization studies show that alpha 1a receptor expression is highly enriched in cortical and hippocampal neuropeptide (NPY) inhibitory interneurons. Axonal sprouting of neuropeptide Y (NPY) interneurons and reduced expression of Fos in hippocampal

granule cells have been observed in the human hippocampus in Alzheimer patients and in preclinical Alzheimer disease mouse models (e.g. J20). It has been hypothesized that axonal sprouting is a compensatory mechanism of hippocampal hyperexcitability leading to aberrant circuit inhibition, which might contribute to cognitive impairment in AD [1]. Selective alpha 1a blockade dose-dependently increased the levels of Fos expression in the cortex and hippocampus in wild-type mice and partially restored the number of Fos-positive granule cells in the J20 mouse model of AD model, suggesting that alpha 1a blockade prevents the aberrant inhibition of the granule cells. Importantly, selective alpha 1a blockade also normalized the abnormal hyperlocomotion and disinhibition phenotypes during exploration of a novel environment, indicating that slight disinhibition might be therapeutic in AD. Our highly selective adrenergic alpha 1a antagonists demonstrated a robust procognitive efficacy profile in both rats and mice, including improved recognition memory (novel object recognition test), spatial memory (spatial recognition test), and increased attention (two-choice visual discrimination test). In addition, alpha 1a blockade reversed scopolamine-induced working memory deficits in the Morris water maze task. Using microdialysis, we determined that our alpha 1a antagonist increased extracellular acetylcholine in the cortex and hippocampus in rats. Additional studies in wild type rats suggested alpha 1a blockade increased wakefulness. Our results show that selective inhibition of adrenergic alpha 1a receptors provides procognitive benefit in health and disease mouse models of AD and suggest that adrenergic alpha1a inhibition should be considered as therapeutic treatment of cognitive deficits in neuropsychiatric disorders and potentially AD. [1] Neuron. 2007 Sep 6;55(5):697-711.

Disclosures: **H.H. Schiffer:** A. Employment/Salary (full or part-time):; Takeda. **S. Kikuchi:** A. Employment/Salary (full or part-time):; Takeda. **J. Russo:** A. Employment/Salary (full or part-time):; Takeda. **Y. Chen:** A. Employment/Salary (full or part-time):; Takeda. **J. Bliesath:** A. Employment/Salary (full or part-time):; Takeda. **B. Lam:** A. Employment/Salary (full or part-time):; Takeda. **S. Olsen:** A. Employment/Salary (full or part-time):; Takeda. **K. Ma:** None. **S. Saillet:** None. **J.J. Palop:** None. **J. Ray:** None. **H. Monenschein:** A. Employment/Salary (full or part-time):; Takeda. **S. Hitchcock:** A. Employment/Salary (full or part-time):; Takeda.

Poster

603. Memory and Cognition

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 603.15/Z27

Topic: H.01. Animal Cognition and Behavior

Support: ICMR
DBT

Title: Role of α7nAChR agonist (GTS-21) on ICV-STZ induced altered central insulin signaling leading to cognition deficits

Authors: *Y. PERUMAL[1], R. RAY[1,2], K. CHOPRA[1];
[1]Univ. Inst. of Pharmaceut. Sci., Chandigarh, India; [2]Indian Pharmacopoeia Commission, Ghaziabad, India

Abstract: Central insulin resistance is a pathological condition in which brain cells fails to respond normally to insulin. Central insulin resistance evokes pathological hallmarks of Alzheimer's disease (AD), such as formation of amyloid plaques and neurofibrillary tangles (NFT). Intracerebroventricular administration of streptozotocin (ICV-STZ) leads to central insulin resistance leading to cognitive deficits in mice. The aim of our study is to determine the effect of α7nAChR agonist (GTS-21) on ICV-STZ-induced central insulin resistance leading to cognition deficits. α7nAChR agonist (GTS-21) was administered for 21 days following the ICV-STZ administration (3 mg/kg). Neurobehavioral assessment such as morris water maze and novel object recognition were performed to determine cognitive deficits. Oxidative stress markers (MDA, nitrite and GSH) and inflammatory markers (TNF-α and IL-1β) were estimated in the hippocampus and cortex. Acetylcholine esterase and choline acetyltransferase were determined to evaluate the level of acetylcholine in the hippocampus and cortex. Insulin and glucose levels were also assessed in the hippocampus and cortex. ICV-STZ administration-induced memory impairment in neurobehavioral assessments, coupled with oxidative stress and increased inflammatory markers. Our results demonstrated that α7nAChR agonist (GTS-21) was effective against memory impairment, decreased oxidative stress and subsequently decreased inflammatory markers in hippocampus and cortex. Furthermore, we found that insulin and glucose levels were altered after ICV-STZ administration which were restored by α7nAChR agonist (GTS-21) treatment. Therefore, α7nAChR might be the potential target for the prevention of central insulin resistance induced cognition deficit.

Disclosures: Y. Perumal: None. **R. Ray:** None. **K. Chopra:** None.

Poster

603. Memory and Cognition

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 603.16/Z28

Topic: H.01. Animal Cognition and Behavior

Support: BBSRC Grant BB/M011224/1
MRC Grant MR/N004396/1

Title: Fractionating aberrant salience in rodent models of psychosis

Authors: *T. BLACKMORE[1], L. B. STAHR[1], V. SAMBORSKA[1], G. GILMOUR[2], M. E. WALTON[1], D. M. BANNERMAN[1], M. C. PANAYI[1];
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Abstract: Psychosis is a prominent feature of a number of neurological and psychiatric disorders. Aberrant salience to sensory stimuli likely contributes to the generation of psychotic symptoms, but this is a diverse phenomenon with many potential contributing factors. While many rodent models of aberrant salience exist, they may have different underlying psychological or neurobiological substrates. Hyperactivity commonly reported in these models reflects enhanced exploratory attention to sensory stimuli, similar to aberrant salience in humans. This may be due to impaired habituation and/or hyperarousal, but the exact mechanisms remain poorly specified. The current study investigates the relationship between habituation, attention and locomotor activity in three mouse models of psychosis to shed light on the heterogeneity of symptoms seen in human patients.
Two pharmacological (2.5mg/kg amphetamine i.p., 0.2mg/kg MK-801 i.p.) and one genetic (*Gria1*$^{-/-}$, encoding GluA1 AMPA receptor subunit) knockout mouse model were tested in three assays of short-term habituation and locomotor activity; open-field, spatial novelty Y-maze, and novel context recognition.
All models tested displayed a significant hyperactive phenotype, consistent with the literature. However, the nature of this hyperactivity differed between these models. Increased dopamine levels in amphetamine-treated mice led to 'hyperarousal', defined by significantly increased locomotor activity, but were capable of short-term habituation. The NMDA receptor antagonist MK-801 induced significant hyperactivity and impaired short-term habituation; however, animals started off unexpectedly hypoactive to novelty. These deficits may reflect an inability to maintain attention to specific stimuli, where instead stimuli cycle rapidly in and out of focus; 'butterfly attention'. GluA1$^{-/-}$ mice displayed a stimulus-specific form of hyperactivity, with exploratory attention initially similar to wild-types but failing to habituate and ramping up over time; 'sticky attention'. Thus, whilst all models showed hyperactivity, the aetiology and psychological underpinnings were markedly different following manipulation of dopamine, NMDA or AMPA receptor function. This finding may help to explain the heterogeneity of symptoms in schizophrenic populations.

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Poster

603. Memory and Cognition

Location: Hall A

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Program #/Poster #: 603.17/Z29

Topic: H.01. Animal Cognition and Behavior

Title: CART peptide protects the behavioral deficits in rat model of Huntington's disease

Authors: *M. A. UPADHYA[1,2], H. M. UPADHYA[2], N. SUBHEDAR[1], D. KOKARE[2]; [1]Dept. of Biol., Indian Inst. of Sci. Educ. and Res., Pune, India; [2]Pharm., Dept. of Pharmaceut. Sci., Nagpur, India

Abstract: Huntington's disease (HD) is an inherited progressive neurodegenerative disorder, characterized by severe degeneration of GABAergic neurons in the striatum and cerebral cortex, exhibiting motor abnormalities, impaired cognitive functions and emotional disturbances. A neuroprotective peptide cocaine and amphetamine regulated transcript (CARTp) closely interacts with the GABAergic system. Although its expression in striatum is altered in HD like conditions, there is no information on the neuroprotective activity of CARTp with reference to this condition. The present study was designed to elucidate the role of CART in 3-nitropropionic acid (NP)-induced animal model of HD in rats. The effect on walking pattern, learning and memory, and locomotion was assessed using foot print analysis technique, Morris water maze and actophotometer, respectively. Rats treated with 3-NP showed significant decrease in the stride length and foot print length as compared to that of the rats treated with aCSF. The actophotometer count, taken as an index of locomotion, was decreased significantly in these rats. In addition, the escape latency was significantly increased in 3-NP treated rats, which may be attributed to retarded swimming speed or dementia like condition as compared to normal rats. Intracerebroventricular CART treatment prior to 3-NP for four days prevented all the motor deficits as observed in gait analysis and altered swimming pattern in rats. CART-immunoreactivity was decreased significantly in Dentate gyrus of hippocampus, striatum and LC. In view of this evidence and that CART positively modulates GABAergic neurons directly or indirectly via dopamine, it seems that endogenous CART might play a pivotal role in the HD like conditions. Further, activation of CART system in striatum might help to improve the symptoms related to neurological ailments like HD.

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Poster

603. Memory and Cognition

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Topic: H.01. Animal Cognition and Behavior

Support: CB250870
N212919

Title: Inhibition of cellular palmitoylation impairs the formation and maintenance of spatial memory and synaptic plasticity

Authors: *O. URREGO MORALES[1], I. DELINT-RAMÍREZ[2], F. BERMUDEZ-RATTONI[3]; [1]Inst. De Fisiologia Celular - UNAM, Ciudad de México, Mexico; [2]UT Southwestern Med. Ctr., Dallas, TX; [3]UNAM, Mexico City DF 04510, Mexico

Abstract: Protein palmitoylation (addition of lipid palmitate) is a post-translational modification that changes the hydrophobicity of proteins. This process allows the interaction of proteins with the lipids of the cell membrane and the subcellular membranes, regulating the location and function of these proteins. In the nervous system, palmitoylation regulates vesicular trafficking and the localization of neurotransmitter receptor proteins in processes of synaptic plasticity. Genetic and pharmacological approaches in murine models have reported the participation of palmitoylation in spatial memory processes. However, these approaches have not evaluated the effects of palmitoylation during the different phases of spatial memory; that is, acquisition, consolidation and retrieval. Therefore, in this work, we studied the participation of palmitoylation during the three phases of memory to understand a possible regulatory mechanism of the proteins involved on memory processes. For this, we evaluated the effect of the inhibition of the palmitoyl acyltransferase enzymes in the dorsal hippocampus with the irreversible 2-bromopalmitate inhibitor. The drug was administered to different groups of animals during the three phases of memory in two different behavioral models of spatial memory that depend on the activity of the hippocampus. The results showed that the inhibition of palmitoylation affected the acquisition and consolidation, but not spatial memory retrieval. In addition, the inhibition of the protein palmitoylation prevented the induction but did not affect the maintenance of the *in vivo* long-term potentiation in the CA1 of the hippocampus. In conclusion, palmitoylation of proteins mediated by palmitoyl acyltransferase enzymes participates in the formation and maintenance of spatial memory throughout plastic changes in the hippocampal synapses, possibly through AMPA and NMDA receptors.

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Poster

603. Memory and Cognition

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Program #/Poster #: 603.19/Z31

Topic: H.01. Animal Cognition and Behavior

Support: National Science Foundation of Georgia № YS_2.3.1_34

Title: Neuroprotective effects of chronic memantine treatment on okadaic acid (ICV) induced neurotoxicity at behavioral, structural and molecular level in rats

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Abstract: In the present study, intracerebroventricular (ICV) injection of okadaic acid **(**OA) in rats was used as a memory impairment and hippocampal neurodegeneration animal model. The possible beneficial effect of memantine - NMDA (N-methyl-D-aspartate) receptor antagonist on the OA-induced spatial memory impairment was examined in Morris water maze (MWM). The neuroprotective potential of memantine on OA-induced structural and molecular changes in the hippocampus and medial septum (MS) was evaluated by immuno and Nissl staining. The OA induced neurotoxicity and neuroprotective effects of chronic memantine treatmentat behavioral, structural and molecular level was evaluated in 4 groups of animals: control rats injected i.p. with saline or memantine and **OA injected rats** treated i.p. with saline or memantine. OA was dissolved in artificial cerebrospinal fluid (aCSF) and injected ICV 200 ng in avolume of 10 µl bilaterally. Vehicle control received 10 µl of aCSF ICV bilaterally. Memantine (5 mg/kg, i.p) or saline were given daily for 13 days starting from the day of OA injection. Experimental protocol was approved by Animal Studies Committee of I. Beritashvili Center of Experimental Biomedicine. The results described in this chapter showed that bilateral injection of OA causes a deficiency of spatial memory and loss of hippocampal cells in this model and demonstrated for the first time, to our knowledge, reduces the number of cholinergic and GABAergic medial septal neurons. These changes are observed in patients with Alzheimer's disease and, therefore, reinforce the importance of this model for the investigation targets of new therapeutic strategies. The results have shown that the chronic exposure of memantine can prevent a deficiency of spatial memory and that an improvement in memory function correlates with the prevention of OA-induced neuropathological changes in the hippocampus and MS. This fact, on the one hand, points to the involvement of neuropathological processes developed in the hippocampus and MS in memory impairment caused by OA, and, on the other hand, the involvement of NMDA receptors in the neurotoxicity of OA.

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Poster

603. Memory and Cognition

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Program #/Poster #: 603.20/Z32

Topic: H.01. Animal Cognition and Behavior

Support: CNPq 465458/2014-9 / FAPESP 14/50891-1

Title: Influence of maternal deprivation on recognition memory and global DNA methylation in adult rats: How epigenetics modulation can contributes to vulnerability or resilience to stress

Authors: *M. N. M. DE LIMA[1], B. S. DE FREITAS[1], K. C. R. RAPACH[1], M. A. FREYMUTH[1], R. B. M. SILVA[1], N. SCHRODER[2];
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Abstract: Exposure to stress early in life may negatively impact nervous system functioning, including increasing the proneness to learning and memory impairments later in life. Maternal deprivation, a model of early stress, impairs memory in adult rats in a very heterogeneous way between individuals, resulting from either greater vulnerability or resilience to stress. It has been suggested that maternal care influences DNA methylation, a well-studied form of epigenetic regulation of gene expression, in hippocampus. Thus, the aim of the present study was to investigate if DNA methylation is underlying recognition memory impairment of adult maternally deprived rats. Maternally deprived animals were submitted to object recognition memory task (NOR1) in order to discriminate the `inferior learners' and the 'superior learners' in comparison to controls. After fifteen days of washout, they were submitted one more time to object recognition memory task (NOR2) receiving a methyl group donor (l-methionine), or vehicle, 1h prior to training session or a DNA methyltransferase (DNMT) blocker (5-Aza-2´-deoxycytydine), or vehicle, immediately after the training session. Results showed that acute administration of the methyl group donor improved recognition memory in inferior learner subjects, whereas DNA methyltransferase (DNMT) blockade had no effect. Global DNA methylation in hippocampus was measured 3h after the training session (to determine if there was alterations in DNA-methylation during this critical period for memory consolidation) and 24h after the LTM test (to determine if these alterations were persistent). Data were analyzed to verify the relationship between DNA-methylation status and cognitive performance among these individuals. The better comprehension of the mechanisms related to persistent alterations observed in adult life induced by early stressful circumstances could contribute to develop novel therapies to improve cognitive performance in subjects more vulnerable to stress.

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Poster

603. Memory and Cognition

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant K01 MH106824
NARSAD
Nellie Ball
Pappajohn Biomedical Institute
NIH Grant R01 MH118240

Title: Effect of lateral cerebellar nucleus inactivation on supra-second interval timing performance across changing task demands in rats

Authors: *K. A. HESLIN, B. J. DE CORTE, S. J. FARLEY, H. HALVERSON, K. L. PARKER;
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Abstract: The cerebellum is necessary for the acquisition and proper timing of sub-second Pavlovian conditioned responses (e.g., eyelid closures in eyeblink conditioning). However, reports conflict on whether the cerebellum is necessary for successful supra-second interval timing (i.e., timing in the seconds to minutes range). Some past findings indicate that, under certain task demands, the dentate nucleus (homologous to the rodent lateral cerebellar nucleus) may be necessary for supra-second interval timing. Therefore, we evaluated the necessity of the lateral cerebellar nucleus to interval timing across a variety of operant task demands. One cohort of rats was trained in a standard 'peak interval procedure', in which the onset of a stimulus (light) cued rats to make an operant response after a specific time interval elapsed (12 seconds). A second cohort was trained in a variant of the same task, in which they were required to self-initiate each trial. Once trained, we evaluated the effects of reversibly inactivating the lateral cerebellar nuclei with bilateral Muscimol (GABAA agonist) infusions on baseline task performance. Following this, the duration associated with the learned cue was shifted from 12 seconds to 24 seconds in both cohorts. Half of subjects underwent lateral cerebellar nuclei inactivations during the new duration acquisition phase, while the remaining half was infused with vehicle. Preliminary results suggest that the lateral cerebellar nucleus may play a subtle role in the performance of supra-second interval timing, depending on task demands.

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Poster

603. Memory and Cognition

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Program #/Poster #: 603.22/Z34

Topic: H.01. Animal Cognition and Behavior

Title: The effects of nutritional supplementation on memory in adolescent male rats exposed to cannabinoids

Authors: *L. M. BUYNACK[1], L. M. PACK[1], H. M. PARRISH[1], C. E. YULE[1], R. D. LUNDY, III[2], G. D. MEDLEY[1], D. M. HAYES[1], P. A. JACKSON[2];
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Abstract: Many developmental changes occur during adolescence that are critical for cognitive functioning including neuroplastic shaping, reorganization of synapses, and neurochemical transformations (Spear, 2000). Adolescent rats that are exposed to cannabinoids experience negative brain development repercussions (Lubman, et al., 2014) that often leads to memory deficits during adulthood (O'Shea et al., 2004). Rats exposed to cannabinoids in adulthood exhibited little or no impairment of memory during an object location recognition (OLR) task. However, a different explanation for these cognitive deficits is that rats display a reduction in both food intake and body weight during the period of injections although they recover once injections cease (Biscaia et al., 2003; Schneider, 2009). Impaired weight gain during this period that is critical for neural development may result in behavioral changes separate from those caused by cannabinoids. The current study included multiple litters of male siblings, semi-randomly assigned to each of ten groups. On postnatal day (PND) 35 through PND 48, Long-Evans male rats were administered intraperitoneal injections of either vehicle or a synthetic cannabinoid (CP55,940) at 0.35 mg/kg. Starting on PND 34 and ending on PND 50, food intake was observed and altered such that ten conditions were created to manipulate drug exposure and food consumption. The conditions included drug, yoked control, and supplement-yoked control with each individual condition receiving no supplementation, a small supplementation, or a large supplementation. Yoked controls were matched for food and supplement to drug matched siblings, whereas supplement-yoked rats received free-food but were matched for amount of supplement. One group of untreated control rats did not receive injections nor did they receive any supplement. A battery of behavioral tasks was conducted, however, the current report is on an OLR memory task. Rats were habituated to the open field apparatus for four days prior to the task. The OLR task consisted of two 5-minute trials that occurred 10 minutes apart. In the first trial two identical objects were placed on the open-field and the rat could explore both objects. In

the second trial, one object from the previous trial remained in the same location, but the second object was placed in a new location. Results indicate that food supplementation may be beneficial to performance in drug groups compared to yoked conditions.

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Poster

603. Memory and Cognition

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Program #/Poster #: 603.23/Z35

Topic: H.01. Animal Cognition and Behavior

Title: Development of novel and selective Kv3.1/3.2 channel modulators with improved potency for the treatment of social and cognitive deficits in schizophrenia

Authors: *N. IDRIS[1], J. C. NEILL[1], B. GRAYSON[1], G. PODDA[1], M. BURGESS[1], L. WATSON[1], S. MUNNI[1], A. MARASCO[2], G. ALVARO[2], C. LARGE[2];
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Abstract: Introduction: Cognitive dysfunction and negative symptoms remain a major clinical unmet need in schizophrenia and have been associated with NMDAR hypofunction at cortical, parvalbumin (PV) -positive, fast-spiking interneurons. The voltage-gated potassium channel, Kv3.1 is predominantly localized in PV-positive interneurons, and is reduced in un-medicated schizophrenia patients (Yanagi et al. Mol Psychiatry 2014; 19: 573-579). Sub-chronic treatment of rodents with the NMDAR antagonist, phencyclidine (scPCP) impairs cognition and reduced expression of the calcium binding protein, PV in fast spiking GABAergic interneurons (Cadinu et al. Neuropharm 2018;142:41-62). We shave shown that the novel Kv3.1/Kv3.2 channel modulator, AUT6, reverses cognitive and social deficits in scPCP rats, and reverse the decrease in PV expression, confirming the importance of this target for the treatment of schizophrenia. Here we aim to compare the efficacy of novel high potency Kv3.1/3.2 modulators in cognitive and social behaviour tests in the scPCP rodent model. **Methods:** Four cohorts of adult female Lister Hooded rats (240 in total) received PCP (2 mg/kg, i.p.) or saline i.p. for 7 days, followed by 7 days washout. Rats were then treated acutely with Kv3.1/3.2 channel modulators, AUT6 (3.0, 10, 30 mg/kg), AUT15 (1.0, 3.0, 10 mg/kg,), AUT16 (3.0, 10, 30 mg/kg,) or vehicle, orally 90 min prior to testing in novel object recognition (NOR), social interaction (SI) and reversal learning (RL) tasks. Data were analysed by ANOVA and post-hoc LSD test or a paired Student t-test. **Results:** scPCP significantly impaired behaviour in these tests. See table for the minimum effective dose of each compound to restore scPCP-induced deficits:

Compound	Test & minimum effective dose				
	NOR: increase in novel exploration time	RL: improve in % correct responding	SI: increase in sniffing behaviour	SI: increase in following behaviour	SI: decrease in avoiding behaviour
AUT6	10 mg/kg, $p<0.001$	30 mg/kg, $p<0.01$	10 mg/kg, $p<0.05$	30 mg/kg, $p<0.01$	10 mg/kg, $p<0.05$
AUT15	3.0 mg/kg, $p<0.001$	10 mg/kg, $p<0.01$	1.0 mg/kg, $p<0.001$	3.0 mg/kg, $p<0.05$	3.0 mg/kg, $p<0.001$
AUT16	10 mg/kg, $p<0.001$				

Conclusion: These in vivo results demonstrate superior potency of AUT15 compared to AUT6 and AUT16 in NOR and AUT15 compared to AUT6 in both RL and SI. In addition, the improvement of the in vivo potency from AUT6 to AUT15 is in agreement with the rank order of the in vitro activity of those compounds at both Kv3.1 and Kv3.2 channels. This result increases the confidence that restoration of scPCP-induced cognitive and social behaviour deficits is via modulation of Kv3.1/Kv3.2 channels.

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Poster

603. Memory and Cognition

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Program #/Poster #: 603.24/Z36

Topic: H.01. Animal Cognition and Behavior

Support: Futuro in Ricerca MIUR (RBFR13M6FN)

Title: The newly synthesized compound CN-PYB2 and a knock-in mice for the Na^+/Ca^{2+} exchanger 1 (NCX1) show the involvement of the antiporter in hippocampal-dependent spatial learning and memory

Authors: S. NATALE[1], **P. MOLINARO**[1], S. ANZILOTTI[3], T. PETROZIELLO[1], R. CICCONE[1], A. SERANI[1], L. CALABRESE[1], F. FRECENTESE[2], A. SECONDO[1], A. PANNACCIONE[1], L. D'ESPOSITO[1], *A. G. SADILE[4], S. CABIB[5], G. DI RENZO[1], L. ANNUNZIATO[3];
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[4]Exptl. Med., Univ. of Campania "Luigi Vanvitelli", Naples, Italy; [5]Psychology, Sapienza Univ., Rome, Italy

Abstract: The Na^+/Ca^{2+} exchanger 1 (NCX1) is highly expressed in the hippocampus, cortex, and amygdala where it participates in the maintenance of $[Ca^{2+}]_i$ and $[Na^+]_i$ homeostasis. However, the activity of NCX1 was also associated to the regulation of some intracellular pathway such as AKT1 phosphorylation and NMDA-mediated Ca^{2+} influx, two events that participate in the synaptic plasticity and long-term memory. We hypothesized whether NCX1 expression/activity might affect some hippocampal-dependent learning and memory processes. To test this hypothesis, we used a genetically-modified mouse that selectively overexpresses NCX1 in hippocampal, cortical, and amygdala neurons (ncx1.4over) and a newly synthesized compound named CN-PYB2 that selectively stimulates NCX1 activity. Both *ncx1.4over* and CN-PYB2-treated mice showed increased phosphorylated CaMKII levels in the hippocampus and improved long-term spatial learning and memory performance in Barnes maze and context trace fear conditioning. On the other hand, both mouse models bearing an increase of NCX1 activity did not show amelioration in non-spatial memory tests including novel object recognition and cued trace fear conditioning. In addition, both *ncx1.4over* and CN-PYB2-treated mice also displayed an increased level of corticosterone levels 1h after a weak foot-shock and an increased susceptibility to a context-dependent anxiety. Altogether, these results demonstrate that neuronal NCX1 participates in a selective hippocampal-dependent spatial learning and memory processes.

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Poster

603. Memory and Cognition

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Program #/Poster #: 603.25/Z37

Topic: H.01. Animal Cognition and Behavior

Title: Acute acetaminophen exposure impairs object recognition memory in female mice

Authors: *C. A. STAPF[1], A. A. WISLOTSKY[1], P. T. ORR[2,1];
[1]Neurosci. Program, [2]Psychology Dept., Univ. of Scranton, Scranton, PA

Abstract: Animal research has often been done with only male animals due to the variable hormonal effects on physiological function experienced by female animals. Previous work has established that a post-training subcutaneous injection of 50mg/kg or 100mg/kg acetaminophen

disrupts memory consolidation in a hippocampal-dependent object recognition memory task in male mice, but it is not currently known if acetaminophen disrupts memory formation in this task in female mice. In this study, we examined the influence of acetaminophen on performance in an object recognition task in female C57Bl/6 mice. Mice were raised in typical housing conditions until around 8 weeks. These mice were then habituated and trained in an object recognition task. Immediately after training, mice were randomly assigned to receive an injection of vehicle (saline) or one of three doses of acetaminophen (10, 50, or 100 mg/kg). Mice were tested 24 hours later. Control mice spent significantly more time with the novel object when compared to time spent with the familiar object showing memory of the previously introduced familiar object ($t(12)=2.114$, $p=0.028$). Mice in the 50 mg/kg group showed evidence of memory in the object recognition task ($t(10)=1.918$, $p=0.042$) while mice in the 10 mg/kg ($t(9)=1.036$, $p=0.163$) and 100 mg/kg ($t(8)=-0.525$, $p=0.307$) dosage groups did not show evidence of memory consolidation. Two weeks after behavioral testing, mice were again injected and culled so hippocampal brain sections can be analyzed via Western blotting for differences in the presence of cell-signaling molecules associated with memory formation. Overall, the data demonstrate that acute acetaminophen injection significantly impairs object recognition memory in female mice, which is consistent with the previously observed effects in males. More research is needed to determine the mechanism through which this impairment occurs.

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Poster

603. Memory and Cognition

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Topic: H.01. Animal Cognition and Behavior

Title: The effects of AM4113, a neutral cannabinoid antagonist, on object recognition memory in male mice

Authors: *F. A. WALTER, III[1], M. R. JOHNS[1], P. T. ORR[2,1];
[1]Neurosci. Program, [2]Psychology Dept., Univ. of Scranton, Scranton, PA

Abstract: Cannabinoid receptors are found throughout hippocampus and signaling in these receptors is thought be critical for the impairment of memory by cannabinoids (Elphick & Egertova, 2001; Murray, J.B., 1986). Antagonism of cannabinoid signaling via rimonabant (SR141716) facilitates object recognition memory in rats (O'Brien, et al., 2014) and increases in endogenous cannabinoid signaling demonstrably impair this kind of object recognition and other assessments of hippocampal memory (Basavarajappa, et al., 2014). However, rimonabant is sometimes characterized as an inverse CB1 agonist. It is currently unknown if object recognition memory is sensitive to the CB1 neutral antagonist, AM4113. Thus, this study attempted to

determine if AM4113 could facilitate object recognition memory consolidation in mice. Mice were trained in an object recognition task with a 48 hour delay. They were randomly assigned to receive an immediately post-training intraperitoneal injection of vehicle (1:1:8 ratio of dimethylsulfoxide (DMSO), Tween 20, and .9% saline), 2 mg/kg, 4 mg/kg, or 8 mg/kg of AM4113 in vehicle. This formulation and dose range is based off of previously published work (Sink, et al, 2013), and should be safe. As expected, during testing at a 48 hour delay, vehicle treated mice did not differ significantly from chance performance ($t(12) = -1.685$, $p = .118$). However, we did not observe object recognition memory in the 2 mg/kg ($t(13) = 1.101$, $p = .291$), 4 mg/kg ($t(10) = -.6$, $p = .562$), or 8 mg/kg ($t(9) = 1.132$, $p = .287$) groups, suggesting that this neutral CB1 antagonist did not influence object recognition memory. Future work is needed to refine the effect of AM4113 in this model and to explore the relationship of the cannabinoid system to object recognition memory.

Disclosures: F.A. Walter: None. **M.R. Johns:** None. **P.T. Orr:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 604.01/Z39

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Whitehall Foundation
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Office of Naval Research Young Investigator Program Award
Klingenstein-Simons Award
Simons Foundation
James S. McDonnell Foundation

Title: Behavioral state interactions with single neuron and population-wide spatial representations in medial entorhinal cortex

Authors: *I. I. C. LOW, A. H. WILLIAMS, L. M. GIOCOMO;
Stanford Univ., Stanford, CA

Abstract: Behavioral state – such as alertness – profoundly impacts how we think and perform. Yet, in spite of the key role that it plays in both healthy and disordered cognition, how behavioral state influences brain function remains a central mystery in neuroscience.
Medial entorhinal cortex (MEC) is an ideal test-bed to study how behavioral state impacts cognitive processing. MEC is located at the intersection of sensation and behavior, and MEC firing tightly correlates with navigationally relevant variables, such as position. MEC was long

considered to statically represent space; however, intriguing recent work indicates that non-spatial factors such as task context modulate MEC coding. Whether this non-spatial modulation is related to behavioral state remains unknown.
To interrogate the impact of behavioral state on spatial coding by MEC, we have built a high-throughput virtual reality rig that allows for simultaneous neural and behavioral recording. As mice traversed a virtual linear track, we precisely measured arousal correlates (pupil dilation, whisking, running speed, reward consumption). Simultaneously, we used Neuropixels silicon probes to record from hundreds of neurons along the length of MEC. Using a modified linear-nonlinear model, we find that behavioral markers of arousal have diverse impacts on MEC neural activity.
Critically, this work challenges a long-standing belief in the navigation field that MEC statically represents space. Further, it provides a potential explanation for recent findings that non-spatial factors modulate MEC coding. Broadly, our work lays the groundwork to explore an enduring question in neuroscience – how behavior and neural activity dynamically interact with one another – thus enabling new scientific inquiry across a range of neural systems.

Disclosures: I.I.C. Low: None. **A.H. Williams:** None. **L.M. Giocomo:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 604.02/Z40

Topic: H.01. Animal Cognition and Behavior

Support: Simons Collaboration on the Global Brain

Title: Coding of medial entorhinal cortex during navigational decision making

Authors: *A. GONZALEZ, L. GIOCOMO;
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Abstract: A fundamental behavior is the ability to successfully navigate through the environment to reach a goal. An important brain region for navigation and the representation of space is the medial entorhinal cortex (MEC). During open-field foraging, MEC encodes necessary components of navigation: position (grid-cells, border-cells), head-direction, and speed. The stabilty of MEC coding has led to theories about how its invariant representation of space is a critical component of the brain-wide navigation circuit. However, it is not clear what computations or behavioral representations this apparently specialized circuit performs under complex behaviors. Recent results indeed suggest a more flexible role for MEC (e.g. coding for auditory frequency - Aranov et al. 2017, time- Kraus et al. 2015, and reward related changes in the representation of space - Butler et al. 2019). We hypothesize that this region is indeed

flexible in its coding, enabling task-relevant representations and computations. To test this hypothesis, we developed a maze and a task in which the animal performs cue-based goal-directed navigation for a food reward. The maze is a double-Y linear track (two branches, each with two branches to goal locations) with reward wells at a 'home', 'decision', and at the 4 'goal' locations. A visual cue indicates to the animal to go left or right at the decision location (first branching) towards two of the goal locations (final reward location chosen at random). We trained 5 rats to perform this task (reliably ~200 trials, accuracy >80%), each implanted with tetrodes to the MEC. Critically, during the task all environment factors were simultaneously recorded with the electrophysiological data (cue, reward, detections, animals' position). We then trained Poisson Generalized Linear Models on the time by time behavioral and environment states to predict spiking activity of single neurons. As expected, model selection results are mostly dominated by models with positional variables. However, we find models for mixed-selectivity cells that jointly code for cue and position, position-reward, and their combination. Importantly, by also collecting open-fiend foraging data, we demonstrate how single cells adapt their coding properties to task-relevant features.

Disclosures: **A. Gonzalez:** None. **L. Giocomo:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

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Title: Large scale recordings reveal algorithms for combining landmark and self-motion cues in entorhinal cortex

Authors: *M. G. CAMPBELL[1], A. ATTINGER[2], S. A. OCKO[3], S. GANGULI[4], L. M. GIOCOMO[2];
[2]Neurobio., [1]Stanford Univ., Stanford, CA; [3]Applied Physics, Stanford Univ., Menlo Park, CA; [4]Sloan-Swartz Ctr. For Theoretical Neurobiology, UCSF, San Francisco, CA

Abstract: The brain builds its spatial maps by combining input from external landmarks with cues arising from the animal's own movement. In previous work, we developed a coupled oscillator attractor network model for how these cues are integrated by entorhinal grid, border, and speed cells that explained a range of neurophysiological and behavioral data (Campbell et al. 2018). Here, we further test the predictions of this model by recording large populations of neurons along the whole dorsal-ventral axis of medial entorhinal cortex using Neuropixels probes while mice ran down a virtual linear track. First, we show that the main prediction of our model holds in large populations of entorhinal neurons: manipulating the gain between the animal's running speed and its progression down the virtual hallway caused maps to shift for small changes in gain, and remap for gain changes larger than a critical threshold. We then experimentally manipulated the strength of the landmark input to entorhinal cortex by reducing the contrast of the visual cues. Lowering the contrast reduced the stability of the spatial maps, and impacted cells' responses to gain changes accordingly. Finally, we leverage our large-scale recordings to test how cell activity correlations, measured in darkness, depend on responses to gain and contrast changes during the task.

Disclosures: M.G. Campbell: None. **A. Attinger:** None. **S.A. Ocko:** None. **S. Ganguli:** None. **L.M. Giocomo:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

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Simons Foundation
James S McDonnell Foundation awarded to L.M.G.

Title: Leveraging neuropixels probes and virtual reality in order to identify the mechanisms underlying ketamine's effect on spatial coding

Authors: *F. K. MASUDA[1], L. M. GIOCOMO[2];
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Abstract: Anesthetic drugs have proven to be helpful for elucidating the fundamental mechanisms of spatial memory. Ketamine—a commonly used dissociative anesthetic—has

received significant clinical and scientific attention due to its ability to acutely treat depression. Yet, despite the immense excitement surrounding the clinical use of ketamine, its mechanism of action and its effects on spatial memory remain poorly understood. Ketamine's clinical potential could be expanded if its effects on memory and spatial navigation at sub-anesthetic doses were better understood. To address this gap, we examine how ketamine affects the hippocampal-entorhinal memory circuit from a molecular and circuit perspective. We leveraged the ability of Neuropixels probes to record large populations of spatially-tuned neurons from mice traversing a virtual reality environment in order to examine how ketamine affects the medial entorhinal cortex (MEC). Notably, ketamine disrupts the firing patterns of spatially tuned cells in the MEC. Additionally, hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are known to modulate grid firing patterns in the MEC (Giocomo 2011). While ketamine is traditionally regarded as an NMDA antagonist, recent work has suggested that the ketamine's mechanism of action and receptor affinity is more heterogenous. Thus, we compared the effect of ketamine on hippocampal-entorhinal neural coding in HCN1 knockout animals and neural coding in wild type animals and found differences in the coding of spatial cells and in LFP frequency.

Disclosures: F.K. Masuda: None. **L.M. Giocomo:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

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Title: Entorhinal cortex encodes a wide repertoire of self-motion signals

Authors: *C. S. MALLORY[1], K. HARDCASTLE[2], J. L. RAYMOND[3], L. M. GIOCOMO[2]; [1]UC Berkeley, Berkeley, CA; [2]Neurobio., Stanford Univ., Stanford, CA; [3]Stanford Univ. Sch. of Med., Stanford, CA

Abstract: Recent reports have revealed that rodents move their eyes considerably during active navigation, raising questions about whether and how eye movements guide navigation and influence the underlying neural computations. Visual input plays a key role in navigation, and

accurate interpretation of visual signals requires appropriate consideration of eye movements. To estimate the position of visual objects, the direction that the retina is pointing must be considered, which is influenced by the position of the eye within the orbit (eye direction in the head) as well as head direction and body position within the environment. Likewise, to estimate the distance to landmarks or self-motion relative to environmental landmarks from retinal optic flow signals requires consideration of eye velocity, along with angular head velocity and body speed. Two of the self-motion cues needed to integrate visual cues into a global representation of space, head direction and body speed, were previously shown to be encoded by medial entorhinal cortex (MEC), a key hub in the brain's circuitry supporting navigation. We tested whether eye direction, eye velocity and angular head velocity are also encoded, utilizing a recently developed magnetic eye tracking system to monitor eye movements and an LED head tracking system or nine-axis inertial measurement unit to monitor head movements in freely moving mice, while simultaneously performing electrophysiological recordings in the MEC. We report that neurons in MEC encode several previously unrecognized self-motion signals: eye direction, gaze direction, eye speed, and angular head velocity. The representation of these signals is highly mixed with other cues in individual neurons.

Disclosures: C.S. Mallory: None. **K. Hardcastle:** None. **J.L. Raymond:** None. **L.M. Giocomo:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA042012
Neurochoice

Title: Re-organization of long-term spatial representations during methamphetamine place conditioning

Authors: *Y. SUN, L. M. GIOCOMO;
Neurobio., Stanford Univ., Stanford, CA

Abstract: Methamphetamine (MA) is a potent stimulant that exerts a powerful psychological effect. During MA administration, a strong association is formed between the experience of MA and the surrounding spatial context. In humans, this association can manifest in MA cravings and relapse with exposure to spatial contexts previously associated with drug administration. However, the underlying mechanism and circuit basis of MA's impact on spatial cognition remains unknown. As the neural basis for representing space depends on neural circuits in the

hippocampus, we used a miniaturized fluorescence microscope in freely moving mice to examine CA1 place cell representations during the entire process of methamphetamine conditioned place preference (CPP). The CPP protocol included a pre-conditioning baseline, 3 x MA (2mg/kg) or saline conditioning, and 2 post-conditioning tests (4 days apart). Compared to baseline, we found the Ca^{2+} event rate of place cells showed a long-term reduction in the MA-paired side relative to saline-paired side during the post-test sessions. This effect was not observed in control animals, in which saline was paired on both sides. We also observed rate remapping during baseline between place cells with homotopic fields in the two CPP chambers. After MA administration, however, the spatial distance between place fields in the saline versus MA-paired side increased significantly, resulting in a lower spatial correlation between place fields in the two sides of the CPP chamber. Again, these effects were not observed in control animals. Interestingly, the degree to which the spatial correlation between place fields decreased was linearly correlated with the degree of behavioral CPP expression. Longitudinal analysis further revealed, in control animals, place cell ensembles are more stable in the naturally preferred side across sessions compared to the non-preferred side. However, this pattern is reversed in the MA-conditioned animals, in which stable ensembles switch from the naturally preferred side to the MA-paired side (naturally non-preferred side). Together, the data suggest MA administration re-organizes the spatial representations of place cell ensembles by increasing the orthogonality between the MA-paired environment and drug free environment and further strengthen the representation stability in the MA-paired environment for long-term.

Disclosures: Y. Sun: None. **L.M. Giocomo:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

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Title: Experience drives discrete representations of continuous stimuli in the hippocampus

Authors: *M. H. PLITT[1], L. M. GIOCOMO[2];
[2]Neurobio., [1]Stanford Univ., Stanford, CA

Abstract: The hippocampus is a crucial structure for contextual and spatial learning, and principal cells in this region show striking correlations with behavior. Place cells, for example, fire specifically when an animal occupies one to few restricted locations in space and change their firing properties with context. However, we know very little about how hippocampal populations behave when contextual cues are ambiguous. To answer this question, we trained mice to run in two similar virtual hallways while imaging the calcium activity of large populations of CA1 neurons. Once the animals were experienced in the two hallways, we probed their representations with randomly chosen morphed environments that were a blend of the two hallways. On single trials, the population coherently and rapidly picked one of its previously stored representations for the environments and did not take on intermediate representations. In contrast, if mice were trained by being shown all of the morphed environments from the first session, the population instead represented the ambiguity by blending its representation, or in the case of a small population of cells, specifically forming a separate representation for the morphed environments. A separate cohort of mice were then trained to actively distinguish between the two extreme environments. In this case, the proportion of cells which were classified as place cells increased dramatically; however, the "all-or-none" voting behavior of the population activity was largely similar to the previous task. This fixed point attractor-like representation to ambiguous stimuli appears to be somewhat divorced from the animal's decision of which environment it is in, i.e., population activity near the animal's perceptual threshold is not informative about the animal's decision on that trial. Together, these results suggest that hippocampal activity may approximate something like sampling from a prior distribution over previously experienced states.

Disclosures: **M.H. Plitt:** None. **L.M. Giocomo:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

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Title: Entorhinal velocity signals reflect environmental geometry

Authors: *R. G. K. MUNN[1], C. S. MALLORY[1], K. HARDCASTLE[1], D. M. CHETKOVICH[2], L. M. GIOCOMO[1];
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Abstract: The entorhinal cortex contains neural signals for representing self-location, including grid cells that fire in periodic locations and velocity signals that encode an animal's speed and head direction. Recent work revealed that the size and shape of the environment influences grid patterns. Whether entorhinal velocity signals are equally influenced or provide a universal metric for self-motion across environments remains unknown. Here, we report that changes to the size and shape of the environment result in re-scaling in entorhinal speed codes. Moreover, head direction cells re-organize in an experience-dependent manner to align with the axis of environmental change. A knockout mouse model allows a dissociation of the coordination between cell types, with grid and speed, but not head direction, cells responding in concert to environmental change. These results align with predictions of grid cell attractor models and point to inherent flexibility in the coding features of multiple functionally-defined entorhinal cell types.

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Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

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Title: Functional network topography of the medial entorhinal cortex revealed by miniaturized large-field-of-view two-photon microscopy in freely moving mice

Authors: *H. A. OBENHAUS[1], W. ZONG[1], T. ROSE[2], F. DONATO[1], L. CHEN[3], H. CHENG[3], T. BONHOEFFER[2], M.-B. MOSER[1], E. I. MOSER[1];
[1]Kavli Inst. for Systems Neurosci., Trondheim, Norway; [2]Synapses – Circuits – Plasticity, Max

Planck Inst. of Neurobio., Planegg-Martinsried, Germany; [3]Inst. of Mol. Medicine, Peking Univ., Beijing, China

Abstract: The medial entorhinal cortex (MEC) creates a map of local space, based on the spatial firing patterns of grid, head direction, border, and object-vector cells. How these various cell types are organized anatomically in the MEC is still debated, although reports of clustering among functional properties of grid cells (Heys et al. 2014; Gu et al. 2018) point towards a structured anatomical organization of the MEC network at both micro and macro scales. In-depth analysis of this question has been held back by the absence of suitable recording methods. In vivo single unit electrophysiological methods permit only indirect inference of anatomical organization. Although calcium imaging via miniaturized one-photon microscopes enables large-field-of-view recordings of superficial cortical layers, it falls short of resolving detailed anatomical organization in densely labeled neuronal networks. In contrast, in vivo two-photon microscopy allows for the precise characterization of firing properties of hundreds of simultaneously recorded cells within and across layers. However, the majority of current two-photon imaging experiments require the animal to be head-fixed and to navigate in virtual environments, which can impede the analysis of most spatially tuned cell types (Donato and Moser, 2016). Here we show results from imaging large areas of MEC in more than six mice using a new generation of miniaturized, portable two-photon microscopes (Zong et al., 2017) that have undergone significant development since our previous report (Obenhaus et al., SfN 2018). With its large-field-of-view objective (400x400 μm), decreased weight (2.2g) and axial scanning capability, the microscope enables multiplane, dual channel recordings of hundreds of neurons expressing GCaMP as well as a second red-shifted fluorophore in freely moving animals. We obtained stable long-term recordings through chronic implants consisting of combinations of a gradient refractive index (GRIN) lens and a micro prism positioned between MEC and the cerebellum. The second, non-functional channel was used to label specifically cells with projections from MEC to ipsilateral hippocampus (retrograde AAV carrying tdTomato and injected into the hippocampus; Tervo et al. 2016). The resolution of this improved two-photon system allows us to record from all known spatially modulated cell classes in widespread regions of MEC while mice are moving freely inside an 80x80 cm environment. We are currently investigating how spatial firing properties are topographically organized across layers in superficial MEC, within and between groups of imaged grid cells, object vector cells and head direction cells.

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Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

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Title: Stereotyped network waves in the medial entorhinal cortex

Authors: *F. DONATO[1], S. GONZALO COGNO[1], H. A. OBENHAUS[2], R. JACOBSEN[3], M.-B. MOSER[4], E. I. MOSER[4];
[1]Kavli Inst. for Systems Neurosci., Trondheim, Norway; [2]Moser Group, Kavli Inst. For Systems Neurosci., Trondheim, Norway; [3]Kavli Inst. for Systems Neurosci. / Ctr. for Neural Computation, The Norwegian Univ. of Sci. and Technol., Trondheim, Norway; [4]Kavli Inst. Systems Neurosci, Trondheim, Norway

Abstract: The medial entorhinal cortex (MEC) supports the brain's representation of space with distinct cell types whose firing is tuned to features of the environment (grid, border, and object-vector cells) or navigation (head-direction and speed cells), and whose somata are anatomically intermingled in layer 2 of the MEC (MEC-L2). Since no single sensory stimulus can faithfully predict the firing of these cells, and activity patterns are preserved across environments and brain states, attractor network models postulate that spatially-tuned firing emerges from specific connectivity motives among neurons of the MEC. To determine how activity is self-organized in the MEC-L2 network, we tested mice in a spontaneous locomotion task under sensory-deprived conditions, when activity likely is determined primarily by the intrinsic structure of the network. Using 2-photon calcium imaging, we monitored the activity of large populations of MEC-L2 neurons in head-fixed mice running on a wheel in darkness, in the absence of external sensory feedback tuned to navigation. To reveal network dynamics under theses conditions, we applied both linear and non-linear dimensionality reduction techniques to the spike matrix of each individual session. When we applied principal components analysis and sorted cells according to their contribution to the first principal component (PC1), we were able to unveil the presence of stereotyped motifs involving the sequential activation of neurons over epochs of tens of seconds to minutes ("sequences" or "waves"). The same temporal progressions were found with non-linear techniques. To characterize the nature of sequences, we sorted neurons into clusters according to their contribution to PC1, and characterized the transition probabilities between clusters. Transitions between clusters that were close in principal-component space were favored, while transitions between clusters farther apart happened with a lower frequency than chance. The temporal analysis of transitions revealed stereotyped trajectories across multiple clusters ("waves"), lasting up to 2-3 minutes. Similar sequences were not found in spike-time-shuffled or non-sorted data.
Waves swept through the entire network of active cells with slow temporal dynamics, in the order of tens of seconds to minutes, and did not exhibit any anatomical organization. Taken

together, our results suggest that a large fraction of MEC-L2 neurons participates in common global dynamics that often takes the form of stereotyped sequences. These activity patterns might progress through multiple subnetworks and couple the activity of neuron with distinct tuning characteristics in MEC-L2.

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Poster

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Title: Mixed selectivity in outputs from the medial entorhinal cortex to non-hippocampal targets

Authors: *D. C. ROWLAND[1], H. A. OBENHAUS[2], E. I. MOSER[3], M.-B. MOSER[3]; [1]NTNU, Trondheim, Norway; [2]Moser Group, Kavli Inst. For Systems Neurosci., Trondheim, Norway; [3]Kavli Inst. Systems Neurosci, Trondheim, Norway

Abstract: The entorhinal-hippocampal circuit forms a processing loop, whereby outputs from the entorhinal cortex are processed by the hippocampus and returned to the entorhinal cortex. Previous work has focused extensively on how the various functional cell types in the medial entorhinal cortex (grid cells, border cells, head direction cells, speed cells and object vector cells) contribute to the formation and maintenance of hippocampal place fields and vice versa within the context of this processing loop. However, we still do not know what kind of information the medial entorhinal cortex (MEC) broadcasts to other telecephalic targets, such as the nucleus accumbens, amygdala, prefrontal cortex and retrosplenial cortex. Here, we injected retrograde AAVs (Tervo et al., 2016) into the retrosplenial cortex of mice to label projections from the MEC. Consistent with earlier results, we found that the population of retrogradely labelled cells

was nearly exclusively localized to Layer Va of the MEC (Surmeli et al., 2015). We then used the same retrograde AAV system to deliver excitatory or inhibitory opsins for *in vivo* functional characterization of the cells using a phototagging approach. Cells were identified as layer Va cells if they responded immediately and robustly to light delivered from a fiber-coupled laser. In contrast to cells in other layers, the phototagged cells in layer Va were notable for the amount of mixed selectivity they displayed during open field sessions (80x80 cm arena): layer Va cells were frequently tuned to some combination of space, head direction, and speed. The identified population included less than 10% grid cells and grid scores (a measure for six-fold symmetry) for those cells were lower than other layers. Thus, much of the functional specialization that characterizes cells in superficial layers of the medial entorhinal cortex appears to be replaced by a mixed code in the output cells of layer Va. As layer Va is likely to play an important role in sleep-mediated transfer of information from the MEC to other cortical areas, we are currently studying whether Va cells show consistent firing correlations with each other and with other cells between wake and sleep, as seen in other layers of the MEC.

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Poster

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Title: Similar firing properties of neurons in the medial entorhinal cortex in male and female mice

Authors: *M.-B. MOSER[1], D. C. ROWLAND[2], E. I. MOSER[1];
[1]Kavli Inst. Systems Neurosci, Trondheim, Norway; [2]NTNU, Trondheim, Norway

Abstract: Many studies in humans have suggested that males show superior performance in tests of allocentric spatial navigation (Maguire et al., 1999), while females show an advantage in object location memory (Voyer et al., 2007). However, studying sexually dimorphic behaviors in humans is challenging because cultural factors are likely to play an important role (Lawton and Kallai, 2002). This problem can be circumvented by using animal models. Many wild rodents,

including the common house mouse, display sexually dimorphic spatial behaviors, most notably larger home ranges in male compared with female animals (Mikesic and Drickamer, 1992). Perhaps relatedly, in laboratory-reared rodents, males frequently show better performance in the standard version of the water maze task (Perrot-Sinal et al., 1996), while females show better memory for object locations (Saucier et al, 2008). At the subcellular level, CA1 pyramidal cells of laboratory-reared rats undergo a roughly 30 percent fluctuation in spine density over the course of the estrous cycle (Woolley et al., 1990). These results hint at a possible fundamental difference in the neural representation of space in the two sexes. However, recordings from CA1 place cells of female laboratory-reared rats found little difference in the spatial coding properties of the cells over the course of the estrous cycle (Tropp et al., 2005). Here we decided to examine the firing properties of layer II medial entorhinal cells in male and female laboratory-reared mice. The medial entorhinal cortex contains a set of functionally specialized cell types: grid cells, head direction cells, border cells, speed cells and object vector cells. These cell types presumably contribute to different aspects of spatial navigation and are therefore valuable for examining whether the brain's neural representation of space differs between the sexes. We found a striking amount of similarity between the sexes. Male and female mice had similar percentages of cells in each functional category and no significant differences in the key measures of spatial tuning. We found no difference in grid spacing and no difference in grid orientation (i.e. the grid pattern of both males and females was oriented to the walls of the environment with a 5-10 degree offset). The implications of our results are two-fold. First, our analyses suggest that male and female rodents have strikingly similar neural representations of space, in spite of hormonal fluctuations in female mice that drive considerable synaptic plasticity. Second, our results should encourage researchers in the field to use and pool results from both sexes, thereby reducing the total number of animals used.

Disclosures: **M. Moser:** None. **D.C. Rowland:** None. **E.I. Moser:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 604.13/AA9

Topic: H.01. Animal Cognition and Behavior

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Advanced Investigator Grants from the European Research Council (GRIDCODE, Grant Agreement No 338865)
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Title: A novel directional signal expressed during grid-cell theta sequences

Authors: *R. J. GARDNER, A. Z. VOLLAN, M.-B. MOSER, E. I. MOSER;
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Abstract: Theta sequences (TS) are a fundamental feature of position coding in rodents, whereby position-coding cell ensembles encode prospective trajectories originating at the animal's present location. Grid cells are a promising candidate for driving TS, since some influential theoretical models predict that grid modules could generate trajectories from an arbitrary directional input. We were therefore motivated to examine TS in rats implanted with 384-channel Neuropixels silicon probes in medial entorhinal cortex and parasubiculum (MEC/PaS), while the animals ran in an open-field arena.

First, we observed that coding for remote locations during TS substantially distorted grid cells' spatial responses. The maximum spatial offset scaled with grid spacing, suggesting that grid modules encode trajectories across different spatial scales.

Second, by decoding position from MEC/PaS ensemble activity during open-field foraging, we observed TS as forward-directed, linear trajectories which extended as much as 1 m across the environment. Most trajectories were oriented within 60 degrees of the animal's head direction, and their angular offset from the head direction alternated frequently between left and right, resembling 'vicarious trial-and-error' in place cells (Johnson and Redish, 2007).

Finally, we describe a novel 'sweep direction' signal, encoded by theta-rhythmic, directionally selective MEC/PaS cells whose firing sharply coincided with the forward-sweeping phase of the theta cycle. Sweep-direction ensemble activity predicted the direction of TS trajectories substantially better than the animal's true head direction. Conversely, non-theta-rhythmic directional cells did not predict sweep direction, and instead more closely followed the animal's head direction.

Alternation of TS trajectory angles provides a more basic explanation for the phenomenon of theta cycle-skipping in grid and directional cells. Moreover, diffuse tuning to head direction, which is a widespread characteristic of MEC/PaS cells, may be explained as a side effect of selectivity for sweep direction.

In summary, we observed that grid-cell ensemble activity during TS encodes position trajectories whose common alignment across modules is signalled by a novel 'sweep-direction' code. Our results may have important implications for theoretical models of grid cells which use directional input to shift activity across a continuous attractor manifold. Although models typically use this capability to perform path integration, the existence of a sweep-direction code suggests that the same models could alternatively provide a mechanism for grid-cell TS trajectories.

Disclosures: R.J. Gardner: None. **A.Z. Vollan:** None. **M. Moser:** None. **E.I. Moser:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

Location: Hall A

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Program #/Poster #: 604.14/AA10

Topic: H.01. Animal Cognition and Behavior

Support: Norwegian Research Council Centre of Excellence Grant
Kavli Foundation
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Title: Early postnatal ablation of Cajal-Retzius cells affects hippocampal circuit development

Authors: *G. QUATTROCOLO, E. I. MOSER;
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Abstract: The hippocampal formation plays a major role in the encoding, association, consolidation and retrieval of memories. In particular, it creates spatial maps that animals use to navigate the environment. The microcircuits for these features are refined around birth as well as during the first weeks of postnatal development. In fact, hippocampal-dependent behaviors do not reach maturity until the first couple of months of age in rodents (Wills et al., 2013) and the first years in humans (Lavenex and Banta Lavenex 2013). During this critical time, the hippocampus harbors a transient populations of neurons, the Cajal-Retzius (CR) cells. CR cells are critical orchestrators of cortical development. While cortical CR cells die during the first week of postnatal development, CR cells persist in the hippocampus for several months after birth (Anstötz et al. 2016; 2017). Previous work has showed that CR cells are an active component of the hippocampal circuit (Quattrocolo and Maccaferri 2013; 2014). However, little is known about their role in the hippocampal network. What is the function of hippocampal CR cells during postnatal development? To address this question we decided to ablate CR cells at early time points of postnatal development and determine how their ablation affects maturation of the hippocampal network and hippocampal-dependent behaviors. To achieve the ablation, we inject a Cre-dependent virus expressing diphtheria toxin fragment A (DTA) into the hippocampus of P0 pups of the Pde1c-cre transgenic mouse line. This line is highly selective for CR cells, in the hippocampus, therefore CR cells are the only neurons affected by virally-induced DTA expression. We here show that the toxin successfully ablates hippocampal CR cells, reducing their number, in the dorsal hippocampus, to around 40% by the second postnatal week. Our data show so far that hippocampal levels of BDNF are significantly increased after ablation of CR cells, suggesting an alteration in the maturation of pyramidal cells. In addition, we performed whole-cell patch clamp in CA1 pyramidal cells while electrically stimulating

glutamatergic fibers in Stratum Lacunosum-Moleculare. We find that the AMPA/NMDA ratio is affected after the loss of CR cells, hinting at alterations in the glutamatergic connectivity. These results suggest that the presence of CR cells in the postnatal hippocampus is necessary for the proper maturation of the hippocampal circuit. We are now aiming to perform *in vivo* recordings of hippocampal place cells to understand the role of CR cells in the maturation of the spatial mapping system.

Disclosures: G. Quattrocolo: None. **E.I. Moser:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

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Title: Ontogenesis of stereotyped network waves in the medial entorhinal cortex

Authors: *S. GONZALO COGNO[1], F. DONATO[1], H. A. OBENHAUS[2], R. JACOBSEN[3], M.-B. MOSER[4], E. I. MOSER[4];
[2]Moser Group, [1]Kavli Inst. For Systems Neurosci., Trondheim, Norway; [3]Kavli Inst. for Systems Neurosci. / Ctr. for Neural Computation, The Norwegian Univ. of Sci. and Technol., Trondheim, Norway; [4]Kavli Inst. Systems Neurosci, Trondheim, Norway

Abstract: Several functionally-specific cell types in the entorhinal-hippocampal network contribute to the brain´s representation of space. Among them we find grid, border, and head-direction cells. While head-direction and border cells are adult-like at the onset of spatial exploration, grid cells undergo refinement within the first month after birth, a process that might depend on the establishment of connectivity motifs between superficial and deep layers of the entorhinal cortex and the hippocampus. The functional maturation of grid cells is accompanied by the structural maturation of the entorhinal-hippocampal network: our work showed that an activity-dependent instructive signal, originating from stellate cells of layer 2 of the medial entorhinal cortex (MEC-L2), propagates through the whole network to drive the stepwise maturation of excitatory and inhibitory neurons, as well as synaptogenesis, during the first month

after birth. Studying the functional ontogenesis of the entorhinal-hippocampal circuit offers a unique opportunity to understand the contribution of individual stages of circuit development to MEC-L2 network dynamics and computations.
Here, we investigated how activity in MEC-L2 self-organizes while juvenile mice perform a spontaneous locomotion task under sensory-deprived conditions. For this we performed daily measurements of activity from large populations of neurons with 2-photon calcium imaging, while animals were head-fixed and ran on a wheel in darkness, i.e. in the absence of external sensory feedback tuned to navigation. While in adult mice, the activity of MEC-L2 neurons progressed through stereotyped motifs involving the temporally sequential activation of clusters of neurons ("sequences" or "waves", Donato et al., SfN 2019), similar sequences were not observed in juvenile mice (P14-P21). Sequences emerged only at later time points, their occurrence increased during the fourth postnatal week, and their temporal dynamics refined with age. The earliest sequences progressed through the network over a time course often of 2-3 minutes, whereas from P30 and onwards, sequences were shorter, usually in the order of tens of seconds. Sequence stabilization coincided with the time when grid cells are known to adopt fully mature firing properties. Taken together, our results indicate that a large fraction of MEC-L2 neurons are coupled by global activity dynamics that emerge progressively during postnatal development. The prolonged maturation of these stereotyped dynamics mirrors the structural maturation of the whole entorhinal-hippocampal network, suggesting that their emergence involves multiple stages of the circuit.

Disclosures: S. Gonzalo Cogno: None. **F. Donato:** None. **H.A. Obenhaus:** None. **R. Jacobsen:** None. **M. Moser:** None. **E.I. Moser:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

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IRDC Grant 108877-001

Title: The mammillary bodies convey the ingredients for path integration

Authors: *G. VIEJO, A. PEYRACHE;
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Abstract: Animals can successfully find their way, even in the absence of external signals, by using vestibular and proprioceptive information. This process, referred to as 'path integration', is

believed to be achieved by integrating in time the direction of movement with ongoing speed. Head-direction (HD) and speed cells have been characterized in various structures of the mammalian navigation system, but so far only the medial entorhinal cortex was believed to be modulated by both signals. The mammillary bodies (MBs) are a key relay in the Papez circuit, forming a loop with the anterior thalamus and the hippocampal and parahippocampal systems, yet its dynamics and behavioral correlates remain largely unclear. Here, using silicon probe recordings in freely moving mice, we show that MB neurons are correlated with various aspects of movement, including angular head velocity, head-direction and speed, sometimes conjunctively in the same neurons. Additionally, MB neurons that relay speed or HD signals are sometimes also non trivially modulated by ongoing brain states, preferentially firing either during Rapid Eye Movement (REM) or Non-REM sleep. These results suggest that the MBs are an essential actor for path integration and that they play an active role in the selective transmission of signals to thalamo-cortical networks.

Disclosures: G. Viejo: None. **A. Peyrache:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

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Program #/Poster #: 604.17/AA13

Topic: H.01. Animal Cognition and Behavior

Support: CIHR 155957
NSERC RGPIN-2018-04600
IRDC 108877-001

Title: Head direction and place cells interaction during wake and sleep

Authors: *S. ANGELES-DURAN[1,2], G. VIEJO[1], A. J. DUSZKIEWICZ[1,3], A. PEYRACHE[1]; [1]Montreal Neurolog. Inst. and Hosp., [2]Integrated Program in Neurosci., McGill Univ., Montreal, QC, Canada; [3]Ctr. for Discovery Brain Sci., Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: The hippocampus plays a central role in navigation and memory consolidation. During exploration, hippocampal place cells increase their firing rate when the animal explores a particular location in its environment, forming sequences associated with the animal's trajectories. During sleep, these sequences are replayed, a phenomenon believed to be instrumental in memory consolidation. The formation of place cells depends on the processing of multiple sensory inputs. Perhaps one of the most important is conveyed by the head-direction (HD) cells, which fire for a particular direction of the animal's head. Yet, how HD and place cells interact, during the formation of awake neuronal sequences and subsequent sleep replay, remain unknown. We hypothesised that the activity of hippocampal place cells and the HD

signal in the antero-dorsal nucleus of the thalamus (ADn) may be coupled, and this synchronized activity could modulate the direction of recent replayed trajectories. To this end, we performed high-density dual recordings in hippocampal CA1 and ADn as the mice performed a spatial alteration task on a Y-maze. Preliminary analysis has indicated that HD cell-assemblies in ADn are modulated by hippocampal sharp-wave ripple oscillations during sleep, pointing to a functional relationship between ADn and the hippocampus in the offline state. Further analysis will determine whether there exists any relationship between hippocampal reactivation events and activation of specific cell-assemblies in ADn.

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Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

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Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Trust 206491/Z/17/Z
CIHR 155957
NSERC RGPIN-2018-04600
IRDC 108877-001

Title: Thalamic reticular nucleus controls the gain of the thalamic head-direction signal

Authors: *A. J. DUSZKIEWICZ[1], E. BROWN[1], E. R. WOOD[2], A. PEYRACHE[1];
[1]Montreal Neurolog. Inst. and Hosp., McGill Univ., Montreal, QC, Canada; [2]Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: The representation of animal's current direction originates from the vestibular system and is continuously calibrated based on the visual information. Head-direction (HD) cells serve as the brain's internal 'compass' and each of them is tuned to the specific direction the animal is facing, independently of its location and ongoing behavior. The anterodorsal thalamic nucleus (ADn) is a key relay of the HD signal to downstream cortical targets, yet its exact role in the processing of the HD signal remains unclear. Here, using a combination of high-density single unit recordings and optogenetic interrogation in freely moving mice, we demonstrate that the thalamic stage of the HD circuit is involved in spatial attention.Using viral-genetic tract tracing as well as fluorescent Retrobeads in VGAT-Cre mice, we mapped reciprocal projections between the ADn and the thalamic reticular nucleus (TRN) - an inhibitory thalamic nucleus that controls the routing of sensory information according to attentional demands. In order to assess the functional importance of the inhibitory projection from TRN to ADn, we recorded assemblies of

ADn-HD cells in freely moving VGAT-Cre mice expressing inhibitory opsin ArchT in GABA-ergic TRN neurons. Optogenetic inactivation of TRN neuron terminals in ADn caused widespread increase in ADn-HD neuron firing rates as well as modest broadening of their angular receptive fields, which indicates that TRN is involved in gain modulation of the HD signal in the thalamus. In light of these results, we hypothesized that TRN input to ADn may act to modulate the gain of the thalamic HD signal when there is a mismatch between vestibular and visual directional cues. To this end, we recorded assemblies of up to 20 HD cells in the postsubiculum (PoSub) - the main cortical target of ADn-HD cells and the postulated site where vestibular HD signal is calibrated based on the visual input. Mice then explored a small circular open field with a prominent distal visual cue that was unexpectedly shifted by 90 degrees every few minutes. We found that PoSub-HD cells reliably and coherently realigned their angular receptive fields in sync with the cue. Importantly, preliminary data suggest that increasing the gain of the thalamic HD signal via optogenetic inactivation of the TRN-ADn input slows down the realignment of the PoSub-HD cell receptive fields. Overall, these results indicate that TRN attenuates the thalamic HD signal to facilitate the updating of the current HD representation by the visual system.

Disclosures: **A.J. Duszkiewicz:** None. **E. Brown:** None. **A. Peyrache:** None. **E.R. Wood:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

Location: Hall A

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Program #/Poster #: 604.19/AA15

Topic: H.01. Animal Cognition and Behavior

Support: Starting Grant from the European Research Council ('Navigation Circuits' Grant Agreement no. 714642)
Humboldt Research Fellowship for postdoctoral researchers

Title: Representation of goal location in rat prefrontal cortex

Authors: *R. BASU, S. KOLB, T. HERFURTH, T. TCHUMATCHENKO, H. ITO;
Max Planck Inst. For Brain Res., Frankfurt am Main, Germany

Abstract: The daily activity of rodents includes visiting several distinct bait areas in their territories. Before starting such a journey, they need to decide a pertinent goal location from the others. Previous research has identified neurons in the hippocampus and the medial entorhinal cortex that get activated when an animal visits specific locations, and a population of these neurons together can provide an animal with a rich representation of its current location. However, although place cells in the hippocampus sometimes exhibit brief spike sequences that

are correlated with the animal's immediate future trajectories, it is still largely unclear where and how the brain maintains distinct representations of the goal locations themselves. As the goals may be represented upstream of the hippocampus thereby enabling place cells to generate spike sequences towards the destination, we focused on medial prefrontal (mPFC) and orbitofrontal (OFC) cortices that are anatomically connected to the hippocampus through the thalamus. These brain regions have been implicated in decision making when animals are confronted with multiple alternatives, and a human patient with mPFC lesion has been reported to exhibit difficulty in keeping the goal locations in mind. To investigate the roles of mPFC and OFC in goal representations, we made a linear track with multiple reward sites, and rats were required to visit two given sites alternately to obtain rewards. The reward sites changed after several successful trials in order to renew the animal's goal locations throughout an experimental session. Preliminary electrophysiological recordings from mPFC and OFC of behaving rats revealed two key observations. First, mPFC and OFC neurons showed distinct firing patterns at individual reward sites in the maze. Notably, in contrast to place cells in the hippocampus, we found that the representations of these neurons preserved the topological relationship of positions; the representations are more similar for closer reward locations, and more different for farther sites. Using a decoding approach for mPFC and OFC neurons, we could successfully identify the reward site where the animal is at that moment. Second, before starting the journey towards the next reward site, we observed an abrupt transition of the neural representation from the current to the future reward site that the animal was planning to visit, indicating distinct representations of the next goals in these areas. In summary, our results suggest that prefrontal neurons can create a topologically accurate map of reward locations that can be subsequently used to represent the remote goals that the animal is planning to visit.

Disclosures: R. Basu: None. **S. Kolb:** None. **T. Herfurth:** None. **T. Tchumatchenko:** None. **H. Ito:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 604.20/AA16

Topic: H.01. Animal Cognition and Behavior

Support: ERC Grant 714642

Title: Sensory integration of environmental features in rat retrosplenial cortex to compute spatial information of boundaries

Authors: *J. VAN WIJNGAARDEN, S. BABL, H. ITO;
Max Planck Inst. For Brain Res., Frankfurt am Main, Germany

Abstract: Internal representations of space are critically dependent on environmental features. Manipulations of the environment, such as morphing the shape of the arena, directly affect receptive field properties of spatially tuned cells (*e.g.* place, grid or border cells). A recent study further proposed direct contact with environmental boundaries to act as an error-correction mechanism of grid cells (*Hardcastle et al. 2015*). However, it remains unclear how sensory information about such features is processed and integrated for the accurate formation and updating of neural representations of the environment. Human fMRI and patient studies suggest an important role here for the Retrosplenial Cortex (RSC), a cortical brain region involved in landmark processing and known to have orientation-selective cells anchored to salient cues (*Auger et al. 2012; Takahashi et al. 1997; Jacob et al. 2017*). While it is densely connected with (para) hippocampal regions and part of several sensory pathways (including vision and somatosensation), its exact role in spatial and sensory processing remains to be determined. Hence we performed a series of experiments to characterize the influence of environmental variables on the coding principles of neurons in the retrosplenial cortex. We recorded single-unit activity using 28-tetrode drives - implanted along the rostral-caudal axis of the right RSC - in freely foraging rats (n=5) and found consistent firing in a subset of neurons as a function of the animal's position that was anchored to the closest boundary. Cells fired predominantly when the animal was at a specific distance and orientation towards a nearby wall, where new fields formed alongside added walls, yet they remained silent upon introducing objects. The preferred tuning across this population of RSC cells was highly biased for a particular distance and direction, and consistent between days and animals, indicating a strong sensory drive. This is further corroborated by the invariance of their boundary tuning to environmental rotations, in contrast to the remapping of local head-direction cells. Taken together these results suggest that the RSC can play an important role in integrating sensory information, providing both landmark and border information within a self-centred reference frame. This information can then inform downstream regions of the surrounding context, and allow for anchoring and referencing of internal representations to the external world.

Disclosures: **J. Van Wijngaarden:** None. **S. Babl:** None. **H. Ito:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

Location: Hall A

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Program #/Poster #: 604.21/AA17

Topic: H.01. Animal Cognition and Behavior

Support: Starting Grant from the European Research Council ('NavigationCircuits' Grant Agreement no.714642)

Title: A role of nucleus reuniens in goal-directed navigation

Authors: *H.-A. KIM, H. ITO;
Memory and Navigation Circuits Group, Max Planck Inst. For Brain Res., Frankfurt am Main, Germany

Abstract: During navigation, animals require information about their current location as well as the goal destination. While the hippocampus and parahippocampal regions are thought to provide accurate information about the animal's instantaneous position, it is still largely unclear where and how the goal location is represented in the brain. A potential candidate is the medial prefrontal cortex (mPFC), as neurons in this area exhibit enhanced temporal coordination with the hippocampus during trajectory decisions (Jones and Wilson, 2005; Ito et al., 2018), and lesions of mPFC led to impairment in goal-directed navigation (Granon and Poucet, 1995). Since there is no direct projection from the mPFC to the hippocampus, the midline thalamic nucleus reuniens (RE) is considered a key node to link between mPFC and the CA1 region of the hippocampus (Vertes et al., 2007). Our previous study has shown that mPFC-RE input is essential for the next trajectory coding in CA1 place cells (Ito et al., 2015), implying a role of this input in goal-directed navigation. However, animals with lesions in RE did not show significant impairment in the Morris water maze task (Dolleman-van der Weel et al., 2009), putting the RE's role in the navigation into question. To clarify this discrepancy, we used optogenetic and chemogenetic methods to inactivate RE neurons reversibly during goal-directed navigation. Male Long-Evans rats were injected with AAVs expressing either SwiChR or hM4Di in RE, and an optical fiber was implanted together for SwiChR-injected animals. To test goal-directed navigation, we used an open field arena with evenly-distributed 25 wells on the floor to deliver water as rewards. The task is composed of repetitively-alternating two task phases, goal-directed and random-foraging phases (Pfeiffer & Foster, 2013). In the random foraging phase, animals are required to explore the arena to find a randomly-chosen well that delivers water. In the goal-directed phase, the fixed home well is always rewarded, and thus rats usually took a direct path to this remembered well. When RE is inactivated by either laser application or agonist injection, animals took a longer path or spent more time particularly at the initial part of the journey to reach the home well. This is not likely due to the impairment of goal representation or memory, because the error rate of choosing incorrect wells did not increase during RE inactivation, indicating that animals were able to distinguish the home well from others. Our result together points to RE as a key structure for route planning in navigation, probably by interfacing mPFC with an internal spatial map in the hippocampus.

Disclosures: H. Kim: None. **H. Ito:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

Support: Helen Hay Whitney Fellowship
New York Stem Cell Foundation - Robertson Neuroscience Investigator Award
Beckman Young Investigator Award

Title: Interaction of place and gaze representations in the hippocampus of food-caching birds

Authors: *H. L. PAYNE, D. ARONOV;
Columbia Univ., New York, NY

Abstract: A key function of the hippocampus is to support navigation to remembered goals. Across animals, hippocampal activity represents a variety of spatial variables, including the animal's physical location (e.g. in foraging rodents) and viewed target (e.g. in head-fixed primates). However, it is unclear how these activity patterns interact and drive goal-directed behavior. Food-caching birds, including chickadees and titmice, are an excellent model for studying this question. They have a greatly enlarged hippocampus necessary for retrieving remembered food caches, and rely on vision for this behavior. Because birds primarily use head saccades to direct vision, both physical location and gaze location can be readily monitored during free motion. We present the first recordings of neural activity in the hippocampus of a food-caching bird, the tufted titmouse. We found robust place cell activity in birds freely foraging for seeds, in contrast to previous studies reporting a lack of place cells in other avian species. Avian place cells shared several similarities with place cells reported in rodents: they occurred with similar frequency and displayed a similar range of spatial specificities, from cells with single sharp firing fields to cells with multiple regions of selectivity. Remarkably, the distribution of sharply tuned place cells varied along the anterior-posterior axis of the hippocampus, analogous to the distribution of such cells along the dorso-ventral axis of the rodent hippocampus. To estimate gaze, we built a marker-based system for tracking 3D head movements. We found that many neurons exhibited firing fields at specific gaze (viewed) locations. In some cells, gaze tuning matched place tuning, but in other cells it did not, indicating that the avian hippocampus encodes both physical location and viewed targets. Neural information about place and gaze varied in time, such that neural activity encoded information about place that was more predictive (related to where the animal will be in the future), while encoding information about gaze that was more reactive (related to where the animal was currently or previously looking). Our results suggest that the avian hippocampus dynamically processes information about the animal's relationship to the world in a way that may support goal-directed navigation.

Disclosures: H.L. Payne: None. **D. Aronov:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

Location: Hall A

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Program #/Poster #: 604.23/AA19

Topic: H.01. Animal Cognition and Behavior

Support: New York Stem Cell Foundation - Robertson Neuroscience Investigator Award
Beckman Young Investigator Award
Helen Hay Whitney Fellowship (HLP)

Title: Imaging activity of large neuronal populations in the hippocampus of freely behaving food-caching birds

Authors: *E. L. MACKEVICIUS, M. C. APPLEGATE, H. L. PAYNE, D. ARONOV; Columbia Univ., New York, NY

Abstract: In humans, the hippocampal formation is critical for forming instantaneous (one-shot) memories. In rodents, hippocampal neurons fire at specific environmental states (e.g., locations) and, as a population, tile the environment. The population replays trajectories through the state space during events called sharp wave ripples. However, the relationship between these firing patterns and the one-shot function of the hippocampus is not well understood. We aim to bridge ideas in the rodent and human fields by recording hippocampal neurons in birds from the food-caching *Paridae* family. These birds, including chickadees and titmice, prolifically cache food in scattered locations, then return later to retrieve their caches using memory. Cache memory requires the hippocampal formation, which is grossly enlarged in these birds.
Previous studies in non-mammals have not found activity patterns akin to place cells or sharp-wave ripples. However, recordings have never been performed during navigation in spatial memory specialists like food-caching birds. Birds offer experimental advantages for functional imaging because the avian hippocampus is on the dorsal surface of the brain, rather than under the neocortex.
We expressed the calcium indicator GCaMP6f in the hippocampus of tufted titmice and recorded large neuronal populations using a head-mounted miniaturized microscope (Inscopix). Birds foraged for food and cached in an arena outfitted with hidden cache sites. Several aspects of our data bear a detailed resemblance to the rodent hippocampal recordings. First, nearly half of the imaged neurons exhibited spatial patterns that closely resembled rodent place cells. These cells were also present in electrophysiological recordings, presented in a companion poster. Second, a prevalent feature of these data were near-synchronous patterns of network activity, reminiscent of sharp wave ripples. Electrophysiological recordings revealed LFP signatures of sharp wave ripples during synchronous events, including low-frequency deflections and ripple-band oscillations. Our findings suggest strong similarities between the hippocampus of food-caching

birds and its mammalian counterpart, paving the way for using this system to investigate one-shot memory in the hippocampus.

Disclosures: E.L. Mackevicius: None. **H.L. Payne:** None. **D. Aronov:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 604.24/AA20

Topic: H.01. Animal Cognition and Behavior

Support: New York Stem Cell Foundation - Robertson Neuroscience Investigator Award
Beckman Young Investigator Award
T32 EY013933
NSF Graduate Research Fellowship (MCA)

Title: Development of a hippocampus-dependent memory task for neural recordings in food-caching birds

Authors: *M. C. APPLEGATE, K. S. GUTNICHENKO, D. F. SCHECK, D. ARONOV; Columbia Univ., New York, NY

Abstract: The hippocampus is necessary for forming episodic memories. However, the exact circuit mechanisms of this process are unknown, partly due to the difficulty of studying episodic memory in lab animals. Food-caching birds like black-capped chickadees offer unique advantages for studying this process. In the wild, chickadees cache up to thousands of food items per day and use memory to recover their caches. This behavior contains discrete instances of caching (memory formation) and retrieval (memory recall), providing well-defined time points for investigating the underlying neural mechanisms. To utilize this natural behavior in the lab, we developed a paradigm which 1) takes advantage of the birds' caching tendencies, 2) permits high-throughput, automated behavioral tracking, and 3) is compatible with modern neuroscience techniques, such as awake-tethered recordings.

We designed an arena with a grid of 64 sites covered by silicone flaps that can be pulled back to cache or retrieve seeds. Site contents were invisible to the bird unless a flap was lifted. The contents and the bird's interactions with each site were tracked automatically through a transparent floor via a camera and custom real-time video processing software. We tested chickadees on sequential trials in which they obtained seeds from motorized feeders, cached 1-3 seeds, and retrieved caches after a 2-min delay (blackout) period.

Most birds learned to cache reliably in this arena and tended to cache into unique sites on each trial. We compared how many attempts it took birds to find their caches relative to trajectories shuffled across trials. Birds required 2-5x fewer attempts than expected by chance, indicating

their use of episode-specific memory. We next asked whether our task required the hippocampus. We designed a method to inactivate a large fraction of the avian hippocampus, taking advantage of its location on the dorsal surface of the brain. Using a drug reservoir, we infused the $GABA_A$ agonist muscimol directly through the brain surface. Hippocampus-inactivated birds continued to cache, but required significantly more attempts to find seeds than on saline control days.
Our results confirm that we have developed a hippocampus-dependent episodic memory paradigm, using an arena compatible with many neuroscience techniques.

Disclosures: M.C. Applegate: None. **K.S. Gutnichenko:** None. **D.F. Scheck:** None. **D. Aronov:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 604.25/AA21

Topic: H.01. Animal Cognition and Behavior

Support: BBSRC LiDO studentship
Welcome Trust Grant 548682

Title: Long-term changes to the hippocampal place code as a function of experience and reactivation

Authors: *A. O'LEARY, L. MUESSIG, T. WILLS, F. CACUCCI, C. BARRY;
Univ. Col. London, London, United Kingdom

Abstract: CA1 place codes are thought to evolve with time and experience. New place cell ensembles develop rapidly over the course of the minutes and hours following exposure to a novel environment. Current theory indicates that changes should continue to accumulate over longer time-frames as cells are reactivated during rest and memories are increasingly integrated into cortical networks. However, the potential role of reactivation or 'replay' as a mechanism for stabilizing and subsequently consolidating new place codes over the long term has received little experimental attention. Largely this has been due to a limited ability to robustly record from the same cells across days using typical electrophysiological approaches. Therefore, the aim of the current study was to use chronic two-photon calcium imaging to observe changes to the spatial tuning of hippocampal CA1 cells as a function of experience and replay recruitment. Preliminary data demonstrate 1) detection of replay sequences in two-photon imaging data recorded from head-fixed mice during awake, goal-oriented behaviour and offline rest and 2) changes to the content of offline reactivation as a function of learning.

Disclosures: **A. O'Leary:** None. **L. Muessig:** None. **T. Wills:** None. **F. Cacucci:** None. **C. Barry:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 604.26/AA22

Topic: H.01. Animal Cognition and Behavior

Support: ONR DURIP N00014-17-1-2304
Wellcome Senior Research Fellowship

Title: Investigation of medial septal cholingergic activity using calcium fibre photometry across behavioural states

Authors: *K. A. YOUNG;
Boston Univ., Boston, MA

Abstract: While the presentation of familiar stimuli is thought to allow efficient activation of recurrent hippocampal excitatory activity in CA3, data and modelling also suggest that low cholinergic states may be permissive of recall of previously stored associations. We therefore predicted there may be an observable decrease in Medial Septal cholinergic cell activity during hippocampal reactivation events. We selectively targeted medial septal cholinergic neurons using a Cre-dependent GCAMP6f virus in IRES-ChAT-Cre mice and implanted an optical fibre at the injection site to measure the bulk fluorescence activity from the medial septum, the main source of hippocampally projecting cholinergic afferents. We used a custom-built fibre photometry system to record calcium photometry during animal exploration of an open field environment and initial analyses examine the relationship between animal behavioural state (exploratory vs stationary) and cholinergic calcium signals. Animal exploration is marked by a prominent rise in hippocampal theta activity, whereas sharp wave ripples are often observed during periods of quiet wakefulness, therefore we predict that cholinergic calcium activity will be enhanced during periods of exploration and reduced during quiet stationary behaviour. Implantation of a silicon probe to the hippocampus will enable to align cholinergic calcium activity to the occurrence of sharp wave ripples in upcoming experiments.

Disclosures: **K.A. Young:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 604.27/AA23

Topic: H.01. Animal Cognition and Behavior

Support: WT 548682

Title: The scale of grid cell firing patterns is modulated by spatial uncertainty in rodent virtual reality

Authors: *G. CASALI[1], S. J. SHIPLEY[2], C. BARRY[1];
[1]UCL, London, United Kingdom; [2]Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Medial entorhinal (mEC) grid cells display discrete firing fields organized in a regular hexagonal pattern (Fyhn et al., 2004). Although early studies indicated that the scale of the grid-pattern was constant between environments - supporting the notion that they represent a universal spatial metric (Hafting et al., 2005) - more recent work has demonstrated that grid scale is not static. For example, in response to environmental novelty grid patterns transiently expand (Barry et al., 2012) and on the vertical plane grid scale is permanently increased (Casali et al., 2019). These scenarios are characterised by reduced or unreliable spatial cues and previously we proposed that grid expansion was an adaptive response to elevated spatial uncertainty - computational simulations demonstrated that expansion of grid-patterns mitigated the reduction in accuracy resulting from reduced spatial information (Towse et al., 2014).
We tested this hypothesis by recording grid cells from head-fixed mice running through distinct virtual reality environments characterised by differing levels of spatial uncertainty. Grid firing in these impoverished environments showed clear periodic patterns across trials, consistent with their activity in 2D real world environments. Moreover, in support of our hypothesis, we found that grid scale increased in the environments characterised by the highest levels of spatial uncertainty. Together, these findings suggest that the scale of grid-patterns are modulated to optimise the encoding accuracy of entorhinal networks.

Disclosures: G. Casali: None. **S.J. Shipley:** None. **C. Barry:** None.

Poster

604. Cortical and Cortico-Hippocampal Circuits: Spatial Navigation III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 604.28/AA24

Topic: H.01. Animal Cognition and Behavior

Support: ERC Consolidator Grant (CoG), LS5, ERC-2016-COG; Mnemozyne
Doctoral fellowship from Ecole des Neurosciences de Paris Ile-de-France

Title: Effect of appetitive and aversive intracranial stimulation on place cell reactivations during sleep

Authors: *D. BRYZGALOV, S. LAVENTURE, T. BALENBOIS, K. BENCHENANE; MOBs team, Lab. Plasticité du Cerveau, ESPCI, PSL Univ., Paris, France

Abstract: In spatial memory processes, hippocampal place cells discharge when the awaken animal is in a particular location of the environment called place fields. Reactivations of these place fields occur mostly during sleep and are thought to represent key moments where the memory is active and labile. Yet, whether sleep reactivations are sensitive to reconsolidation remains unknown. In the current three-part project, we modified the emotional valence associated to a location and investigated the following behavioral and physiological changes. First, building on our previous work (de Lavilleon, 2015), we investigated the role of sleep stages (non-rapid eye movements (NREM) and REM sleep), in the reactivation and reconsolidation of spatial-dependant emotional memories. During the targeted sleep stage, stimulation of the medial forebrain bundle (MFB) was synchronized to the activity of hippocampal place cells associated to a specific location in a U-shaped maze (U-maze). In the second part, using the same behavioral assay we asked how hippocampal place code changes after aversive experience. We are specifically interested in whether the representations of avoided locations are more reactivated during sleep and whether the aversive stimuli induce re-mapping of place code. We used electrical periaqueductal gray matter (PAG) stimulation that induced robust avoidance of the location in the U-maze where the stimulation was triggered. Finally, using a similar protocol we will attempt to reverse a spatial aversive conditioning through MFB stimulation during sleep. This will allow us to explore the possibility to reverse behavioral association and to examine relationships between reward and fear in the brain. Our preliminary results show that both MFB and PAG stimulations induced reliable U-maze location preference and avoidance, respectively. We report that, despite non-altered post-aversive conditioning sleep architecture, hippocampal neurons became more responsive to ripple events, and occurrence of ripples during sleep increased after the aversive experience compared to the baseline sleep. Additional preliminary results from the first and third part of the experiment will also be presented.

Disclosures: **D. Bryzgalov:** None. **S. Laventure:** None. **T. Balenbois:** None. **K. Benchenane:** None.

Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.01/AA25

Topic: B.09. Network interactions

Support: NIH Grant MH099085

Title: Sex differences and effects of estrous stage on the ventral hippocampal-prefrontal anxiety circuit

Authors: *K. J. SCHOEPFER[1], Y. XU[2], W. WU[2], A. A. WILBER[3], M. KABBAJ[1];
[1]Biomed. Sci., [2]Statistics, [3]Psychology, Florida State Univ., Tallahassee, FL

Abstract: Synchronized oscillations in the local field potentials (LFPs) between interconnected brain structures are hypothesized to reflect interactions between these brain regions. In mice and rats, excitatory neurons in the ventral hippocampus (vHPC) monosynaptically project to the medial prefrontal cortex (mPFC) ipsilaterally and bilaterally. As members of the corticolimbic system, the vHPC and mPFC are thought to update and evaluate internal and external cues to assign a behaviorally-relevant emotional valence to the environment. Anxiety is a naturally-occurring adaptive response to potential threat, and inappropriate overrepresentation of the anxiety response can classify an anxiety disorder. Women are ~60% likelier than men to be diagnosed with anxiety disorders, yet possible neural correlates to sex differences in valence processing remain underexplored. In females, natural cycling of the gonadal hormones estradiol (E2) and progesterone (P4) dynamically modifies the expression of anxiety-like behavior in rodents, electrical excitability of HPC and mPFC pyramidal cells, and HPC-mPFC functional connectivity in women. This suggests a role for the hormonal milieu to act on the vHPC-mPFC circuit to regulate anxiety expression. Synchronized theta (4-12 Hz) oscillations between the vHPC and mPFC causally underlie innate anxiety-like behaviors in male rodents. However, in females, the vHPC-mPFC circuit's role in anxiety-like behavior remains unexplored. Here, we directly compare male and female vHPC-mPFC circuit dynamics in relation to anxiety-like behavior and also assess the female estrous stage as a potential additional factor contributing to variance in vHPC-mPFC circuit dynamics and anxiety-like behavior. Rats were chronically implanted with electrodes in vHPC CA1, prelimbic mPFC, infralimbic mPFC, and dorsal HPC (dHPC) CA1 and were acclimatized to a square arena. LFPs were recorded daily in this familiar arena, and theta outputs were analyzed as a function of sex and of estrous stage. Rodents were then recorded on the elevated plus maze (EPM), a validated behavioral test for innate anxiety-like behavior; females were tested either in diestrus (low E2/P4) or proestrus (high E2/P4)

stages. In the familiar arena, we found that vHPC theta phase was preferentially tuned to prelimbic mPFC, but did not observe sex or estrous differences. However, diestrus decreased vHPC-mPFC theta power correlations without affecting single-region theta powers or power correlations in other frequency bands, suggesting that estrous stage may play an indirect role in altering vHPC-mPFC theta signaling in a nonthreatening environment.

Disclosures: K.J. Schoepfer: None. **Y. Xu:** None. **W. Wu:** None. **A.A. Wilber:** None. **M. Kabbaj:** None.

Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.02/AA26

Topic: B.09. Network interactions

Support: LLUSP Faculty Research Grant #360027

Title: Amphetamine-like stimulants promote cortical up state: Role of adrenergic receptors

Authors: *G. SHEN[1], W.-X. SHI[2];
[1]Sch. of Pharm., [2]Sch. of Pharm. and Med., Loma Linda Univ., Loma Linda, CA

Abstract: Evidence suggests that norepinephrine (NE) in the prefrontal cortex (PFC) plays a crucial role in the mechanism of action of amphetamine-like psychostimulants. We have recently reported that the stimulant methylphenidate promotes PFC UP state, leading to a marked decrease in the slow oscillation of PFC activity (SO). To understand the significance and underlying mechanism of this effect of methylphenidate, we made *in vivo* local-field-potential recordings from the PFC in chloral hydrate-anesthetized rats. Like methylphenidate, d-amphetamine dose-dependently promoted PFC UP state and suppressed the SO. Surprisingly, cocaine mimicked those effects only at low, but not high doses. The selective NE reuptake blockers nisoxetine and atomoxetine also promoted PFC UP state and suppressed the SO, whereas the selective 5-HT transporter inhibitor fluoxetine and the dopamine transporter blocker GBR 12909 were much less effective. To further investigate the role of NE receptors in these effects, we pretreated rats with antagonists selective for adrenergic α1 (prazosin), α2 (idazoxan), and β receptors (propranolol). The UP-state promoting effect of d-amphetamine was completely blocked in prazosin-pretreated rats, but it persisted in the presence of either idazoxan or propranolol. To identify the α1 receptor subtype involved in the effect, we pretreated rats with α1A receptors antagonist WB4101, silodosin, and α1B receptors antagonist cyclazosin. WB4101 blocks both central and peripheral α1A receptors, while silodosin blocks only peripheral α1A receptors. The UP-state promoting effect of d-amphetamine was blocked by WB4101 but not by silodosin. Cyclazosin, on the other hand, reduced the effect induced by high, but not low, doses

of d-amphetamine. These results suggest that the effect of d-amphetamine requires activation of central, but not peripheral α1A receptors to express, and that α1B receptors also contribute to the effect induced by high doses of d-amphetamine. Currently, d-amphetamine and methylphenidate are the most effective medications for ADHD. Our findings described above may have important implications in understanding not only the therapeutic effects of the two stimulants but also their addictive and psychotomimetic properties.

Disclosures: G. Shen: None. **W. Shi:** None.

Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.03/AA27

Topic: B.09. Network interactions

Support: NIH Grant AA025120
NIH Grant AA023786
NIH Grant P60-AA007611

Title: Assessing the impact of excessive alcohol consumption on corticostriatal function in mice

Authors: *C. ARDINGER, D. N. LINSENBARDT;
Psychology, Indiana University-Purdue Univ. Indianapolis, Indianapolis, IN

Abstract: Addiction to substances such as alcohol is believed to involve functional adaptations in corticostriatal projections regulating its reinforcing properties. However, very little is known about the direct effect of alcohol on corticostriatal function. To address this gap in knowledge, extracellular electrophysiological recordings were collected from ventral striatal (nucleus accumbens; Acb) and cortical (medial prefrontal; mPFC) brain areas of female and male C57BL/6J mice voluntarily consuming alcohol or water using 'drinking-in-the-dark' (DID) procedures. Following a three-day acclimation period wherein mice were only given access to water, animals were given 15 consecutive days of access to alcohol. Each session consisted of a 30 minute baseline period where water was available, and was followed immediately by a 2 hour period where sippers containing water were replaced with new sippers containing either unsweetened 20% (v/v) alcohol (days 4-18) or water (days 1-3). Excessive alcohol consumption was associated with decreases in power at beta frequencies within the mPFC, and decreases in power at delta, beta, and gamma frequencies within the Acb. Furthermore, there was a strong positive correlation between the amount of alcohol consumed and beta power in the mPFC (R = .68) and Acb (R = .64), whereas the amount of water consumed was only weakly correlated with beta power in the mPFC (R = .33) and Acb (R = .26). These observations provide evidence that

excessive alcohol consumption has direct effects on corticostriatal function, and that these effects are dose-dependent.

Disclosures: C. Ardinger: None. **D.N. Linsenbardt:** None.

Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.04/AA28

Topic: B.09. Network interactions

Support: UQ International Scholarship

Title: Neural activity in the medial prefrontal cortex and hippocampus that encodes novel object recognition

Authors: *C. WANG[1], R. MAREK[1], T. M. FURLONG[2], P. STRATTON[1], P. SAH[1];
[1]Queensland Brain Inst., Univ. of Queensland, Brisbane, Australia; [2]Neurosci. Res. Australia, Univ. of New South Wales, Sydney, Australia

Abstract: Novel object recognition (NOR) refers to the ability to distinguish the occurrence of a stimulus that was previously presented in a certain environment from one that was not. Recognition memory is fundamental for animals and human beings to record events and to guide prospective behaviour. Several brain regions have been implicated in this process including the hippocampus (HPC) and the medial prefrontal cortex (mPFC). However, the roles of the mPFC and the HPC and their interaction are not extensively studied.
Subjects (male SD rats, N=10) were trained in an environment with two identical objects on day 1 and tested for object discrimination using a familiar and a novel object on day 2 and 3. We simultaneously recorded local field potentials (LFPs) in the HPC and the mPFC from freely-moving rats that performed this NOR task to assess changes in LFP activity and functional connectivity.
Our results reveal that there is a consistent exploration preference towards the novel object compared to the familiar object. During the training session, theta LFP (2-6Hz) power in the mPFC (n=10), but not the HPC (n=7), was enhanced during object exploration with no difference between the two identical objects. In contrast, during the test session, both the mPFC (n=10) and the HPC (n=7) showed significant enhanced theta power during the exploration of a novel object compared to the familiar one. Coupled theta-oscillations between the mPFC and the HPC showed no difference in training, but was found to be significantly higher during novel object exploration compared to the time animals were exploring the familiar object in test (n=7). The phase difference between these two regions and the Granger Causality analysis suggested that the directionality of the coupling is from the HPC to the mPFC in the NOR phase.

Together, our findings show that the mPFC and its synchronized activity pattern with the HPC play a role in object recognition and novelty discrimination.

Disclosures: C. Wang: None. **R. Marek:** None. **T.M. Furlong:** None. **P. Stratton:** None. **P. Sah:** None.

Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.05/AA29

Topic: B.09. Network interactions

Support: CPS-18-01-KIST
CRC-15-04-KIST
NRF 2017R1A2B3012659

Title: Gamma oscillations in basolateral amygdala during escape behaviors: Observations in a group

Authors: *J. KIM[1,2], C. KIM[1,3], W. YOUM[5], S. LEE[5], J. CHOI[1,4];
[1]Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of; [2]Korea Univ., Seoul, Korea, Republic of; [3]Univ. of Sci. & Technol., Seoul-City, Korea, Republic of; [4]Univ. of Sci. & Technol., Seoul, Korea, Republic of; [5]Electronics and Telecommunications Res. Inst., Daejeon, Korea, Republic of

Abstract: The basolateral nucleus of the amygdala (BLA) is thought to be essential for rapid escape. These are often thought to be comprised of feedforward action of BLA on the central amygdala. Neither well-understood nor often considered are BLA dynamics during escape behavior, which likely cause neural oscillations particularly in gamma band oscillation (GBO, 30 - 80 Hz). Indeed, GBOs are known to occur in BLA and their occurrence is associated with regulation of emotion, and yet their association with escape behavior remains unknown. To address this, we used a novel technique, cBRAIN (collective brain research aided by instant neurodisplay) to monitor GBO of BLA in a group-housed mice during escape behavior. The headstage of cBRAIN features in (i) wireless recording and transmission of raw data, (ii) blue LED light for tracking the position of the animal, and (iii) red LED light for signaling certain brain activity. We set the threshold for red LED so that it turns on when GBO power exceeds the confidence level of baseline GBO power. In an arena (60 cm x 60 cm), we divided the zone into safe and threat zones with a diagonally cross-sectioning wall. We tested the individual behavior first by applying cBRAIN in one mouse. We observed GBO occurred more frequently when a threat (spider robot) was introduced to the animal. GBO occurred more or less transiently rather than in an ongoing way and the occurrence of GBO was noticeable when the threat was firstly

introduced or attack the animal. On the other hand, GBO occurrence was reduced after the animal successfully escaped from the threat zone to the safe zone. Next, we applied cBRAIN in a group of 8 mice. All 8 mice were placed in the threat zone at the beginning. Likewise, GBO occurred more frequently as the robot was introduced and diminished as the most of the group escaped to the safe zone. But interestingly, the GBO occurrence was significantly less frequent in a group compared to the individual test. Moreover, in many cases, the most dominant mice did not present the GBO when the robot introduced to the threat zone, which was different from its individual test. To sum up, GBO in BLA is associated with escape behavior and the occurrence rate is altered with a company as per its social ranks.

Disclosures: **J. Kim:** None. **C. Kim:** None. **W. Youm:** None. **S. Lee:** None. **J. Choi:** None.

Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.06/AA30

Topic: B.09. Network interactions

Support: NINDS IRP (ZIA NS003168 01)

Title: Frequency-specific sinusoidal optogenetic stimulation of hippocampal-prefrontal circuit differentially alters locomotion and avoidance behavior

Authors: *R. M. MIKOFSKY[1], E. ALWAY[1], N. PADILLA-COREANO[3], M. V. MYROSHNYCHENKO[1], J. PASSECKER[1], S. HUPALO[1], D. A. KUPFERSCHMIDT[1], J. A. GORDON[2];
[1]Integrative Neurosci. Section, Natl. Inst. of Neurolog. Disorders and Stroke, [2]Natl. Inst. of Mental Hlth., NIH, Bethesda, MD; [3]The Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: Anxiety disorders are highly prevalent yet inadequately understood. Neural activity in the ventral hippocampus (vHPC) and medial prefrontal cortex (mPFC) has been implicated in avoidance behavior in the elevated plus maze (EPM), a rodent model for the study of anxiety-related behavior. In mice, oscillatory synchrony in the theta range (~8 Hz) between vHPC and mPFC increases during avoidance behavior in the EPM. Optogenetic inhibition of vHPC inputs to mPFC disrupts both theta synchrony and avoidance behavior, but it remains unclear whether theta synchrony per se is causally related to avoidance. It is similarly unclear whether 8-Hz synchrony in the vHPC-mPFC circuit has a privileged role relative to lower frequencies in promoting avoidance behaviors. To these ends, mice expressing ChR2 (or a control fluorophore) in vHPC projection neurons underwent bouts of sinusoidal light stimulation at 8, 4 and/or 2 Hz while exploring the EPM. While 8-Hz stimulation increased vHPC-mPFC theta synchrony and EPM avoidance behavior, 4-Hz stimulation produced inconsistent avoidance effects and 2-Hz

stimulation had no effect on avoidance. Furthermore, 4- and 2-Hz, but not 8-Hz, stimulation decreased distance traveled, increased compartment bias (the propensity of a mouse to spend more time in the compartment where it was located at stimulation onset) and increased time spent immobile. These results support the hypothesis that 8-Hz oscillatory synchrony in the vHPC-mPFC circuit has a privileged role in driving avoidance, and suggest that lower frequency oscillations in this circuit may affect locomotion.

Disclosures: R.M. Mikofsky: None. **E. Alway:** None. **N. Padilla-Coreano:** None. **M.V. Myroshnychenko:** None. **J. Passecker:** None. **S. Hupalo:** None. **D.A. Kupferschmidt:** None. **J.A. Gordon:** None.

Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.07/AA31

Topic: B.09. Network interactions

Title: Maternal microchimeric cells shape the functional development of offspring prefrontal-hippocampal networks

Authors: *S. SCHEPANSKI[1,2], M. CHINI[2], K. THIELE[1], V. STERNEMANN[1,2], C. URBSCHAT[1], D. ZAZARA[1], I. L. HANGANU-OPATZ[2], P. C. ARCK[1];
[1]Lab. for Exptl. Feto-Maternal Med., [2]Developmental Neurophysiol., Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract: Maternal immune cells migrate from the mother to the fetus via the placenta during pregnancy. These maternal microchimeric cells have recently been identified to enter the fetal brain; however, their functional role in the brain is still unknown. Early circuit assembly and cognitive abilities of offspring can be envisioned by identifying how these specific cells modulate neural maturation.
To address this knowledge gap, we developed a mouse model to assess the functional role of maternal microchimeric cells on fetal brains. We mated $Rag2^{-/-}$IL-$2r\gamma^{-/-}$ C57BL/6 (CD45.2, H-$2^{b/b}$) females with congenic WT Balb/c (CD45.1, H-$2^{d/d}$) males and *vice versa*, WT C57BL/6 females with $Rag2^{-/-}$IL-$2r\gamma^{-/-}$ males as controls. These reciprocal mating combinations led to an F1 generation with a significantly lower amount of maternal microchimeric cells in offspring's brains (termed 'MMc^{low}'), compared to the control F1 (termed 'MMc^{+}'), as confirmed by flow cytometry. Phenotyping of the maternal microchimeric cells revealed that the majority of them were microglial cells, whilst fewer T- and B cells could also be detected. Concomitantly, an increased number of host microglia cells was detectable in the brain of MMc^{low} offspring. Via confocal microscopy-based morphometric analysis, an enhanced engulfing of neuronal spines could be detected in the hippocampus and prefrontal cortex of MMc^{low} offspring, along with a

decreased neuronal firing and broad band (4-100 Hz) power of oscillatory activity within prefrontal-hippocampal networks *in vivo*. The MMc^{low} offspring also showed poorer performance in ultrasonic vocalizations. Since adoptive intravenous transfer of immune cells from pregnant wild-type C57BL/6 mice into the $Rag2^{-/-}IL\text{-}2r\gamma^{-/-}$ C57BL/6 dams largely restored the effects observed in MMc^{low} offspring, a causal role of maternal microchimeric cells in modulating circuit wiring and brain function in the offspring can be postulated. These effects may be mediated via suppression of fetal microglia activity or proliferation which are possible candidate functions of maternal microchimeric cells in the fetal brain.

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Poster

605. Cortical Oscillations II

Location: Hall A

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Program #/Poster #: 605.08/AA32

Topic: C.03. Parkinson's Disease

Support: R01MH116043A1 to NN
NINDS R25 grant to QZ
pilot project grant from the Aging Mind and Brain Initiative at University of Iowa
Physician Scientist Training Program Fund at University of Iowa to QZ

Title: Scopolamine and medial frontal stimulus-processing during interval timing

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Abstract: Neurodegenerative diseases such as Parkinson's disease (PD), dementia with Lewy Bodies (DLB), and Alzheimer's disease (AD) involve loss of cholinergic neurons in the basal forebrain. Here, we investigate how cholinergic dysfunction impacts the frontal cortex during interval timing, a process that can be impaired in PD and AD patients. Interval timing requires participants to estimate an interval of several seconds by making a motor response, and depends on the medial frontal cortex (MFC), which is richly innervated by basal forebrain cholinergic projections. Past work has shown that scopolamine, a muscarinic cholinergic receptor antagonist, reliably impairs interval timing. However, the effect of cholinergic inhibition on the MFC network activities during interval timing has not been studied. We tested the hypothesis that scopolamine would attenuate time-related ramping, a key form of temporal processing in the MFC. We trained 8 mice in a 12-s fixed-interval timing task and implanted 16-channel

microelectrode arrays into the MFC. During interval-timing, mice were trained to respond 12 seconds after a discriminative stimulus. Responses prior to 12 seconds were not rewarded. We recorded neuronal ensembles during the interval timing task, 30 min after mice received intraperitoneal injections of normal saline (vehicle) or scopolamine (1mg/kg). Consistent with past work, scopolamine impaired timing. We recorded from 225 neurons during interval timing. To our surprise, we found that time-related ramping was unchanged, but stimulus-related activity was enhanced in the MFC. Principal component analyses revealed no consistent changes in time-related ramping components, but did reveal changes in higher components. Taken together, these data indicate that scopolamine changes stimulus-processing rather than temporal processing in the MFC. These data could help understand how cholinergic dysfunction affects cortical circuits in diseases such as PD, DLB, and AD.

Disclosures: Q. Zhang: None. **D.Y. Jung:** None. **T. Larson:** None. **Y. Kim:** None. **N.S. Narayanan:** None.

Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.09/AA33

Topic: C.03. Parkinson’s Disease

Support: NIH Grant R01 NS 100849

Title: Midfrontal cortical signatures of lower-limb movement in Parkinson's disease

Authors: *A. SINGH, R. C. COLE, A. ESPINOZA, N. NARAYANAN;
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Abstract: Patients with Parkinson's disease (PD) suffer from lower-limb motor abnormalities. Many PD patients fall during walking or lose their balance when they initiate movement, which can cause head injuries or even death. Deep brain stimulation and levodopa therapies typically alleviate only upper-limb motor symptoms. Therefore, there is a critical need for therapies that improve lower-limb symptoms in PD. Evidence suggests an association between lower-limb motor disturbances and cognitive decline in PD patients, but these experiments have not examined the neural mechanisms. Here, we tested the hypothesis that PD patients with freezing of gait (FOG) had abnormalities in mid-frontal theta-band (4-8 Hz) and beta-band (13-25 Hz) activity, which has been linked with PD-related cognitive and motor dysfunctions. We recruited a total of thirty-nine subjects, including PD patients without freezing of gait (PDnoFOG; n=13) and with freezing of gait (PD+FOG; n=13), and demographically-matched healthy subjects (n=13). Scalp electroencephalogram signals were collected from 64 scalp electrodes during a lower-limb pedaling motor task. Pedaling required intentional initiation and stopping of a motor

movement with the lower limbs. FOG scores were significantly correlated with disease severity and cognitive assessment scores. PD+FOG patients pedaled with reduced speed and took more time to reach peak acceleration compared to PDnoFOG and control subjects. PD+FOG patients exhibited attenuated theta-band power and increased beta-band power in the frontal region at mid-frontal Cz electrode during pedaling. Midfrontal theta and beta power values were also correlated with FOG scores. Our data indicate that midfrontal theta and beta oscillations are predictors of lower-limb motor movement in PD and could inform neuromodulation therapy for PD-related lower-limb disorders.

Disclosures: A. Singh: None. **R.C. Cole:** None. **A. Espinoza:** None. **N. Narayanan:** None.

Poster

605. Cortical Oscillations II

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Program #/Poster #: 605.10/AA34

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01 NS100849 01A1

Title: Susceptibility to distraction in Parkinson's disease mediated by midfrontal theta oscillations and basal ganglia spiking activity

Authors: *R. C. COLE[1], A. SINGH[1], A. ESPINOZA[1], J. R. WESSEL[3], J. F. CAVANAGH[4], J. D. GREENLEE[2], N. S. NARAYANAN[1];
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Abstract: Humans instinctively react to novelty. When a novel event is irrelevant to the task at hand, the resulting distraction can manifest as slow or incorrect responses. We studied this issue in Parkinson's disease (PD), a neurodegenerative disease that can involve attenuated responses to novelty in addition to motor impairments. Previous research has shown that dopamine in the frontal cortex mediates the neural response to novel stimuli and may influence novelty-related distraction. Based on this, we hypothesized that novelty processing and susceptibility to distraction would be affected in PD. We tested this idea using a cross-modal distractor task in which participants (37 PD patients and 39 healthy older adults) responded to a central arrow. The arrow was preceded by two cues, a tone and a colored shape. On each trial, the cues were either both standard or one was standard and the other was an oddball (the visual stimulus was a novel shape and color or the auditory stimulus was a novel birdcall). We found that PD patients were overall slower at responding than healthy adults, and PD patients had attenuated midfrontal theta (4-7 Hz) activity. These findings align with previous reports of attenuated theta in PD during

cognitive control processes, suggesting that midfrontal theta may be a mechanism of cognitive dysfunction in PD. We also collected spiking activity from the basal ganglia and midfrontal electrocorticography during an oddball task from patients undergoing deep brain stimulation electrode implantation. During surgery, patients listened to a series of tones and non-tones (novel birdcall sounds) and responded by pressing left or right buttons, respectively. We found slowed responding to novel stimuli and we will examine basal ganglia novelty-mediated spiking activity. Our results help elucidate the neural mechanisms by which humans respond to novelty.

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Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.11/AA35

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01MH116043-01A1

Title: Temporal processing and probability in nigrostriatal dopamine circuits

Authors: *R. A. BRUCE[1], M. A. WEBER[2], C. INMAN[3], N. S. NARAYANAN[2];
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Abstract: Mammals guide their behaviors in time based on temporal probabilities. Previous work has shown time-related ramping activity in both medial frontal cortex and dorsomedial striatum neurons during an interval timing task. Importantly, both this pattern of activity and interval timing performance are disrupted by drugs that manipulate dopamine receptors. Therefore, frontostriatal circuits are critical for the temporal control of action, but it is unknown how they are influenced by probabilistic experience. Here, we trained male and female C57BL/6 mice to perform an interval-timing switch task and then varied the probabilistic structure of the task. Specifically, mice receive a reward following a short-latency interval (6 s) but are required to "switch" to another response port to receive a reward following a long-latency interval (18 s). We then varied the probability of the short interval from 50% to 75% either early or late in training. First, we lesioned the substantia nigra using 6-hydroxydopamine (1.0 µg/0.5 µL 0.03% ascorbic acid) and found that performance on this task is dependent on nigrostriatal dopamine neurons. Specifically, temporal accuracy was attenuated with animals switching later in the task. Second, we studied how responses were sensitive to the probabilistic structure of the task. Third, we used CAV-Cre to isolate striatally-projecting midbrain neurons and recorded from these neurons using fiber photometry. Finally, we further explored these circuits via multielectrode

neuronal ensemble recordings from striatal medium spiny neurons. We interpret these data in the context of temporal processing in the striatum and how neuronal activity might track temporal probabilities. These data are of particular interest for understanding the circuit mechanisms of impaired temporal processing and cognitive dysfunction in Parkinson's disease patients with midbrain dopamine dysfunction.

Disclosures: R.A. Bruce: None. **M.A. Weber:** None. **C. Inman:** None. **N.S. Narayanan:** None.

Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.12/AA36

Topic: C.03. Parkinson's Disease

Title: Prefrontal D1 dopamine-receptor neurons in delayed non-matching task

Authors: *Y.-C. KIM[1], M. A. KENNEDY[2], A. ESPINOZA[2], N. S. NARAYANAN[3]; [1]Neurol., [2]Univ. of Iowa, Iowa City, IA; [3]Neurol., Univ. of Iowa Roy J and Lucille A Carver Col. of Med., Iowa City, IA

Abstract: The prefrontal cortex is known to play a key role in active maintenance of task-relevant information short tasks involving working memory. During delayed non-matching task, prefrontal neurons exhibit memory-specific modulation. Prefrontal neurons expressing D1-type dopamine receptors (D1DRs) have been shown to be critical for cognitive processes such as working memory, flexibility, and timing, leading to the hypothesis that prefrontal D1 neurons directly encode cognitive processing. We developed a mouse version of delayed non-matching position task performed in operant chambers. The task was specifically designed to eliminate non-mnemonic strategies. We tested dopamine dependency of the task performance with the D1 dopamine receptor agonist SKF82958; mice specifically were impaired with dopamine receptor agonism. We hypothesized the medial frontal cortex D1DR+ neurons would task specific activity during delayed non-matching task. We tested the idea using a delayed non-matching task, in which we used optogenetics to tag D1DR+ neurons in the mouse medial frontal cortex and recording medial frontal neuronal ensembles. In addition, we stimulated prefrontal D1DR+ neurons optogenetically at 4Hz and 20Hz during delay period. The findings from the study will provide insight into prefrontal networks and have relevance for neuropsychiatric disorders such as ADHD, schizophrenia, bipolar disorder, and major depressive disorder.

Disclosures: Y. Kim: None. **M.A. Kennedy:** None. **A. Espinoza:** None. **N.S. Narayanan:** None.

Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.13/AA37

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01 NS 100849

Title: Gamma oscillations as a potential cortical signature for Parkinson's disease-related depression

Authors: *A. I. ESPINOZA, A. SINGH, R. C. COLE, N. S. NARAYANAN;
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Abstract: Depression is a common non-motor symptom of Parkinson's disease (PD) that impacts quality of life. Furthermore, physicians often overlook depression in PD, complicating their ability to treating PD patients effectively. Depression can also impair already-reduced functional abilities of PD patients, further impacting administration of adequate interventional therapy. Our goal was to identify cortical signatures of PD-related depression objectively via EEG. We recruited a total of thirty-nine subjects, including PD patients without depression (PD; n=19) and with depression (DPD; n=19), and demographically-matched healthy subjects (Control; n=19). Scalp EEG signals were collected from 64 scalp electrodes during resting state activity. We did not find a strong relationship between the Geriatric depression scale (GDS) score and PD severity. However, we observed markedly attenuated gamma power in the right and left motor cortical regions in DPD patients compared to PD and controls. Topographic analysis revealed attenuated gamma oscillations at the global level in DPD compared to PD and controls, with gamma deactivations predominantly to the occipital region. Occipital gamma power values were also correlated with GDS scores in PD patients. These data suggest that attenuated gamma oscillations might be linked with PD-related depression, and this could reflect cortical synaptic dysfunctions that underlie network deficits in PD. Our data indicate that motor cortical and occipital gamma oscillations could be potential signatures of PD-related depression and could inform neuromodulation therapy for depression in PD patients.

Disclosures: A.I. Espinoza: None. **A. Singh:** None. **R.C. Cole:** None. **N.S. Narayanan:** None.

Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.14/AA38

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01 MH116043-01A1

Title: Dopamine depletion in the ventral tegmental area impairs interval timing precision

Authors: *M. A. WEBER[1], R. A. BRUCE[2], N. S. NARAYANAN[3];
[1]Dept. of Neurol., The Univ. of Iowa, Iowa City, IA; [2]Interdisciplinary Grad. Program in Neurosci., [3]Dept. of Neurol., Univ. of Iowa, Iowa City, IA

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder in the U.S and is characterized by deficits in motor function and cognition. Motor dysfunction in PD is directly associated with neuronal loss in the substantia nigra. However, the neural mechanisms underlying cognitive dysfunction in PD are poorly understood but may result from neuronal loss in the ventral tegmental area (VTA). Interval timing, i.e. estimation of time over seconds to minutes, is ideally suited to investigate cognitive dysfunction as it is disrupted in PD and requires cognitive processes such as working memory and attention. Previous work has shown that dopamine (DA) receptors in the medial frontal cortex (MFC) are crucial for interval timing, but it is unclear how DA neurons in the VTA that project to the MFC contribute to this cognitive process. Here, we investigated how VTA DA lesions affect interval timing using a switch task in adult male and female C57BL/6 mice. In 50% of trials, subjects receive a reward following a short-latency interval (6 s) but are required to "switch" to receive a reward following a long-latency interval (18 s) in the other 50% of trials. The time to switch is un-cued, so this decision is time-based and guided by interval timing. Following acquisition of the task, all subjects underwent stereotactic surgical procedures in which 6-hydroxydopamine (1.0 µg/0.5 µL) or vehicle (equivalent volume 0.03% ascorbic acid) was bilaterally injected into the VTA (from bregma: AP -3.3 mm, ML ±1.1 mm, and DV -4.6 mm at 10-degree angle). After one week of recovery, all mice were tested on the switch task and measures of timing accuracy and precision were collected. Preliminary results indicate that VTA DA lesions increase the variability of switch timing, suggesting decreased interval timing precision. Together with previous work, these results indicate that VTA DA neurons are necessary for optimal interval timing performance. Future studies will determine if performance on this task is sensitive to drugs that manipulate D1 and D2 receptors. In addition, we will incorporate fiber photometry in MFC-projecting VTA neurons, which will allow us to determine if neural activity in this region encodes temporally-relevant signals.

Disclosures: M.A. Weber: None. **R.A. Bruce:** None. **N.S. Narayanan:** None.

Poster

605. Cortical Oscillations II

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.15/AA39

Topic: B.09. Network interactions

Support: NIH NIA R01AG053582
NIH NIGMS P01GM118269

Title: Towards unified EEG dynamics of anesthesia-induced altered brain arousal states

Authors: S. CHAMADIA[1], J. PEDEMONTE[3], E. HAHM[2], J. MEKONNEN[1], R. IBALA[1], J. GITLIN[1], B. ETHRIDGE[1], J. QU[1], R. VAZQUEZ[1], J. RHEE[1], E. LIAO[4], E. BROWN[5], *O. AKEJU[1];
[2]Dept. of Anesthesia, Critical Care and Pain Med., [1]Massachusetts Gen. Hosp., Boston, MA; [3]Pontificia Univ. Católica de Chile, Santiago, Chile; [4]Tulane Univ. of Med., New orleans, LA; [5]Inst. for Med. Engin. and Sciences, Picower Inst. for Learning and Memory, Boston, MA

Abstract: Understanding anesthetic mechanisms with the goal of producing anesthetic states with limited systemic side effects is a significant objective of neuroscience research in anesthesiology. Sevoflurane is an ether anesthetic that is routinely administered in clinical practice. Coherent frontal alpha oscillations, a known electroencephalogram signature of the sevoflurane anesthetized brain, has been postulated as a fundamental mechanism of sevoflurane-induced unconsciousness that remains unproven. In this research, we address and investigate the mechanisms of ether anesthetic action. We recorded high-density 64 channel EEG data by targeting and studying sub-anesthetic, general anesthetic, and deep general anesthetic states using sevoflurane anesthetic concentrations that are consistent with current clinical practice and epidemiologically based characterizations (n = 12). We implemented multitaper spectral analysis, global coherence analysis, non-linear cross-frequency coupling, and phase dependent measures to capture the complex neural dynamics underlying sevoflurane anesthetic states.We found that subanesthetic and general anesthetic brain states emerge from impaired information processing instantiated by a delta-higher frequency phase-amplitude coupling syntax. Our findings also suggest that this syntax may be conserved across drug classes. These results provide fundamental new insights into the neural circuit mechanisms of sevoflurane anesthesia and suggest that anesthetic states may be produced by extracranial perturbations such as direct current stimulations that cause delta-higher frequency phase-amplitude interactions.

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are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIGMS P01GM118269. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); speaker's honoraria from Masimo Corporation, inventors on pending patents on EEG monitoring that are assigned to Massachusetts General Hospital, ENB is a cofounder of PASCALL. **O. Akeju:** A. Employment/Salary (full or part-time):; Massachusetts General Hospital. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH NIA R01AG053582, NIH NIGMS P01GM118269. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); speaker's honoraria from Masimo Corporation, inventors on pending patents on EEG monitoring that are assigned to Massachusetts General Hospital, ENB is a cofounder of PASCALL.

Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.16/AA40

Topic: B.09. Network interactions

Support: Foundational Questions Institute
Arkansas Biosciences Institute

Title: Stabilization of cortical population firing rate by paradoxical response to GABA modulation

Authors: *W. L. SHEW[1], V. AGRAWAL[3], P. KELLS[4], J. LI[2], S. GAUTAM[1];
[2]Physics, [1]Univ. of Arkansas, Fayetteville, AR; [3]Univ. of Arkansas-Fayetteville, Fayetteville, AR; [4]NIH, Rockville, MD

Abstract: Among the simplest and most fundamental roles played by inhibition in cerebral cortex is counterbalancing excitation, keeping the ongoing firing rates of the neural population in check. A commonly held view is that if inhibition is disrupted within a cortical circuit, the firing rates of the population will become unstable, decreasing for excessive inhibition or increasing insufficient inhibition. Here we show that, while this view is accurate for extreme disruptions of inhibition, more subtle modulation of inhibition results in a very different and surprising phenomenon. We studied freely behaving rats, and found that moderate levels of GABA agonist (muscimol) or antagonist (bicuculline) in motor cortex caused dramatic shifts in firing rates of individual neurons, while leaving the population firing rate relatively stable. For decreased inhibition (bicuculline), we found that many neurons paradoxically exhibited decreased firing rates, while others fired at greater rates, as expected. Similarly for increased inhibitions

(muscimol) we observed both increases (paradoxical) and decreases (expected) changes in firing. Increases and decreases in firing rates largely canceled, resulting in relatively stable firing at the population level. Using a network level computational model, we show that disinhibitory effects of a small fraction of very strong inhibitory connections in the network may explain this phenomenon. Taken together, our experimental and modeling results point to a new type of homeostasis of population firing rates.

Disclosures: W.L. Shew: None. **V. Agrawal:** None. **P. Kells:** None. **J. Li:** None. **S. Gautam:** None.

Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.17/AA41

Topic: B.09. Network interactions

Support: Dartmouth Fellowship to JEC

Title: A physiological basis for communication through coherence in the rodent striatum

Authors: *J. E. CARMICHAEL, M. A. A. VAN DER MEER;
Psychological & Brain Sci., Dartmouth Col., Hanover, NH

Abstract: The striatum receives multiple converging inputs from brain structures which show prominent rhythmic activity. How these inputs are flexibly combined in support of motivated behavior is an issue of ongoing interest. One influential suggestion is that rhythmic fluctuations in postsynaptic excitability may be exploited for dynamic gain control: those inputs that arrive at peak excitability will be more effective than others ("communication through coherence", Fries, 2015).
Could this idea apply to the striatum and its inputs? Previous work in anesthetized animals has found synchronized membrane potential oscillations, but whether the striatum exhibits rhythmic fluctuations in excitability in awake, behaving states remains unknown. In support of this possibility, striatal local field potentials (LFPs) exhibit a full spectrum of rhythmic oscillations, including cross-frequency coupling, which dynamically synchronize with LFPs in input areas. However, it is unknown whether striatal LFPs in fact indicate the rhythmic excitability fluctuations required by the communication through coherence hypothesis. If they do not, there is no physiological basis for ascribing functional relevance to striatal LFP synchrony and its coherence with other areas. To address this fundamental issue, we applied direct optogenetic stimulation to ChR2-expressing striatal fast-spiking interneurons (FSIs) in head-fixed awake mice who could run freely on a running wheel. We calibrated the stimulus intensity to near-threshold levels, such that a single spike was evoked on some, but not all, trials. We then

determined how well we could predict whether a spike response occurs based on the phase of the LFP in key frequency bands (delta, theta, beta, and different gamma bands).
A total of 23 FSIs (out of a total of 51 recorded, n = 6 mice, of which 5 were female) met our eligibility criteria of eliciting a spike on 20% to 80% of all stimulation trials. Of these eligible neurons, 12/23 (52%) showed significant response modulation by the phase of at least one LFP frequency band, even after correcting for pre-stimulus baseline activity. Delta phase was the strongest modulator overall (35% of eligible neurons), followed by gamma (22% of eligible neurons). Surprisingly, there was substantial diversity across cells in what LFP phase corresponded to maximum excitability.
These results suggest that the striatal LFP, despite is pitfalls, can be interpreted as indicating rhythmic fluctuations in excitability, providing a firmer foundation to work reporting LFP synchrony with the striatum by suggesting a possible physiological basis for communication through coherence.

Disclosures: J.E. Carmichael: None. **M.A.A. van der Meer:** None.

Poster

605. Cortical Oscillations II

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.18/AA42

Topic: B.09. Network interactions

Support: Foundational Questions Institute
Arkansas Biosciences Institute

Title: When random variation among cortical neurons results in functional significance

Authors: *J. BARFIELD[1], P. KELLS[1], J. LI[2], S. GAUTAM[1], W. L. SHEW[3];
[2]Physics, [1]Univ. of Arkansas, Fayetteville, AR; [3]Univ. of Arkansas Fayetteville, Fayetteville, AR

Abstract: As technological innovations push towards recordings of larger and larger populations of neurons, it becomes feasible to assess similarities and differences across neurons with greater statistical rigor. Many functional properties vary dramatically across neurons in cerebral cortex. Two fundamental goals of systems neuroscience are to determine which neurons execute which functions and how the different functional properties of a neuron are related. Often, it is assumed that if two properties are uncorrelated, then there is no interesting relationship to report.
Here we show that this assumption can lead to wrong conclusions; functional segregation can emerge, by chance, due to random variation when that variation is distributed according to skewed, heavy-tailed distributions. We recorded single neuron spiking activity in motor cortex and body movement of freely moving rats. For each neuron, we assessed two functional properties: population coupling and body coupling. Population coupling quantifies how a

neuron's firing rate covaries with the rest of the cortical population. Body coupling quantifies how a neurons firing rate covaries with body movement. Both population coupling and body coupling varied greatly across neurons according to highly skewed distributions. Body coupling and population coupling were nearly uncorrelated across neurons. Nonetheless, there was a clear functional segregation; one group of neurons was strongly coupled to the body, while a different group of neurons was strongly coupled to the population. We contend that these results are a prime example of the more general phenomenon of functional segregation due to random variation.

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Poster

605. Cortical Oscillations II

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Topic: B.09. Network interactions

Support: NIMH 1K99MH116100
NIMH R01MH115592

Title: Testing the mechanisms of cortical fragmentation with propofol induced loss of consciousness and large scale cortical recordings in the non human primate

Authors: *A. M. BASTOS, J. DONOGHUE, C. SHVARTSMAN, J. YANAR, M. LUNDQVIST, J. TAUBER, M. MAHNKE, A. WAITE, E. N. BROWN, E. K. MILLER; MIT, Cambridge, MA

Abstract: The neuronal mechanisms of anesthetic action point strongly towards the drugs producing oscillations that impair communication among brain regions. One prominent model, cortical fragmentation, suggests that a loss of cortico-cortical coordination in the slow-delta frequency range is one such mechanism for producing unconsciousness. To test this, we anesthetized 4 macaques with propofol and recorded LFP and single-unit neuronal activity from a network of frontal, parietal, and mid-level sensory (Superioral Temporal Gyrus and V4) cortical areas both during and before/after loss of consciousness. The awake state was characterized by within-area and between-area coherence in the theta (4-6 Hz), and alpha/beta (10-30 Hz) frequency bands. The anesthetized state was characterized by a marked reduction in theta-beta coherence and the emergence of delta (0.5-2 Hz) coherence. To investigate sensory processing, we used two paradigms. In the visual paradigm, the screen was flashed from black to white. In the auditory paradigm, we used a sequence of deviant/oddball tones. We used multi-contact laminar probes placed perpendicular to the cortex in V4 to investigate the patterns of

sinks and sources evoked in visual cortex to the screen flash. Sink/source pairs were frequently observed to reverse in awake vs. anesthesia, suggesting a re-organization of intra-laminar processing. In the auditory cortex, oddball (unexpected) sounds resulted in more spiking compared to expected sounds. This effect was significantly attenuated during anesthesia. These results suggest that a form of cortical fragmentation is the result of a shift in coherence from theta/beta during wakefulness to slower frequencies during anesthesia-induced unconsciousness rather than a loss of coherence in the slow-delta band. These slower frequencies may impede neuronal coordination by imposing long periods of relative hyperpolarization lasting hundreds of milliseconds. In addition, the loss of inter-regional coherence in the theta-beta bands under anesthesia could explain the reductions in the oddball effect. Those frequencies have been hypothesized to underlie information transmission as well as the regulation and updating of expectation. Finally, in normal cortical communication different layers support feedforward vs feedback flow. Thus, changes in the intralaminar signal flow under anesthesia could interfere with communication between areas. Together, our results shed light on how cortical coordination is compromised during anesthesia-induced unconsciousness.

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Poster

605. Cortical Oscillations II

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Topic: B.09. Network interactions

Support: ONR MURI N00014-16-1-2832 The MIT Picower Institute Innovation Fund
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NIMH R01MH115592

Title: Thalamic stimulation reverses GABAergic but not anti-glutamatergic general anesthesia in monkeys

Authors: J. A. DONOGHUE[1,2,3], *J. YANAR[1], M. M. KOWALSKI[4], S. KORNBLITH[1], M. K. MAHNKE[2], M. LUNDQVIST[2], J. E. ROY[2], A. BASTOS[2], N. J. KOPELL[5], E. N. BROWN[2,3], E. K. MILLER[2];
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Abstract: General anesthesia (GA) reversibly induces unconsciousness. It is arguably the most powerful brain state manipulation that clinicians and researchers can reliably perform. However, the systems-level mechanisms underlying GA are not understood. In order to explore the neural correlates of GA, we recorded spiking activity and local field potentials (LFPs) from multiple cortical and thalamic regions while rendering monkeys unconscious through the use of two distinct anesthetics. In our first set of experiments, we administered the GABAergic anesthetic propofol. Propofol decreased brain-wide spiking activity and high-frequency LFPs (gamma, 30-80 Hz) while producing prominent slow oscillations (0 - 4 Hz). Slow rhythms were incoherent within the prefrontal cortices (PFC), yet synchronized across frontoparietal cortex and with the intralaminar nuclei of the thalamus. Spiking activity became tightly phase-locked to local slow oscillations, alternating between hyper-active UP states and silent DOWN states. These states could be predicted from the thalamic LFP, suggesting a role for the thalamus in entraining cortex during propofol anesthesia. We sought to test the causal role of the thalamus in maintaining unconsciousness by activating the intralaminar nuclei with high-frequency electrical stimulation. Remarkably, thalamic DBS immediately and continuously reversed GA, characterized by eye opening, air-puff responses and restored limb movement, despite continued anesthetic infusion. DBS produced an awake-like cortical state, eliminating slow oscillations and inducing a shift to higher-frequency rhythms and awake-like spiking dynamics. In our second set of experiments, we explored an alternative unconscious state mediated by the anti-glutamatergic anesthetic ketamine. Ketamine substantially increased spiking and gamma power throughout cortex, while eliminating beta (13 - 25 Hz). During GA, slow waves periodically interrupted gamma activity and PFC entrained central thalamic LFPs. DBS of the central thalamus did not produce anesthesia reversal effects, despite eliciting a massive arousal response as measured by increased sympathetic activity. Seemingly, ketamine harnesses an excitatory mechanism to disrupt conscious processing, overwhelming cortex with disordered spiking activity and entraining the thalamus. Both anesthetic regimes caused slow oscillations, disrupted cortical beta rhythms, and affected thalamocortical connectivity. Together, this collection of work demonstrates the distinct network mechanisms that can each drive GA and a systems-level approach to enhanced control of conscious states.

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Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.21/BB1

Topic: B.09. Network interactions

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Title: Coherent alpha dynamics during recovery from traumatic coma detected using global coherence analysis

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Abstract: The disruption of brain networks following severe traumatic brain injury (TBI) has been shown to alter brain synchrony, motivating the development of coherence-based electroencephalographic (EEG) biomarkers [1]. One of the canonical oscillations of the uninjured brain is the alpha rhythm, emerging from healthy thalamocortical activity. One method to study synchrony is global coherence analysis, an eigendecomposition technique that characterizes the dominant modes of coherence in multivariate time series. The objective of this study was to develop a coherence-based signature of severe TBI. Here, we apply global coherence analysis to EEG recordings collected at early and late recovery stages in 12 severe TBI patients, as well as in 16 control subjects during waking rest. Three patients were administered propofol for sedation before or during EEG acquisition. All subjects were given physical and auditory stimulation preceding rest blocks (median epoch size = 298 seconds, IQR = 2s) in which global coherence was computed. We analyzed the within-cohort and between-cohort separation between coherence patterns, obtained by computing the principal angle between two eigenvectors. In the alpha frequency, within-cohort angular separation values were higher in patients in early recovery (median 1.09, IQR=0.20) than in control subjects (median 0.914, IQR = 0.398), suggesting patient-specific perturbations of coherence patterns from normal occipital alpha patterns of resting wakefulness. Control/early and early/late between-cohort angular separations (medians 1.21 and 1.20, IQRs = 0.19 and 0.15, respectively) were greater than within-cohort separations as well as control/late separations (median 0.99, IQR = 0.41), suggesting late recovery from acute injury to coherence patterns closer to control subjects. Together, these results suggest a robust EEG signature of alpha coherence in patients with acute severe TBI that could enable the systems-level investigation of thalamocortical circuit function in this population. The alpha coherence signature identified in this study is distinct from that of propofol, reflecting thalamocortical dysfunction that may be specific to severe TBI.
[1] Wolf, J. A., & Koch, P. F. (2016). Disruption of Network Synchrony and Cognitive Dysfunction After Traumatic Brain Injury. *Frontiers in Systems Neuroscience*, *10*, 43.

Disclosures: D.W. Zhou: None. **C. Chatelle:** None. **E.N. Brown:** None. **B.L. Edlow:** None.

Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.22/BB2

Topic: B.09. Network interactions

Title: Dynamic spike-field relationships in the rat nucleus accumbens

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Abstract: The nucleus accumbens (NAc) receives convergent inputs from corticolimbic structures that possess rhythmic activity, such as the prefrontal cortex, amygdala, and hippocampus. A prominent theory of NAc function is that it acts as a "switchboard", dynamically gating information flow from different input regions. A prominent proposal of how such dynamic gain control is implemented is through synchronization of rhythmic activity across regions ("communication through coherence"). Could this idea apply to the NAc?
In support of this idea, the NAc itself displays a full spectrum of rhythmic activity that modulates local spiking activity, is related to various behavioral and task components, and is coherent with local field potentials (LFPs) in input regions. This raises the possibility that the NAc contains multiple processing channels defined by rhythmic properties and shaped by interactions with different input and output structures, a property that would support the switchboard hypothesis of NAc function. If this were true, we would expect a relationship between what rhythm(s) a given neuron phase-locks to, and what properties of the task/behavior it encodes. For instance, are neurons that show delta phase-locking more likely to encode reward receipt than to encode lever presentation? Second, this relationship should be dynamic, such that individual neurons flexibly phase-lock to distinct LFP bands during different behavioral or task states.
To address these questions, we recorded single units and LFPs from the NAc of 4 male Long-Evans rats during sequential performance of an autoshaping and a place conditioning task, and evaluated spike-field relationships with the pairwise phase consistency (PPC) measure. (1) We first looked at the distribution of units with significant PPC values across these behavioral and task states. Different task components were associated with different proportions of phase-locked units. For instance, low gamma phase-locking was prominant during the reward receipt epoch (23% of units). (2) Next, we compared PPC values across the various behavioral and task components, and found that ~80% of units showed modulation by the phase of separate frequency bands at mutually exclusive task/behavioral states.
Together, our results of dynamic spike-field relationships helps to develop an "oscillatory taxonomy" account of NAc function, suggesting that the NAc may indeed possess multiple processing channels that are mediated by distinct rhythms. This opens up a new framework for

conceptualizing NAc function, facilitating the development of future work that uses spike-field relationships as a marker for different processing channels.

Disclosures: **J.M. Gmaz:** None. **J.E. Carmichael:** None. **M.A. van der Meer:** None.

Poster

605. Cortical Oscillations II

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.23/BB3

Topic: B.09. Network interactions

Title: A comprehensive characterization of rhythmic spiking activity in the rat ventral striatum

Authors: *M. A. VAN DER MEER, J. GMAZ, J. E. CARMICHAEL;
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Abstract: Oscillations in neural activity are ubiquitous in the brain, readily accessible in the clinic and the lab, and shared by humans and animals to facilitate translational work. The ventral striatum (vStr) is a promising target structure for such a rhythmic activity perspective, not in the least because its local field potential (LFP) shows prominent task-related oscillations across a range of frequencies. However, recent work has shown that major components of the vStr LFP are in fact generated elsewhere in the brain, raising the question of how the LFP relates to local spiking activity. Previous studies of spike-field relationships in the vStr have been limited to specific cell types and/or frequency bands, and to our knowledge there have been no studies of rhythmic spiking activity in the vStr without reference to the LFP.
Thus, we sought to characterize rhythmic activity in vStr spiking by analyzing extracellular recording data (approx. 2500 cells total) collected from 11 male Long-Evans rats performing modified T-maze tasks. Spike train rhythmicity was generally limited to low frequencies such as delta and theta, whereas spike-field relationships were seen across a broad spectrum of frequencies, with about 90% of neurons showing spike-field locking to at least one rhythm. Overall, putative medium spiny neurons (MSNs) tended to favor theta-band phase preferences, while FSIs favored delta and gamma overall. Spike train rhythmicity without reference to the LFP showed more modest frequency content, and was generally independent of phase-locking except for theta and beta bands - that is, a theta phase-locked neuron is likely to spike at theta frequency, but a gamma phase-locked neuron is no more or less likely to spike at gamma frequency.
Next, using a novel time-resolved generalized linear model (GLM) approach, we further show that the contribution of LFP phase to spike timing is dynamic over time, and was enhanced by the inclusion of the LFP from the hippocampus - a new measure of inter-area coupling. Taken together, hese results provide a foundation for providing more accurate interpretation of the vStr LFP, suggest the possibility of an oscillatory taxonomy of ventral striatal neurons, and provide a

starting point for investigating the role of rhythmic activity in linking cell-, circuit-, and systems-level dynamic coordination in the vStr.

Disclosures: **M.A. van der Meer:** None. **J. Gmaz:** None. **J.E. Carmichael:** None.

Poster

605. Cortical Oscillations II

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Topic: B.09. Network interactions

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Wisconsin National Primate Research Center Pilot Grant

Title: Central lateral thalamus causally influences states of consciousness by regulating neural interactions within and between areas in fronto-parietal cortex

Authors: *M. J. REDINBAUGH[1], J. M. PHILLIPS[1], N. A. KAMBI[1], S. MOHANTA[1], S. ANDRYK[1], G. DOOLEY[1], A. RAZ[3,2], Y. B. SAALMANN[1];
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Abstract: Thalamo-cortical and frontal-parietal circuits are implicated in the neural correlates of consciousness, yet their precise influence on conscious states remains unclear. Frontal and parietal cortices have direct feedforward (FF) and feedback (FB) connections stemming from different cortical layers, and indirect connections via the central lateral nucleus (CL) of the intralaminar thalamus, which, when damaged, leads to disorders of consciousness. We hypothesized that CL influences consciousness by regulating fronto-parietal information transmission.
We used laminar probes to simultaneously record spikes and local field potentials (LFPs) from the frontal eye field (FEF), lateral intraparietal cortex (LIP), and CL in 2 macaques during general anesthesia (propofol or isoflurane) and wakefulness (resting state). Structural MRI of probes *in situ* verified positioning, and we used current source density to designate cortical layers. To manipulate thalamo-cortical dynamics, we electrically stimulated thalamic sites across 16 probe contacts with 100-300 μA at 10, 50 and 200Hz. Data from stable eye epochs, with and without stimulation, were analyzed. To monitor level of consciousness, we recorded EEG, EMG, eye position, and vital signs. Recordings took place in a dark room with the animal's head stabilized.
Our results show propofol and isoflurane anesthesia affected neural interactions within cortical areas, e.g., decreasing spike-field coherence between superficial and deep layers, and between

areas, altering FF and FB communication. Anesthesia had the largest suppressive effect on the spike rate of cells in deep cortical layers.
CL stimulation at 50Hz, mimicking the wakeful spike rate of a subset of CL neurons, was sufficient to counteract the effects of propofol and isoflurane anesthesia and render animals conscious: stimulation reduced EEG power at delta frequencies and reinstated behavioral signs of arousal, such as eye openings and purposeful movements. These effects were time-locked and specific to stimulation within CL more so than other neighboring thalamic nuclei.
Thalamic stimulation under anesthesia promoted wake-like neural processing, enhancing FF and FB alpha coherence while decreasing delta coherence, and reinstated within-area coherence between superficial and deep cortical layers. Thalamic stimulation also increased cortical spike rate during anesthesia and shifted spiking activity from periodic to tonic patterns.
Our data suggest that anesthesia perturbs multiple circuit mechanisms. CL influences levels of consciousness by modulating neural interactions within and between fronto-parietal cortical areas.

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Poster

605. Cortical Oscillations II

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Topic: B.09. Network interactions

Support: NIH P01GM118269
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Title: Electrophysiological differences between unconscious states induced by gabaergic agonists and glutamatergic antagonists

Authors: *F. J. FLORES[1,3], S. B. GONCALVES[4], I. C. RICE[5], J. AN[6], O. AKEJU[2], J. SCHOLVIN[7], E. S. BOYDEN[7], E. N. BROWN[7,2];
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Abstract: The treatment or prevention of certain conditions requires to keep patients in deeply anesthetized states, clinically referred to as *induced coma*. Traditionally, this has been achieved using gabaergic agonists, such as the volatile ethers (sevoflurane, isoflurane, desflurane) or the intravenous propofol. However, the infusion of ketamine, an NMDA receptor antagonists, to

induce a state known as *ketamine coma*, has been gaining clinical attention. Ketamine coma has been used to treat refractory headaches and to alleviate acute pain syndromes that are refractory to standard opioid treatments. The use of EEG recordings during these procedures has revealed that gabaergic agonists produce a comatose state associated with a pattern called *burst-suppression*, where bursts of delta (1-4 Hz) and alpha (8-12 Hz) activity are interspersed with relatively isoelectric periods. Similarly, ketamine-induced unconsciousness produces and EEG pattern called *gamma burst*, as periods of gamma activity (> 30 Hz) are preceded by a slow/delta oscillation (0.1-4 Hz). In order to gain better understanding of the neurophysiology underlying these two phenomena, we recorded spiking activity and local field potentials in the prefrontal cortex of deeply anesthetized mice, either with isoflurane or ketamine, using close-packed probes. We used statistically rigorous models to identify periods of burst suppression and gamma bursts. Both treatments produced conspicuous periods of either burst suppression or gamma bursts, with frequency slightly lower than those observed in human EEG recordings. However, ketamine-induced gamma bursts were always preceded by a positive-going deflection in the LFP, and vigorous spiking that subsided soon. Isoflurane-induced burst suppression was preceded by a short (<1 sec) period of high frequency activity followed by activity in the delta and alpha ranges, and spiking was mostly continuous throughout the bursts. No spiking activity outside the bursts was observed in any case. Spiking was also coherent with the LFP at the initial high-frequency period and at subsequent delta frequencies during burst suppression, but was coherent at delta, theta, and alpha bands during the gamma burst. Our results are consistent with the two different mechanisms proposed for each comatose state, where the gabaergic-induced burst suppression might be the result of cyclic metabolic changes, while the ketamine-induced gamma burst might be related to transient removal of excitatory inputs which results in hyperpolarization followed by rebound spiking.

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Poster

605. Cortical Oscillations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 605.26/BB6

Topic: B.09. Network interactions

Support: NIH Grant P01-GM118269

Title: Aging increases time to recovery from anesthesia but does not affect power and coherence of cortical rhythms in rats

Authors: *E. D. MELONAKOS[1,2,5], K. NIKOLAEVA[3], M. SIEGMANN[3], E. N. BROWN[4,1,2], K. SOLT[1,5], C. NEHS[1,2,5];
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Abstract: General anesthesia is characterized by unconsciousness, analgesia, amnesia, akinesia, and physiological stability. It is a critical component of modern surgical medicine, with over 60,000 patients undergoing general anesthesia each day in the United States. As a result, anesthetics often also cause unwanted side-effects, including cognitive deficits in the elderly. In humans, EEG power and coherence during anesthesia decrease with age, especially in the alpha band (8 - 12 Hz). In rats, the time needed to recover from anesthesia increases with age, and the broadband EEG power during the awake state decreases with age. However, age-related differences in the cortical electrical rhythms of rats during anesthesia have not been fully described. In order to describe these differences, we performed multi-site EEG (left prefrontal and parietal cortices) and LFP (bilateral prelimbic and right parietal cortices) recordings during administration of four anesthetics with different primary molecular targets or routes—propofol ($GABA_A$ receptors, intravenous), sevoflurane ($GABA_A$ receptors, inhalational), ketamine (NMDA receptors, intravenous), and dexmedetomidine (α_2-adrenergic receptors, intravenous)—in young adult (7 months) and aged (25 months) rats. Like previous studies, we used time to righting following cessation of anesthetic delivery as a measure of recovery time. We found that the time to righting increased with age for all anesthetic drugs. However, we found minimal differences in the EEG and LFP power and bilateral prelimbic cortices' coherence across ages, including in the alpha band; only the duration of the anesthetic-induced cortical dynamics differed across ages. This study offers a detailed view of the spectral content of multi-site recordings of the rat cortex during a variety of anesthetics and indicates that differences in time to righting may not be correlated with changes in spectral content between ages.

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Poster

606. Decisions: Action and Corticostriatal Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 606.01/BB7

Topic: H.01. Animal Cognition and Behavior

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Title: Chemogenetic inactivation using double virus vector infection reveals the inhibitory function of the prefronto-striatal pathway in the macaque brain

Authors: *M. OGUCHI[1], S. TANAKA[2], X. PAN[3], T. KIKUSUI[4], K. MORIYA-ITO[5], S. KATO[6], K. KOBAYASHI[6], M. SAKAGAMI[7];
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Abstract: The interaction between the prefrontal cortex and the basal ganglia underlies our value-based decision making. Among subareas of the prefrontal cortex, the lateral part (LPFC) strongly project especially to the caudate nucleus (Cd) in the striatum. Several human fMRI studies assigned different functions to this LPFC-Cd pathway. So far, however, mainly due to technological constraint, no study directly elucidates what role this pathway plays on the value-based decision making. In this study, we used a chemogenetic technique that can reversibly modulate the activity of specific projection neurons by expressing the Designer Receptors Exclusively Activated by the Designer Drugs (DREADDs) through the double virus vector infection and by administering its extrinsic ligand, Clozapine-N-Oxide (CNO). This technique was applied to the bilateral LPFC-Cd pathway in the macaque brain. The monkey was trained one-direction reward (1DR) saccade task, which is a version of the memory-guided saccade task with asymmetric reward schedule. After administering CNO to a doubly-infected monkey, task performance gradually deteriorated. This effect was stronger for small reward trials than large reward trials. Moreover, saccade latency became shorter and peak saccade velocity became faster during choice period. These results are consistent with the inhibitory control hypothesis on the function of the LPFC-Cd pathway. Spike activities and local-field potentials (LFP) were recorded simultaneously from the LPFC and the Cd. Firing rates of LPFC neurons were decreased after CNO administration. We calculated coherence between the LPFC and the Cd based on LFP signals and found that cue-induced elevation of coherence around beta-band was

decreased after CNO administration. The effect was observed only in small reward trials, which may explain increased error especially in small reward trials after CNO administration.

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Poster

606. Decisions: Action and Corticostriatal Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 606.02/BB8

Topic: H.01. Animal Cognition and Behavior

Support: Cluster of Excellence BrainLinks-Brain-Tools (EXC 1086)
Deutsche Forschungsgemeinschaft DI 1908/3-1
Deutsche Forschungsgemeinschaft DI 1908/6-1

Title: Viral strategies to target frontostriatal circuits for the investigation of action control

Authors: *Z. JÄCKEL, S. HARDUNG, B. DE LA CROMPE, I. DIESTER;
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Abstract: Selecting appropriate actions while inhibiting inappropriate ones is crucial to successful interaction with one's environment. The inhibition or stopping of an action can be classified into proactive (i.e. based on a subject's internal processes) and reactive (i.e. based on an external cue) components. Previously, we identified the prefrontal cortex (PFC) as a critical structure in action control, with individual subsections exerting different effects on proactive and reactive motor control (Hardung *et al*., 2017). Here, rats performed in a response preparation task where they were required to press a lever and then release it after a short or long delay period. Asides from interconnectivity within PFC subregions, the PFC is also densely connected with subcortical structures such as the striatum, which is also hypothesized to play a role in motor inhibition. We use optogenetics to target cells in a projection specific manner and test the efficacy of the combination of a cre/double-floxed inverse open reading frame (DIO) system with a recombinant adeno associated retrograde virus expressing cre recombinase (rAAV2-retro-cre) vs. a canine adenovirus expressing cre recombinase (CAV2-cre). While both viral constructs showed similar expression patterns for corticostriatal pathways, we found differing expression patterns in other circuits; in the corticothalamic circuit, CAV2-cre infected mostly layer VI cells, while rAAV2-retro-cre mainly targeted layer V cells in the PFC, confirming prior findings (Collins *et al*., 2018). Also, only CAV2-cre sufficiently targeted the thalamocortical circuit. In the response preparation task, we observed similar effects on performance with both viral constructs: an increase in early releases in long delay trials while inhibiting PL-striatal projecting cells, and an increase in late releases in short delay trials while inhibiting IL-striatal projecting

cells. However, the percent change in the performance was greater and more significant for inhibition of PL-striatal projecting cells while using rAAV2-retro-cre. Thus, rAAV2-retro-cre seems better suited for targeting the corticostriatal pathway, while CAV2-cre more effectively targets the thalamocortical path.
When applying this projection specific targeting to a cohort of rats (n=3) in the behavioral task, we found similar effects of inhibition of PL- and IL-striatal projecting cells on performance as for the inhibition of PL and IL populations. This suggests that previously identified roles of PL and IL in proactive inhibition depend on these striatal projections, underlining the relevance of the frontostriatal circuit for motor inhibition.

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Poster

606. Decisions: Action and Corticostriatal Circuits

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Topic: H.01. Animal Cognition and Behavior

Support: R01DA031695
UMD BBI Seed Grant

Title: Neural correlates of dorsolateral striatum under HDAC5 overexpression during a decision-making task

Authors: *H. J. PRIBUT[1,2], D. VAZQUEZ[1,2], A. D. WEI[2], S. TENNYSON[2], I. R. DAVIS[2], M. R. ROESCH[1,2], X. LI[1,2];
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Abstract: Relapse is a key issue in the treatment of drug addiction, influenced by both drug-associated cues and poor decision-making. Previous studies in rats have identified that histone deacetylase 5 (HDAC5), an epigenetic enzyme crucial for gene suppression, plays a novel role in the time-dependent increase of methamphetamine seeking after forced abstinence (incubation of methamphetamine craving). Knocking down or overexpressing HDAC5 in the whole dorsal striatum (DS) attenuates or potentiates the incubation of methamphetamine craving, respectively (Li et al., 2018). Additionally, dorsolateral striatum (DLS), a sub-region of DS, plays important roles in impulsive decision-making after exposure to drugs of abuse. For example, after cocaine self-administration, single-unit activity of DLS during a value-based decision making task is enhanced for higher-valued rewards, biasing rats' choice (Burton et al., 2018). These two lines of research converge on the importance of HDAC5 in DLS in regards to addiction and related decision-making impairments, and yet no work thus far has examined these topics in concert with each other. We attempted to address this gap in knowledge by overexpressing HDAC5 in

DS and recording DLS activity in drug naïve rats as they performed a value-based decision-making task. Thus far, we have observed that HDAC5 overexpression in DS reduced reaction time in the task but it also reduced sensitivity to delay-manipulations of reward. Continued recording from DLS will indicate how HDAC5 overexpression may influence DLS encoding of size-manipulations under drug naïve conditions, and will inform future experiments examining the role of HDAC5 in DLS encoding in decision-making during incubation of methamphetamine craving.

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Poster

606. Decisions: Action and Corticostriatal Circuits

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Title: The activity of nucleus accumbens shell neurons during target-directed locomotion correlates with kinetic parameters and is influenced by motivational factors

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Abstract: The nucleus accumbens (NAc) is proposed to link motivation with action. Motivation is reflected in the speed with which an animal approaches a place where it has previously been rewarded. To test how NAc neurons encode speed during approach to reward, we recorded the unit firing activity of 66 NAc shell neurons in adult male Wistar rats that had been overtrained

on a radial 8 arm maze task in which the same 3 arms were baited with chocolate milk reward. For one group of 2 rats, the same amount of reward was always delivered in each of the 3 arms. For the other group of 3 rats, the 3 arms were baited as follows: 1 drop of chocolate milk was delivered with 100% probability in the low reward arm, 4 drops were delivered with 66% probability in the medium reward arm, and 4 drops were delivered with 100% probability high reward arm. Rats were given 12 trials per day to explore the maze and obtain all the rewards; reward was delivered only on the first arm entry per trial. Pearson's correlations between neuronal activity and speed were calculated in the periods the rats moved from one arm to the reward area of the next visited arm. Significant ($p < 0.001$) positive or negative correlations between firing rate and speed were found in nearly 40% of neurons. To examine these correlations further, we subdivided the data into 6 temporal windows according to the target arm reached during the run and the phase of locomotion (increasing velocity from just prior to locomotion start to the speed peak, or during decreasing velocity from the speed peak or to just after locomotion stop). In the rats that were trained with the same reward in the 3 arms, 20% of neurons exhibited significant correlations (in the same direction) between firing rate and speed in all 6 windows. In contrast, in the rats trained with different reward values in the 3 arms, the correlations between firing and speed were more variable, with no neuron exhibiting significant correlations in all 6 phases. These results suggest that the way NAc neurons encode running speed is influenced by motivational factors such as the amount of reward expected.

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Poster

606. Decisions: Action and Corticostriatal Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 606.05/BB11

Topic: H.01. Animal Cognition and Behavior

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Title: Deletion of beta2* nicotinic acetylcholine receptors expressed by striatal interneurons leads to behavioral alterations

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Abstract: While functional role of nicotinic acetylcholine receptors (nAChRs) expressed by striatal glutamatergic and dopaminergic terminals has been extensively studied, much less is known about function of nAChRs expressed by striatal neurons. The striatal projecting neurons (SPNs) express low levels of nAChRs, hence the vast majority of nAChRs is expressed by striatal interneurons, either cholinergic or GABAergic (CINs and GABAINs, respectively). We hypothesize that acetylcholine released by CINs activates nAChRs expressed by GABAINs and that this activation is important for striatal signaling and function. The main objective of our study is to determine role of nAChRs expressed by striatal interneurons in the control of striatal-based behavior. To do that, we decided to use less specific Cre/loxP approach followed by more precise CRISPR/Cas9 method allowing us to delete nAChRs in specific types of GABAINs. First, we used mice carrying floxed gene *CHRNB2* coding for β2 subunit of the nAChR and we injected them with AAV5-Cre vector into the dorsal striatum. After three weeks allowing for viral expression, we tested mice with the deletion in a battery of behavioral tests mainly focusing on striatal-based behavior. We also measured markers of neuronal activation, Fos and phosphorylated ribosomal protein S6, to see if activity of SPNs was increased after deletion. In the mice with deletion, we detected changes in several behavioral domains: they were impaired in the cued Morris water maze, they had decreased motivation and they showed anti-depressive and anti-social behavior comparing to mice injected with AAV5-GFP control virus. In contrast, mice with deletion did not show any changes in baseline locomotion or in locomotor response to amphetamine and there was no change in Fos expression after acute administration of amphetamine. In addition to non-specific β2 deletion in all striatal neurons , we also decided to target specifically 5HT3a and NPY-expressing GABAINs. For that we used previously published (Peng et al., Eur J Neurosci, 2018) sequences of gRNA targeting *CHRNB2* gene. We confirmed efficiency of these gRNAs in 3T3 cells so they can be virally transduced in striatal cells and used for specific deletion of β2 in 5HT3a and NPY-expressing GABAINs using mouse lines expressing Cas9 under the control of respective promoters. Based on the current data, we conclude that the deletion of β2* nAChRs expressed by interneurons in the dorsal striatum leads to alterations in specific behavioral domains. Acknowledgement: The β2-flox/flox mice for this study were provided by Prof. Michael Crair from Yale University School of Medicine.

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Poster

606. Decisions: Action and Corticostriatal Circuits

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Program #/Poster #: 606.06/BB12

Topic: H.01. Animal Cognition and Behavior

Support: DARPA SUBNETS

Title: Modulation of value and error signals using caudate electrical stimulation

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Abstract: Valuation of alternative actions is a process in decision-making that is indispensable for adaptive and healthy behavior. In many psychiatric patients, dysfunctional decision-making and reward processing are known to contribute to the disease state. Determining the neural circuitry that drives flexible decision-making is thus extremely relevant to understanding healthy and pathological behaviors. In this work, we examine how value information is integrated within the corticostriatal circuitry and used to guide decision-making behavior. The dorsomedial striatum (caudate; Cd) has been shown to encode values of alternative choices prior to choice selection. Many other brain regions, such as the prefrontal cortex, also have value representations and the anterior cingulate cortex (ACC) is known for its role in flexible decision-making. In two rhesus macaque subjects, high-frequency stimulation is administered in the Cd during a two-armed bandit task, resulting both in a change in the functional decision-making behavior and the underlying encoding of value and error signals. High-frequency stimulation paired with a particular stimulus during an instructed trial biased the subjects to select that stimulus with a higher rate in free-choice trials irrespective of the reward likelihood. We hypothesized that caudate microstimulation differentially inflates value independent of action and reward, and that, even though the brain has bilateral value representations, unilateral manipulations of value are sufficient to mediate choice behavior. This is supported by neural data which indicates that value-coding neurons in Cd and ACC are preferentially modulated by stimulation. Stimulation was found to have selective effects on different categories of value-coding neurons in these nuclei. Additionally, changes in firing rate activity of Cd and ACC neurons encoding reward prediction error (RPE) were found, reflecting a change in the distribution of RPEs experienced by the subjects.

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Poster

606. Decisions: Action and Corticostriatal Circuits

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant 5R00DA035251-05
P50DA044118-01A1

Title: Roles for ventral pallidum GABA neurons in appetitive and aversive motivation during risky decision making

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Abstract: The brain is tuned to balance appetitive and aversive drives when making decisions, and this process goes awry in disorders like drug addiction. However, the neural circuits involved in this balance remain poorly understood. The ventral pallidum (VP) lies at an anatomical nexus of appetitive and aversive neural circuits, and contains segregated neuronal populations that seem to regulate both appetitive and aversive motivational states. We previously showed that inhibiting VP neurons decreases translationally-relevant relapse-like behaviors, and inhibiting VP GABA neurons in particular facilitates a shift in decision making towards a small but safe reward option (1 food pellet) and away from a large but risky one (2 food pellets + chance of footshock). We also showed that VP GABA neuron inhibition reduced effortful seeking of palatable food on a progressive ratio task, supporting a role for these neurons in driving appetitive motivation. However, it is unclear how these neurons regulate aversive motivation. Therefore, we tested whether chemogenetic inhibition of VP GABA neurons disrupted active operant avoidance of shock, or affective reactivity to shock. GAD1-Cre rats expressing inhibitory hM4Di designer receptors (hM4Di DREADDs) in VP GABA neurons were trained on an operant active avoidance task (Oleson et al., 2012, *J Neuroscience*). Levers were extended every 20s signaling impending repeated footshock after a 2s delay. A press on the active lever during this delay period prevented footshock (avoidance response), whereas a press after shock initiation terminated ongoing footshock (escape response). A 20s white noise safety signal was presented upon an avoidance or escape response. If VP GABA neurons are required only for appetitive motivation, then DREADD-mediated inhibition of these neurons will not alter avoidance or escape responding. Subsequently, we recorded and quantified ultrasonic vocalizations and motoric responses (Orsini et al., 2017, *J Neuroscience*) to non-contingent, unavoidable footshock (ascending in intensity from 0.15mA-0.50mA) to test whether VP GABA inhibition altered affective responses to shock. These results will tell us a great deal about how VP GABA neurons operate during aversive motivational states, and ultimately during the pathological decisions commonly made by addicted people.

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Poster

606. Decisions: Action and Corticostriatal Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 606.08/BB14

Topic: H.01. Animal Cognition and Behavior

Title: Glutamatergic regulation of reward-related timing in the dorsolateral striatum

Authors: *S. A. YOUSEFZADEH, S. WEN, S. PRAKASH, W. H. MECK;
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Abstract: The ability to time durations in the seconds-to-minutes range is an essential component of reward prediction and reinforcement learning. Reward-related timing is mediated through the dopamine-glutamate pathways in the cortico-striatal-thalamic loops. It has been shown that medium spiny neurons (MSNs) in the dorsal striatum receive glutamatergic and dopaminergic input from various regions of the brain including the prefrontal cortex and substantia nigra pars compacta, respectively, and are critical for processing temporal information. In this study, we investigated the role of glutamatergic neurotransmission in the dorsal striatum and its contribution to reward-related timing mechanisms. Using a bi-peak timing procedure, rats were trained to reproduce two target durations (12 and 36 s). The training phase was followed by bilateral infusions of NMDA or AMPA receptor agonists or antagonists into the dorsolateral striatum 30 minutes prior to the beginning of the test sessions. Our results demonstrated that glutamatergic antagonists produced proportional leftward shifts for both target durations, consistent with an overestimation of time resulting from a faster internal clock. In contrast, glutamatergic agonists produced proportional rightward shifts for both peak functions, consistent with the underestimation of duration as a result of a slower internal clock. These findings indicate that the glutamatergic input received by MSNs has a regulatory effect on their spike patterns, thereby leading to alterations in timing and time perception as reflected in the speed of the underlying timing mechanisms.

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Poster

606. Decisions: Action and Corticostriatal Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 606.09/BB15

Topic: H.01. Animal Cognition and Behavior

Title: Chemogenetic inhibition of ventral tegmental area projections to the medial prefrontal cortex affects decision-making

Authors: *M. D. SINGSTOCK, D. TAPP, B. KLEIN, M. S. MCMURRAY;
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Abstract: Impulsive decisions are a natural component of healthy behavior; however, instances of chronic impulsivity can have a profound impact on the individual and society. Foremost, drug

addiction has been reliably shown as a correlate and cause of increased impulsivity. In addiction, there are abnormalities in the medial prefrontal cortex (mPFC), a region of the brain primarily involved in regulating behavior and goal-directed decision-making, causing an increase in premature and risky decisions. Much is known about the mPFC alone; however, considerably less is known about the neural circuitry that connects the mPFC to other brain regions, especially the circuit connecting it with the ventral tegmental area (VTA), a structure in the midbrain that is crucial to reward assessment. The purpose of this study was to determine if inhibition of the VTA-mPFC neural circuit affects basic decision-making. To test this hypothesis, we selectively silenced this connection using Designer Receptors Exclusively Activated by Designer Drugs and measured impulsivity and risky decision-making in delayed and probabilistic decision-making tasks, respectively. We found that inhibition of this connection does have a significant impact on preference for risky rewards, causing rats that were affected by DREADD activation to undervalue the larger, riskier rewards; however, there was no impact on impulsivity in the delay discounting task. Silencing this connection also impaired behavioral flexibility, measured in a probabilistic reversal learning task. Thus, our results indicate that projections from the VTA to mPFC play a critical role in some forms of decision-making, namely probability estimation, but not delayed reinforcement. These results have important implications on our understanding of the psychiatric diseases that are characterized by excessive risk-taking, and on the role of the prefrontal cortex in these diseases.

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Poster

606. Decisions: Action and Corticostriatal Circuits

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Program #/Poster #: 606.10/BB16

Topic: H.01. Animal Cognition and Behavior

Title: The neurobiology of interval timing is epigenetically regulated

Authors: *M. FALAPPA, V. TUCCI;
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Abstract: Introduction:
The understanding of how timing in the brain is epigenetically regulated is important for a better description of cognitive processes.
For this reason, we investigate the neural basis of interval timing in mice according to their epigenetic landscape. We have previously reported that timing in mice is guided by parent-of-origin effects and that genomic imprinting is one of the epigenetic mechanisms that exerts a control on this neurobiological process. Now, we focused on neuronal populations of the dorsal striatum, that play functionally roles in timing processes, and we checked whether the activity of

these neurons is influenced by a parent-of-origin epigenetic component.

Methods:

We studied the peak procedure timing task in the AKR/J and DBA/2J inbred strains during in vivo calcium recording in the dorsal striatum. Then we compared the activity profiles and the behavior between parental strains and their reciprocal hybrids. The behavioral test was performed in home-cage equipped with the Choora feeder by AM Microsystems, an operant wall with two hoppers with infrared beam and a pellet dispenser. The calcium signals were acquired by using nVista HD (Inscopix). After behavioral training mice were injected with AAV1Camk2aGCaMP6m, then implanted with lens probe and a baseplate above the lens for mounting a miniature fluorescence microscope. The synchronization between the two systems during the recording was ensured by TTL from Choora feeder managed by Phenopy.

Results:

Our results show no differences in the error rate while the timing strategy adopted from the two experimental group was different in different cohorts. Indeed, DBA/2J show less accuracy to choose the right time window to get the reward. They delay their responses. This phenotype was inherited in a prent-of-origin manner. Then, we found an activation on the dorsal striatum related to the judgment of time during the task, as we expected. Preliminary analyses reveal a combination of neuronal and behavioral profiles that are parent-of-origin inherited and that account for the epigenetic differences between the different cohorts.

Conclusions:

While we are performing further studies to confirm these preliminary data, our early results suggest that timing is an interesting endophenotype that is regulated by epigenetic mechanisms. Individual neurons in the brain show different epigenetic changes that account for their variable activity. This phenomenon influences time perception and potentially many different behaviors. Therefore, future studies into the epigenetics of single neuronal profile will be mandatory in Neuroscience.

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Disclosures: M. Falappa: None. **V. Tucci:** None.

Poster

606. Decisions: Action and Corticostriatal Circuits

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Topic: H.01. Animal Cognition and Behavior

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Title: The posterior tail of striatum plays an important role in tonal associative learning

Authors: *M. LIU[1], H. WANG[2], T. LI[4], Y. WANG[5], D. CAI[3], K. YUAN[2];
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Abstract: The striatum is traditionally divided into three subdivisions based on connection and function, including dorsomedial striatum, dorsolateral striatum, and ventral striatum. These subdivisions are critically involved in various brain functions, including associative learning. Very recently, the posterior tail of the striatum (TS) started to be considered as the fourth subdivision because of its independent dopamine source, and the understanding of its function is still very limited. Although a few studies have shown the essential role of TS neurons in learned discrimination task, whether and how these neurons might play a specific role during associative learning remains unknown. To address this question, we adopted a Go-Nogo behavioral task, in which mice learn to associate one tone with reward (sucrose water) and the other tone with punishment (air puff). We firstly expressed GCaMP6 in the TS of Vgat-ires-Cre mice, then we made fiberphotometry recordings from TS neurons expressing GCaMP6 during the training. We found that the medial and lateral part of the TS showed differential responses to tonal cues. The medial part demonstrated significantly stronger adaptation to tones in the first day of training than the lateral part did.. To find out whether difference in connection might account for the difference in neural responses, we used retrograde mono-transynaptic rabies virus to identify the inputs of medial and lateral TS. We found that the lateral part received more inputs from the auditory cortices, while the medial part received substantially more inputs from somatosensory cortices. Our immunohistological results showed that medial TS is rich of D1R neurons and almost absent of D2R neurons, while lateral TS has more D2R neurons than D1R neurons, suggesting that D2R neurons, which are located laterally, might be more important for associative learning using tonal cues. To test this hypothesis, we optogenetically activated either D1R or D2R neurons during training. We found that both the activation of D1R and D2R neurons significantly accelerated learning process by improving the performance of correct rejection. However, the improved performance was preserved after days of light stimulation only in mice received D2R activation. The performance of mice received D1R activation dropped to control level in the first day of light-off. These data suggest that TS neurons are indeed involved in tonal associative learning, and that D2R neurons might play a more important role.

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Poster

606. Decisions: Action and Corticostriatal Circuits

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Title: *In vivo* striatal neural activity during motor skill learning in Huntington's disease mice

Authors: *E. T. KOCH, M. D. SEPERS, L. A. RAYMOND;
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Abstract: Huntington's disease (HD) is a genetic neurodegenerative disorder characterized by motor, cognitive and psychiatric deficits. The dorsal striatum is the major site of neurodegeneration in HD, particularly the spiny projection neurons, along with atrophy of other areas including the cortex. HD patients and animal models display deficits in striatum-dependent learning, such as motor skill learning, that worsen with disease progression. The YAC128 mouse model of HD shows progressive deficits in the accelerating rotarod motor learning task as well as anxiety-like behaviours and changes to locomotor activity. These mice also display aberrant cortico-striatal signalling, including changes to glutamate release and deficits in cortico-striatal plasticity. The contribution of these changes in cortico-striatal signalling to motor skill learning deficits *in vivo* has never been tested. Here, we have combined the accelerating rotarod task with GCaMP7f imaging using fiber photometry to correlate activity in striatal neurons with task performance and motor learning. We have found that population activity in the dorsal striatum increases and remains elevated during rotarod performance, and returns to a relatively low level afterwards. Over days of training, the amplitude of population activity during rotarod performance reduces as mice become more proficient at the task. We also measured GCaMP7f activity of mice freely moving in an open field to assess anxiety-like behaviour and locomotor activity and the corresponding neural activity in striatum. We examined GCaMP7f dynamics during these behavioural tasks in YAC128 mice compared to their wild-type littermates at early stages (2-3 months) and at fully symptomatic stages (6-7 months). This research contributes to our understanding of the changes to striatal signalling that may contribute to motor, cognitive and psychiatric symptoms in HD.

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Poster

606. Decisions: Action and Corticostriatal Circuits

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Title: A computational model of cortico-basal ganglia circuits for deciding between reaching actions

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Abstract: When decisions are made between actions, they appear to involve the same cortical and subcortical regions that are implicated in the control of those actions, but the causal role of each region is difficult to establish. In recent studies, we recorded neural activity in the dorsal premotor (PMd), dorsolateral prefrontal (dlPFC), and primary motor cortex (M1), as well as in the external and internal globus pallidus (GP), while monkeys performed a dynamic decision-making task in which sensory evidence about the choice changed continuously in each trial and decisions could be made at any time. During deliberation, PMd, M1, and dlPFC activity continuously reflected the evidence until a moment of commitment was reached, marked by a peak of activity in PMd. In contrast, GP activity did not reflect evidence at all and instead appeared to provide a ramping "urgency" signal that pushed the monkeys to decide as time elapsed. GP activity only became directionally tuned after the moment of commitment was reached in PMd (Thura & Cisek, 2014; 2017). Here, we model these phenomena with a recurrent attractor model in which dlPFC, PMd, M1, and GP are each represented by a pair of mutually inhibitory cells. The model dlPFC projects to PMd, PMd and M1 are reciprocally connected, and the GP forms a double-inhibitory loop with PMd. Evidence enters as input to PFC while a ramping urgency signal is the (inhibitory) input to GP. The activity in the network evolves over time as a competition between left vs. right-selective cells in each region, until one of each pair fully suppresses the other in a "winner-take-all" fashion. Key to the operation of the model are the sigmoidal functions that govern interactions between regions and mutual inhibition within each. In the cortical regions, these are relatively linear, allowing the sensory evidence to continuously shift neural activity. In contrast, the GP interaction function is flat for much of its range, and therefore only a strong signal from PMd will differentially engage tuning in GP. Once

such tuning begins to emerge, however, it produces a positive feedback with PMd that exaggerates the currently winning population and produces a point-of-no-return. The model reproduces many of the phenomena we observed in our recordings, including the presence of deliberation-related activity in cortex and its absence in the GP, the commitment-related peak in PMd and its absence in dlPFC, variations of activity with shifts of the speed-accuracy trade-off, and the delaying of commitment with cortical microstimulation. It also makes additional predictions for future experiments, including simultaneous stimulation and recording in cortical and subcortical regions.

Disclosures: D. Thura: None. **P.E. Cisek:** None.

Poster

606. Decisions: Action and Corticostriatal Circuits

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant P50NS091856

Title: Striatal glutamatergic signaling elicited by turn cues, but not stop cues

Authors: *M. SARTER[1], C. AVILA[2];
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Abstract: Moving across dynamic surfaces and obstacles requires the integration of extero- and interoceptive cues into movement selection and sequencing. Cortico-striatal projections are thought to transfer information about behaviorally significant, attended cues to the striatum to guide the striatal sequencing of movements. Here we recorded, at real time, dorsomedial (or "associative") striatal glutamatergic signaling in rats trained to walk a treadmill, to utilize one cue (tone or light) to turn prior to the treadmill restarting in reversed direction, and the other cue (light or tone) to stop prior to the treadmill restarting in the same direction. Glutamate-sensitive biosensors were implanted into the dorsomedial caudate nucleus for amperometric recordings of glutamate currents (5 Hz sampling rate). Animals were retrained to reach criterion, defined as 70% correct responses to both cues. Recordings were time-locked to task events (cue on- and offset, treadmill stops and starts). Trials were video-recorded for off-line analysis of the timing and type of turns and stops. Turn cues which elicited turns evoked glutamatergic signals with peak amplitudes (17.31±0.83 µM) robustly greater than turn cues which failed to elicit a turn (4.52±0.31 µM) and stop cues, successful or failed (1.72±0.82 µM). Indeed, peak amplitudes during failed turns and successful and failed stops were within 1 SD of currents seen while rats were walking in the absence of events. Glutamatergic transients during successful turn trials began to rise within 0.31±0.04 s and peaked within 1.27±0.20 s of cue onset. Treadmill stops

produced variable increases in glutamatergic activity. Turn cues - if successful - evoke a complex task shift, including reorienting of the body while maintaining balance, and the selection and sequencing of the steps needed to turn around - often before the treadmill stops. In contrast, stop cues do not need to elicit such a complex task shift; as rats await the treadmill stop. As we previously demonstrated that attentional cues involving task shifts elicit cortical cholinergic signaling (Howe et al., 2013), turn cue-evoked striatal glutamatergic activity may be secondary to this detection. Loss of cortical cholinergic afferents, observed in Parkinsonian fallers, therefore disrupts the transfer of behaviorally significant cues into the striatum, thereby revealing striatal impairments in the orchestration of complex movements. The forthcoming demonstration of attenuated striatal glutamatergic signaling in rats with cholinergic lesions will also support the hypothesis that turn cue-evoked glutamatergic signaling originates from cortico-striatal projections.

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Poster

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Support: NIH Grant HD084593

Title: M_1 muscarinic receptor agonist treatment differentially modulates dorsolateral and dorsomedial striatal glutamate during repetitive behaviors in the BTBR mouse

Authors: *M. E. RAGOZZINO[1], K. E. NISBETT[2], P. TENEQEXHI[3], R. OCAMPO[3], O. ATHNAIEL[3], W. S. MESSER, JR[4];
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Abstract: Recent findings from the laboratory indicate that acute treatment with the partial M_1 muscarinic receptor agonist, CDD-0102A attenuates elevated stereotyped motor behaviors (digging and self-grooming behavior) in the BTBR T+Itpr3^{tf}/J (BTBR) mouse. Past studies indicate that striatal circuitry is involved in the expression of stereotyped motor behavior and glutamate signaling in striatal circuitry contributes to the expression of stereotyped motor behaviors. Further, there is evidence that central muscarinic receptors can modulate glutamate transmission that has been proposed as a key neurotransmitter disrupted in ASD. The BTBR T+Itpr3^{tf}/J (BTBR) mouse serves as a polygenic model of autism displaying elevated repetitive motor behaviors. The present study determined whether systemic treatment with CDD-0102A, concomitantly attenuates repetitive motor behaviors and modifies striatal glutamate signaling in

BTBR and B6 mice. Prior to testing, an enzyme-based, glutamate biosensor was inserted into the dorsolateral or dorsomedial striatum of each mouse. After a 3-hour equilibration period, mice received an intraperitoneal injection of either saline or CDD-0102A 0.12 mg/kg. Twenty-minutes post-injection, nesting material was removed from a mouse's home cage. The time spent digging in bedding and self-grooming was measured for 20 minutes while changes in glutamate efflux were measured with a 1 second time resolution. Treatment with CDD-0102A significantly reduced self-grooming behavior in BTBR mice as observed previously. Change in glutamate efflux from both striatal subregions increased ~1500nM in BTBR compared to ~1000nM in B6 mice during digging and grooming behavior. CDD-0102A treatment reduced this magnitude glutamate change in the dorsomedial striatum to ~700nM, whereas it increased glutamate change in the dorsolateral striatum to ~1800nM during digging and grooming. The current findings suggest that glutamate transmission is dysregulated in BTBR mice, contributing to the elevated stereotyped motor behaviors. Moreover, activation of M_1 muscarinic receptors modulates glutamate signaling in the dorsal striatum in distinct ways based on subregion. Overall, the results suggest that treatment with a partial M_1 muscarinic receptor agonist may alleviate repetitive behaviors and restricted interests in part by modifying glutamate signaling.

Disclosures: **M.E. Ragozzino:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-Patent Holder on Muscarinic Agonists as Enhancers of Cognitive Flexibility. **K.E. Nisbett:** None. **P. Teneqexhi:** None. **R. Ocampo:** None. **O. Athnaiel:** None. **W.S. Messer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-Patent Holder on Muscarinic Agonists as Enhancers of Cognitive Flexibility.

Poster

606. Decisions: Action and Corticostriatal Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 606.16/BB22

Topic: H.01. Animal Cognition and Behavior

Support: CIHR, MOP-136916

Title: Functional characterization of cortical D2 dopamine receptor in adult mice

Authors: *C. QUINTANA, M. BEAULIEU;
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Abstract: The dopamine D2 receptor (DRD2) remains the principal target of antipsychotic drugs used for the management of schizophrenia and other psychotic disorders. DRD2 is highly expressed within the basal ganglia, more specifically the striatal caudate nucleus and the nucleus

accumbens and its general functions in this region are well understood. Early studies have been shown also the presence of DRD2 in several cortical areas. Cortical DRD2 has been at the centre of interest because of its involvement in regulation of cognitive, emotional and social behavioural processes and its regulation by antipsychotic drugs. However, further investigations of cortical DRD2 functions have been hindered by relatively low receptor expression, antibodies and ligand selectivity or limits of gene reporter systems. We used high sensitivity approaches to map cortical DRD2 expressing neurons and its projections. Results from these investigations revealed highly heterogeneous expression of DRD2 in principal neurons and various populations of interneurons which are not exclusively expressed on parvalbumin positive interneurons. Moreover, DRD2 expressing neurons do not always follow the characteristic pattern of projection of the region where they reside (Khlghatyan et al. 2018). We then explored the functional role of DRD2 in prefrontal cortex (PFC) by using somatic CRISPR/Cas9 mediated knockout of DRD2 to investigate the behavioral responses of DRD2 regulation in differential populations of PFC DRD2 expressing. Also, the involvement of DRD2 in different subtype of interneurons expressing these receptors was examined. Chemogenetic manipulation of DRD2 expressing neurons discriminates the role on its involvement of neuronal activity. Then, dopaminergic and glutamatergic modulation was investigated by microdialysis to highlight the implication of the regulation of PFC DRD2 in a network context. Cell type specific DRD2 knockout by using somatic CRISPR/Cas9 is a powerful tool to study the function of DRD2 in selective manner. This comprehensive analysis of PFC DRD2 expressing neurons provides indications for its functional implications in healthy and disease conditions and paves the way for a re-examination of cortical DRD2 functions, which could provide information about neuronal circuits involved in psychotic and mood disorders.

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Poster

606. Decisions: Action and Corticostriatal Circuits

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Topic: H.01. Animal Cognition and Behavior

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NARSAD Young Investigator Award
Inscopix DECODE Award
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Title: Prefrontal adrenergic and cholinergic fluctuations define global arousal after stress

Authors: J. CRESSY[1], A. P. KAYE[1], M. G. RAO[1], J. FENG[2], J.-H. KIM[4], S.-H. LEE[5], Y. LI[3], *A. C. KWAN[1];
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Abstract: Across the cerebral cortex, neurons increase their firing when the pupil dilates, reflecting a combination of adrenergic and cholinergic control of arousal. By recording only the pupil, the global arousal state of neurons throughout the cortex can be inferred. Precisely defining the neurochemical basis of dynamic changes in arousal may offer insight into the mechanisms of arousal dynamics and how they are altered by emotional states. Previous work performing calcium imaging of the axons of acetylcholine (ACh) and norepinephrine (NE) neurons in sensory cortex has suggested distinct timescales of modulation by these neurotransmitters. Direct measurement of ACh and NE concentration fluctuations in relation to the pupil have not been reported, and the existence of spontaneous fluctuations in NE concentrations is disputed. In order to better understand the role of neuromodulators in pupillary arousal, we employed recently developed fast, specific fluorescent G-protein coupled receptor sensors for norepinephrine and acetylcholine (Grab-NE2h and ACh4.3). Here we used a miniature, head-mounted microscope to image NE/ACh fluctuations in medial prefrontal cortex (mPFC). We observed distinct temporal relationships between the pupil and prefrontal NE/ACh concentrations. The relationship between pupillary arousal and neuromodulator fluctuations was differentially altered following exposure to an acute stressor (stress-enhanced fear learning). We performed microendoscope calcium imaging in mPFC and in order to understand neural ensemble coupling to arousal after stress. We propose a computational model for defining arousal states based on pupillary fluctuations, which may facilitate the understanding of their role in stress-related hyperarousal and arousal states at large.

Disclosures: **J. Cressy:** None. **A.P. Kaye:** None. **M.G. Rao:** None. **J. Feng:** None. **J. Kim:** None. **S. Lee:** None. **Y. Li:** None. **A.C. Kwan:** None.

Poster

606. Decisions: Action and Corticostriatal Circuits

Location: Hall A

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Program #/Poster #: 606.18/BB24

Topic: H.01. Animal Cognition and Behavior

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2019 NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation (to EA)
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Title: Prefrontal tDCS of the primate brain has diverse effects on LFP power spectra across cortical and subcortical areas

Authors: *S. E. SEIDL[1], C. RANGANATH[2], W. M. USREY[1], E. G. ANTZOULATOS[1];
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Abstract: Transcranial direct current stimulation (tDCS) is a promising brain-stimulation technique that is used to modulate cortical excitability. However, there is considerable controversy as to whether or how tDCS affects neural activity, and understanding the potential effects is complicated by variability in the location, polarity, and intensity of stimulation. The current study set out to test how tDCS affects neural activity at the population level, and to determine the effects of varying stimulation polarity and intensity. We performed simultaneous multi-electrode intracranial recordings of local field potentials (LFP) in awake non-human primates during prefrontal tDCS. We compared the effects of stimulation on LFP power spectra among frontal areas, including the lateral and caudal prefrontal cortex, anterior cingulate, and dorsal premotor cortex. We also compared frontal cortical regions to dorsal striatum. We find that the neurophysiological effects of tDCS are partly dependent on polarity (anodal/cathodal), intensity of stimulation (0.5-1.5mA), and electrode montage, but also vary in amplitude and direction of change across areas. These results suggest a non-homogeneous effect of tDCS across frontal brain regions and may help us understand the factors that shape the local effects of diffuse stimulation.

Disclosures: S.E. Seidl: None. **C. Ranganath:** None. **W.M. Usrey:** None. **E.G. Antzoulatos:** None.

Poster

606. Decisions: Action and Corticostriatal Circuits

Location: Hall A

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Program #/Poster #: 606.19/BB25

Topic: H.01. Animal Cognition and Behavior

Support: NIGMS SC1DA 034995
CUNY Dissertation Fellowship

Title: Chemogenetic inhibition reveals regional specificity of direct pathway control of action sequencing

Authors: *E. GARR[1], A. R. DELAMATER[2,1];
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Abstract: Humans and non-human animals engage in intricately woven and choreographed action sequences that are constructed from instrumental learning. There is broad consensus that the basal ganglia play a crucial role in the formation and fluid performance of action sequences. To investigate the role of the basal ganglia direct pathway in action sequencing, we virally expressed Gi-DREADDs in either the dorsomedial (DMS) or dorsolateral (DLS) striatum during and/or after action sequence learning in D1 Cre rats. There were four training groups: DREADD+CNO, DREADD+vehicle, mCherry+CNO, and mCherry+vehicle. When DREADDs were expressed in the DMS, CNO injections slowed sequence performance early in training but had no effect on sequence acquisition. When DREADDs were expressed in the DLS, CNO injections facilitated sequence performance and acquisition. A subsequent analysis revealed that quicker task acquisition was likely due to a greater number of sequences performed early in training, and hence more experience with the task. Outcome devaluation tests conducted after training revealed that target sequence rates were goal-directed across all training and testing conditions, as were sequence initiation latencies. Specifically, rats suppressed the rate of sequence performance when rewards were devalued, while also increasing the latency to initiate sequences. Sequence completion latencies were generally not sensitive to outcome devaluation, except in the case where DREADDs were expressed in the DMS and CNO was administered during training and test. This result suggests that the direct pathway via the DMS thwarts the development of goal-directed sequence completion. Gi-DREADD function was verified by comparing c-Fos counts between hemispheres in rats that expressed DREADDs unilaterally and received injections of CNO followed by a high dose of caffeine. Data from D2 Cre rats will also be presented.

Disclosures: **E. Garr:** None. **A.R. Delamater:** None.

Poster

606. Decisions: Action and Corticostriatal Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 606.20/BB26

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01 DA033123
University of Vermont College of Arts and Sciences

Title: Inactivation of the prelimbic cortex attenuates operant responding in both physical and behavioral contexts

Authors: *C. M. P. THOMAS, E. A. THRAILKILL, M. E. BOUTON, J. T. GREEN; Psychological Sci., Univ. of Vermont, Burlington, VT

Abstract: The recognition of the role of context in the control of both voluntary (instrumental) and involuntary (Pavlovian) behavior has led to major changes in the ways that we approach altering behavior, such as addiction therapies and dieting. Generally, research has focused on the importance of the physical context; however, we now know that context can include things such as cues, internal states, time, etc. Recently, evidence has suggested that when a sequence of two instrumental behaviors is required to earn a reinforcing outcome, the first response can be the "behavioral" context for the second response. That is, the second response is performed as a result of having just completed the first response, and the physical context, composed of the surrounding visual, tactile, auditory and olfactory stimuli, is important for the first response and not the second (Thrailkill, Trott, Zerr, & Bouton, 2016). The present experiments aimed to determine if the prelimbic cortex (PL), which we have previously shown to be important for the effect of the physical, training context on instrumental responses (Trask, Shipman, Green, & Bouton, 2017), is also important for behavioral contexts. Rats first learned a heterogenous behavior chain in which the first response (i.e. pressing a lever or pulling a chain) was cued by a discriminative stimulus and led to a second stimulus which cued a second response (i.e. pulling a chain or pressing a lever); the second response led to a sucrose reward. When the first and second responses were tested in isolation in the training context, pharmacological inactivation (baclofen/muscimol) of the PL resulted in a reduction of the first response only. But when the second response was performed in the "context" of the first response (i.e., as part of a behavior chain), PL inactivation reduced the second response. Overall, these results support the idea that the PL is important for mediating the effects of a training context on instrumental responding, whether that training context is physical or behavioral.
Thrailkill, E. A., Trott, J. M., Zerr, C. L., & Bouton, M. E. (2016). Contextual control of chained instrumental behaviors. *J Exp Psychol Anim Learn Cogn, 42*(4), 401-414.
Trask, S., Shipman, M. L., Green, J. T., & Bouton, M. E. (2017). Inactivation of the Prelimbic Cortex Attenuates Context-Dependent Operant Responding. *J Neurosci, 37*(9), 2317-2324.

Disclosures: C.M.P. Thomas: None. **E.A. Thrailkill:** None. **M.E. Bouton:** None. **J.T. Green:** None.

Poster

606. Decisions: Action and Corticostriatal Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 606.21/BB27

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant RO1 DA033123

Title: Separating goal-directed action from habit: Role of the context in which taste aversion learning occurs in creating the reinforcer devaluation effect

Authors: *M. E. BOUTON[1], S. ALLAN[1], A. TAVAKKOLI[2], M. STEINFELD[1], E. THRAILKILL[1];
[1]Psychological Sci., Univ. Vermont, Burlington, VT; [2]Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: Goal-directed actions and habits are two types of instrumental behavior that can be distinguished with reinforcer devaluation methods. For example, after instrumental learning, the reinforcer can be devalued by conditioning a taste aversion to it before the instrumental behavior is tested in extinction. If responding is suppressed by devaluation, it is considered a goal-directed action; if responding is not suppressed, it is considered a habit. Here we show that the *context* in which aversion conditioning occurs influences the reinforcer devaluation effect. In all experiments, female Wistar rats (n = 8) first received brief lever-press training (120 response-outcome pairings on a VI 30-s reinforcement schedule) that earlier research indicated would produce action. In Experiment 1, Paired rats then received pairings of the pellet reinforcer and ip injections of LiCl in either the operant chamber (pellets presented to the food cup on a VT 30-s schedule) or in in the home cage (pellets presented in a dish). Unpaired controls received the LiCl and pellet exposures in either context, but on separate days. When lever pressing was tested in extinction in the operant chamber, it was suppressed if aversion conditioning had occurred there, but not in the home cage. In the latter condition, the Paired and Unpaired groups responded equivalently. Experiment 2 replicated the result and found that an opportunity to consume the home-cage-averted pellets in the operant chamber before testing did not cause the devaluation effect to emerge. Experiment 3 found the same results as Experiment 1 using counterbalanced contexts provided by operant chambers with different odors, visual cues, floors, and locations in the lab. Aversion conditioning in either context involved presenting pellets to the food cup on the VT 30-s schedule. Physical environment, and not mode of pellet delivery, is thus a factor. The results suggest that a goal-directed action can be mistaken for habit if taste aversion conditioning occurs in a different context. The animal evidently encodes the context in which the reinforcer occurs in its representation of the goal. The fact that taste aversion always transferred across contexts, whereas the devaluation effect did not, was especially interesting.

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Poster

606. Decisions: Action and Corticostriatal Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 606.22/BB28

Topic: H.01. Animal Cognition and Behavior

Support: NIH/IRP

Title: A signal for the bayesian update of a learned preference in the macaque prefrontal cortex

Authors: *R. BARTOLO, R. C. SAUNDERS, A. R. MITZ, B. B. AVERBECK;
Lab. Neuropsychology, 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. Knowledge about environmental statistics allows for increased updating flexibility. The primate prefrontal cortex (PFC) integrates information carried by reward circuits and has also been proposed as an integrator of new information and previous knowledge. Thus, the present study explores the PFC computations related to updating current beliefs in multifaceted environments. We conducted high-channel count single-unit simultaneous 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. By 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 (WHERE blocks) at which the images randomly appeared 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. Within each block, reward contingencies were reversed at a randomly defined trial within a fixed interval (trials 30-50), requiring the animals to reverse their choice preference. Monkeys were familiar with the existence of two possible block types and that a reversal would occur within each block. Bayesian modeling of the monkeys' choices allowed us to estimate posterior probability distributions for choice reversal across trials, revealing that they used the prior knowledge to detect reversals and quickly update their choice preferences. We found that populations of PFC neurons deliver a signal that peaks sharply during the trial at which the monkey reversed its behavior with a magnitude that is inversely related to the dispersion of the reversal probability distribution. Furthermore, this signal starts to develop after the outcome of the trial before the monkey's reversal. This finding is consistent with model-based/meta-learning processes that have been previously attributed to the PFC. In addition, at the beginning of each block we found a signal that gradually decreased across trials, consistent with the gradual build-up of new information that characterizes model-free learning processes.

Disclosures: R. Bartolo: None. **R.C. Saunders:** None. **A.R. Mitz:** None. **B.B. Averbeck:** None.

Poster

606. Decisions: Action and Corticostriatal Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 606.23/BB29

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant ZIA MH002928-01

Title: Dopamine signals in ventral striatum code reward prediction errors but not cue values in reinforcement learning

Authors: *H. TANG, V. COSTA, R. BARTOLO, A. MITZA, M. ELDRIDGE, B. AVERBECK;
NIH, NIMH, Bethesda, MD

Abstract: Reinforcement learning (RL) refers to the behavioral process of learning from experience to make better choices in the future. Dopamine appears to play a well-known role in RL, coding temporal difference reward prediction errors. However, most of the work on dopamine has focused on tasks that use Pavlovian paradigms and many of the experiments have not examined learning in choice tasks. To examine the role of dopamine in learning in the context of choice, we trained a monkey on a two-armed bandit reversal learning task and measured dopamine signals in the ventral striatum using the genetically encoded dopamine indicator dLight and photometry. In the task, animals repeatedly learned to associate either actions or objects with rewards. At the beginning of each block, we introduced two new visual stimuli that the animal had never seen before. Each block was either a What block, where rewards were associated with images, or a Where block, where rewards were associated with locations. The block type was not cued. The animal had to learn by trial-and-error whether it was a What block or a Where block. There was also a choice-outcome reversal in the middle of the block, which allowed us to examine changes in values for actions or objects. We found that dopamine coded robust RPEs at the time of reward. The dopamine signal was linearly correlated with the positive RPEs but not negative RPEs. All negative RPEs were encoded with a single amplitude change. Furthermore, we found no responses to the cues, except on the first trial of each block, when a new pair of cues was introduced. These results reveal that dopamine signals in ventral striatum code RPEs at the time of reward during learning, consistent with previous studies. However, we do not find cue related value coding at the time of choice. It is possible that cue related dopamine signals develop on a much slower time-scale than learning, which we will examine in future studies.

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Poster

606. Decisions: Action and Corticostriatal Circuits

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

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Topic: H.01. Animal Cognition and Behavior

Support: NIMH Grant MH106435
NIMH Grant MH045573

Title: Quantification of heterogeneous afferent connections across the ventrolateral prefrontal cortex: Functional implications

Authors: *L. R. TRAMBAIOLLI[1], W. TANG[1], S. N. HABER[2];
[1]McLean Hosp. - Harvard Med. Sch., Belmont, MA; [2]Univ. of Rochester, Rochester, NY

Abstract: Human neuroimaging studies report the existence of a rostro-caudal organization of cognitive control processes across the lateral prefrontal cortex (LPFV). The ventral portion of the LPFC (VLPFC) is large (containing BA 44, 45 and 47) and is involved in several functions relevant to cognitive control, such as sensory integration, memory retrieval, stimulus-outcome estimation, and motor inhibition. The aim of this study was to evaluate this rostro-caudal organization using the precision of quantitative neuroanatomy.
We quantified the number of labeled cells in each frontal cortical area following retrograde tracer injections into different VLPFC areas. These values were then converted in percentage scores, to represent the connectivity strength. Then, we performed a correlation clustering analysis, where the inputs strengths from pairs of injections were compared using Pearson's correlation.
All VLPFC sub-regions are highly interconnected. However, there were two main clusters of injection sites based on their inputs from other frontal cortical areas: 1. a rostral cluster composed by injections in areas 45 and 47L; and 2. a caudal cluster including areas 44 and 47L. The rostral vlPFC has strong connections from the orbitofrontal cortex (OFC) and dorsal portion of the LPFC (DLPFC), areas related to goal-directed memory retrieval. The caudal cluster receives strong inputs from the premotor cortex and the frontal eye field (FEF). This suggests that the caudal vlPFC is involved in monitoring both motor behavior and attentional focus. Interestingly, area 47L had the greatest input from the ACC. Thus, we postulate that the information from both clusters is combined in 47L with inputs from the ACC to monitor conflicting information and, consequently, to start motor inhibition or reflexive reorienting behaviors.
Although preliminary, this study adds to the existing imaging literature by using the precision of anatomical methods to describe the rostro-caudal organization of vlPFC connections. The understanding of the VLPFC organization is crucial to identify future targets for invasive or non-invasive psychiatric therapies.

Disclosures: L.R. Trambaiolli: None. **W. Tang:** None. **S.N. Haber:** None.

Poster

606. Decisions: Action and Corticostriatal Circuits

Location: Hall A

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Title: A connectional hub in the rostral anterior cingulate cortex links areas of emotion and cognitive control

Authors: *W. TANG[1], S. JBABDI[2], Z. ZHU[3], M. COTTAAR[2], G. GRISOT[4], J. F. LEHMAN[3], A. YENDIKI[4], S. N. HABER[3];
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Abstract: The rostral anterior cingulate cortex (rACC) sits at the crossroads of the brain networks that are associated with emotion, cognition and executive control. An important question is how the composition of inputs to the rACC supports its multiple functional roles. One possibility is that information processing changes sequentially across subregions within the rACC, from emotion/motivation in subregions close to the subgenual ACC, to cognition at the center of the rACC, and then to executive control in subregions close to the dorsal ACC. Alternatively, different functional processing may be integrated in a central location, or hub. Hubs are nodes of a network that have unusually high connectivity to other nodes (degree-centrality) and high connectivity to other hubs (eigenvalue-centrality). Networks in this study are based on anatomical connections, which allows for measurement of degree-centrality only. We thus define the hub according to its high degree of inputs and its position in the network for cross-domain integration.
We investigated afferent inputs from all areas in the frontal cortex (FC) to different subregions in the rACC. Using retrograde tracing in macaque monkeys, we found that the projection from different FC regions varied across injection sites in strength, following different spatial patterns. Importantly, a site at the rostral end of the cingulate sulcus showed strong inputs from many

areas in diverse FC regions. Moreover, it was at the integrative conjunction of three projection trends across sites. This site marks a connectional hub inside the rACC. Tractography with monkey diffusion magnetic resonance imaging (dMRI) located a similar hub region comparable to the tracing result. Applying the same tractography method to human dMRI data, we demonstrated that a similar hub can be located in the human rACC.
Based on the FC areas sending convergent inputs to the hub, dysconnectivity with the hub may be involved in the imbalance between goal directed control, emotion and higher cognition in various disorders. Major depression disorder (MDD) and obsessive-compulsive disorder (OCD) both show treatment response in the rACC activity. The distinction in their pathophysiology lies in the type of networks involved: MDD engages the networks for self-reference and cognitive control, while OCD engages those for reward-driven and goal-directed behaviors. The hub connects a majority of FC areas involved in the above networks, which makes it a site prone to damage in both disorders. The precise pattern of its anatomical connections provides important information for testing the disorder-specific disconnections.

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Poster

607. Human Long-Term Memory: Encoding and Retrieval III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 607.01/BB32

Topic: H.02. Human Cognition and Behavior

Support: NSF Grant BCS-1539361 awarded to JDP and EAK

Title: Effects of cortisol reactivity and REM theta activity on emotional memory consolidation

Authors: *S. Y. KIM[1], S. M. KARK[2], R. T. DALEY[2], S. E. ALGER[1], E. A. KENSINGER[2], J. D. PAYNE[1];
[1]Univ. of Notre Dame, Notre Dame, IN; [2]Boston Col., Chestnut Hill, MA

Abstract: Sleep and stress independently have been shown to benefit emotional memory consolidation. In particular, theta oscillations (4-7 Hz) during rapid eye movement (REM) sleep have been linked to coherence in an emotional memory network and enhanced emotional memory. Here, we tested the hypothesis that pre-encoding stress exposure and theta power during REM sleep would interact to predict memory for emotional information. Participants underwent a psychosocial stressor (the Trier Social Stress Task; n = 32) or a comparable control task (n = 32) prior to encoding. Task-evoked cortisol reactivity was assessed by salivary cortisol rise from pre- to post-stressor. Participants in the stress condition were categorized as high or low cortisol responders via median split. During encoding, participants studied 150 negative,

neutral, and positive images. All participants slept overnight in the lab with polysomnographic recording. The next day, they were given a surprise recognition memory task. As predicted, high responders exhibited greater cortisol reactivity relative to both low responders ($t(15.80) = 6.14$, $p < 0.001$) and controls ($t(17.36) = 5.67$, $p < 0.001$). For high responders, REM theta significantly predicted memory for emotional information, specifically for positive items ($b = 0.15$, $R2 = 0.34$, $p < 0.05$). Notably, for low responders and controls, there was no relationship between theta and memory of any valence. These findings provide initial evidence that events occurring at encoding, and accompanying changes in neuromodulators such as cortisol, and theta activity during REM sleep may interact to promote selective consolidation of emotional information during sleep.

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Poster

607. Human Long-Term Memory: Encoding and Retrieval III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 607.02/BB33

Topic: H.02. Human Cognition and Behavior

Title: Medial prefrontal cortex plays a causal role in selectively enhancing consolidation of emotional memories: A TMS-EEG study

Authors: *N. YEH[1], N. S. ROSE[1], J. D. KOEN[1], S. Y. KIM[1], E. A. KENSINGER[2], J. PAYNE[1]; [1]Univ. of Notre Dame, Notre Dame, IN; [2]Dept Psychol, Boston Col., Chestnut Hill, MA

Abstract: Emotional aspects of episodic memory are preferentially benefited at the expense of co-occurring neutral aspects. This is known as the emotional memory trade-off effect, which is enhanced over consolidation delays that include a period of sleep. Previous research implicates an association between retrieval-related activity in medial prefrontal cortex (mPFC) and memory for emotional (versus neutral) stimuli following a night of sleep. Moreover, sleep often exerts its strongest effects on gist-based memory, rather than recollection of specific details. However, it is not clear how mPFC activity during encoding interacts with consolidation processes to enhance emotional aspects of memories after a night of sleep. This study aimed to provide a causal link between mPFC activity during encoding and the enhancement of emotionally salient aspects of episodic memory. Healthy young adult participants incidentally encoded 128 scenes comprised of negative (e.g. snake) or neutral (e.g. chipmunk) objects placed on plausible neutral backgrounds (e.g. forest scene) while undergoing simultaneous TMS and EEG recording during a memory encoding phase. One group of participants ($N = 23$) received 2s trains of intermittent theta burst stimulation (iTBS) to the mPFC (i.e., experimental condition) whereas the other group ($N = 21$) underwent an identical iTBS protocol with a left motor cortex target (i.e., active

control condition). iTBS was conducted at 80% of active motor threshold. Recognition memory for the objects and backgrounds was assessed at two delays (i.e., 30 minutes, 24 hours). The test items included identical studied objects and backgrounds (same), similar but not identical to old items (similar), or entirely new items (foil). Consistent with our hypothesis, iTBS to the mPFC led to enhanced gist memory for negative objects following a 24 hour delay that included sleep compared to active control stimulation, despite equivalent false alarms rates and self-reported emotional ratings (i.e., arousal, valence). Because these findings did not emerge following a short 30 minute delay, they suggest that iTBS to the mPFC during encoding may interact with subsequent consolidation processes to selectively preserve the gist of negatively salient information.

Disclosures: N. Yeh: None. **N.S. Rose:** None. **J.D. Koen:** None. **S.Y. Kim:** None. **E.A. Kensinger:** None. **J. Payne:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 607.03/BB34

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant F32-AG-054204

Title: Neural representations underlying acquisition of category knowledge

Authors: *C. R. BOWMAN, D. ZEITHAMOVA;
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Abstract: Healthy memory function involves both the ability to remember details of specific past events and the ability to link across related events to create knowledge that generalizes to new situations. Both of these functions have been linked to the hippocampus, with substantial debate about how they relate to one another. Some have posited that generalization judgments involve joint retrieval of multiple individual episodes, and that better memory for specific instances leads to better generalization. Others have posited a trade-off between memory for individual events and formation of generalized representations, which may lead to poorer generalization when related events are coded more distinctly. In the present study, we aimed to test the relationship between encoding of individual items and subsequent generalization performance in a category-learning task. While undergoing fMRI, 31 subjects completed observational training where they learned to classify cartoon animals into two species. Following training, participants were tested on their ability to generalize category labels to new examples. Behavioral results showed generalization performance that was well above chance, but not as good as classification of old (training) items. Using representational similarity analyses, we

measured the strength of item representations during training as the neural pattern similarity for repetitions of the same item compared to pattern similarity for items in the same category. In the hippocampus, we did not find reliable item representations when averaging across the group. However, we found that individuals who showed item representations in the posterior hippocampus showed poorer subsequent generalization. Cortical regions showing significant item representations across the group included fusiform, lateral occipital and lateral parietal cortices. Lateral occipital and superior parietal cortices showed a similar pattern to the posterior hippocampus, with a numerically negative relationship between the strength of item representations and subsequent generalization. Other regions with item-specific representations (fusiform, inferior parietal) showed no evidence of a relationship between the strength of item representations and generalization. No region tested showed a positive relationship between the two measures. Together, results show that some regions can form highly specific representations without affecting later generalization. Elsewhere, including in the posterior hippocampus, there may be a trade-off between distinctive encoding of individual items and the subsequent ability to generalize.

Disclosures: C.R. Bowman: None. **D. Zeithamova:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

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Program #/Poster #: 607.04/BB35

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant F32-AG-054204

Title: Generalized memory representations emerge across paired-associate training

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Abstract: Memory studies typically focus either on memory for individual experiences (specificity) or the ability to link information across events (generalization). However, experiences in daily life are rarely separated into specificity vs. generalization tasks. Instead, we have to make different judgments based on the same experiences. Do we spontaneously extract generalized knowledge even when the task at hand demands specificity? We assessed behavioral and neural measures of memory specificity and generalization during a task where participants learned face-name associations. To create an incidental category structure, face stimuli were constructed as 50/50 blends of never-seen “parent” faces. Three parent faces were selected to determine category membership (family names Miller, Wilson, Davis) and blended with other parent faces to create multiple family members. Each blended face was assigned a unique first

name and participants were instructed to memorize the full name for each face while undergoing fMRI. Behavioral results showed that participants successfully remembered specific faces but were also able to generalize last names to new faces. Neural pattern similarity analyses were used to examine evidence for representations of individual faces (i.e. similarity for repetitions of the same face vs. faces within the same family) and representations of family categories (i.e. similarity for repetitions of faces within the same family vs. faces that share a parent but are from different families). Results showed evidence for representations of individual faces in occipital and parietal cortices early in training. These same regions, as well as frontal cortex, showed representations of family categories, but only later during training. Within the hippocampus, representations for individual faces predicted performance on measures of memory specificity but not generalization. These results demonstrate that multiple types of memory representations may form and coexist for the same experiences to support a range of decisions.

Disclosures: S.R. Ashby: None. **C.R. Bowman:** None. **D. Zeithamova:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

Location: Hall A

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Program #/Poster #: 607.05/BB36

Topic: H.02. Human Cognition and Behavior

Support: SNF Doc.CH grant P0BSP1_168917

Title: Eye fixation frequency affects visual episodic memory

Authors: *B. FEHLMANN, D. COYNEL, N. SCHICKTANZ, A. MILNIK, P. HOFMANN, L. GSCHWIND, A. PAPASSOTIROPOULOS, D. J. DE QUERVAIN;
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Abstract: Visual memories fundamentally depend on visual input. It is unclear, however, if eye fixation frequency during encoding affects memory strength. First, we identified individual memory-related scanning characteristics by collecting eye tracking data in a picture encoding task performed by 967 healthy subjects. We found a positive correlation between fixation frequency in semantically informative regions and subsequent free recall and recognition performance. fMRI results indicate a positive correlation of the number of such fixations with functional brain activation in regions related to vision and memory, including the medial temporal lobe. In a further experiment, we manipulated the visual scanning pattern in 64 subjects within a given exploration time. We thereby disentangled two distinct causal mechanisms underlying the exploration-memory relationship: While both increasing fixation frequency and the sampling of semantic regions positively affected free recall, only the latter affected passive recognition. Since successful recognition can be achieved by familiarity, the findings suggest

that eye fixation frequency during encoding visual information primarily affects episodic aspects of memory. Our results have important implications. First, they indicate the importance of measuring eye movements in visual memory studies. Second, altered scanning characteristics that are often observed in neuropsychiatric conditions may contribute to the memory deficits that are also frequently observed in these conditions.

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Poster

607. Human Long-Term Memory: Encoding and Retrieval III

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Topic: H.02. Human Cognition and Behavior

Support: the Medical Research Service of the Department of Veterans Affairs (5IK6CX001644), Award I01CX000359
National Institute of Mental Health Grant 24600

Title: Spared perception of the structure of scenes after hippocampal damage

Authors: *Z. J. URGOLITES[1,2], R. O. HOPKINS[5,6], L. R. SQUIRE[1,2,3,4];
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Abstract: To explore whether the hippocampus might be important for certain spatial operations in addition to its well-known role in memory, we administered two tasks in which participants judged whether objects embedded in scenes or whether scenes themselves could exist in 3D space. Patients with damage limited to the hippocampus performed as well as controls in both tasks. A patient with large medial temporal lobe lesions had a bias to judge objects in scenes and scenes themselves as possible, performing well with possible stimuli but poorly with impossible stimuli in both tasks. All patients were markedly impaired at remembering the tasks. Thus, the hippocampus appears not to be essential for judging the structural coherence of objects in scenes or the coherence of scenes. The results are in accord with earlier findings that the hippocampus is not needed for a variety of spatial tasks and emphasize the importance of the hippocampus for memory. Interestingly, other patients have sometimes been reported to be disadvantaged by spatial tasks such as the ones studied here, despite less hippocampal damage and milder memory impairment. It seems unlikely that these impairments are due to hippocampal damage itself.

Disclosures: **Z.J. Urgolites:** None. **R.O. Hopkins:** None. **L.R. Squire:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

Location: Hall A

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Program #/Poster #: 607.07/BB38

Topic: H.02. Human Cognition and Behavior

Support: NSF Grant 1633873

Title: Neural pattern similarity is moderated by age and subsequent memory in scene-selective but not face-selective cortical regions

Authors: *S. SROKOVA[1], P. F. HILL[1], J. D. KOEN[2], D. R. KING[1], M. D. RUGG[1];
[1]Ctr. for Vital Longevity, Univ. of Texas at Dallas, Dallas, TX; [2]Dept. of Psychology, Univ. of Notre Dame, Notre Dame, IN

Abstract: The aging brain is characterized by decreased selectivity and reduced functional specialization in category-selective cortical regions. These age differences in cortical selectivity have been proposed to play a causal role in cognitive aging. In this experiment, young and older adults underwent fMRI as they studied words paired with images of faces or scenes prior to a subsequent memory test. We employed multivoxel pattern similarity analysis to identify age differences in category-selective neural pattern similarity under the assumption that reduced cortical selectivity would be reflected in lower category-selective similarity. Using univariate analyses, we identified three scene-selective (Parahippocampal gyrus, Middle Occipital gyrus, Retrosplenial cortex) and four face-selective (Fusiform gyrus, Medial Prefrontal cortex, Precuneus, Medial temporal lobe) regions-of-interest (ROIs). The similarity index for a given ROI was operationalized as the difference between average trial-wise within-category and between-category correlations. We identified lower similarity indices in older adults for scene stimuli in all three scene-selective regions, but minimal evidence for age differences in similarity indices for faces in face-selective ROIs. The indices from the scene-selective ROIs were further analyzed as a function of age group and subsequent memory performance, where study items were binned according to whether or not the words went on to receive a source correct memory judgment for their associated image category (face vs. scene). A 2 (Age group) x 3 (Scene-selective ROIs) x 2 (Subsequent memory) ANOVA identified a significant 3-way interaction. This was driven by greater similarity indices for source correct trials relative to incorrect trials in younger adults, especially in retrosplenial cortex and middle occipital gyrus, while no such effects were evident in older adults. An analogous analysis with face-selective ROIs did not reveal moderating effects of age or subsequent memory on neural pattern similarity. These results suggest that older adults show less precise neural representations for scenes and that the moderating effects of age and subsequent memory are category- and regionally-specific.

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Poster

607. Human Long-Term Memory: Encoding and Retrieval III

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Program #/Poster #: 607.08/BB39

Topic: H.02. Human Cognition and Behavior

Support: NIA Grant R21AG054197
NIA Grant RF1AG039103

Title: Differential effects of age and task load on the neural correlates of retrieval monitoring revealed by modulation of univariate fMRI BOLD amplitude and functional connectivity

Authors: *E. D. HORNE, M. DE CHASTELAINE, M. D. RUGG;
The Ctr. for Vital Longevity and Behavioral and Brain Sci., Univ. of Texas At Dallas, Dallas, TX

Abstract: We investigated the impact of a dual task manipulation during associative retrieval on the neural and behavioral correlates of post-retrieval monitoring in a sample of 28 older (65-75 years) and 28 younger (18-30 years) adults. Participants completed an associative recognition task (intact/rearranged/new decision to word pairs) in the MRI scanner. Low (400 Hz) and high (900 Hz) pitch tones played continuously during retrieval, and participants alternated between ignoring tones during single task blocks and responding to occasional target tones during dual task blocks. Consistent with our pre-experimental predictions, older adults' associative memory performance was significantly lower under dual relative to single task conditions due to an elevated false alarm rate. Post-retrieval monitoring effects (difference in BOLD signal for test pairs judged rearranged vs intact) in bilateral dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) were attenuated for younger adults under dual relative to single task conditions. By contrast, older adults' monitoring effects were smaller than younger adults' during single task blocks, but were not significantly modulated by the dual task manipulation. We interpret these results as consistent with the CRUNCH model introduced by Reuter-Lorenz and Cappell (2008). Whereas dual task demands were required to deplete frontal resources supporting monitoring in younger adults, in older adults the mere requirement to ignore tones in single task blocks was seemingly sufficient to deplete resources otherwise available to support monitoring. Despite this age-related difference in the modulation of monitoring effects by the dual-task manipulation, psychophysiological interactions (PPI) analyses revealed age- and task-invariant increases in connectivity between left and right DPLFC and ACC and bilateral occipital cortex, and between the DLPFC and left intra-parietal sulcus. We interpret these latter findings as evidence that post-retrieval monitoring entails interactions both between prefrontal cortex and

posterior cortical regions participating in the representation of retrieved content, as well as between the different members of the 'fronto-parietal control network'. These inter-regional interactions appear to be relatively impervious to the effects of task-demands or age.

Disclosures: E.D. Horne: None. **M. De Chastelaine:** None. **M.D. Rugg:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 607.09/BB40

Topic: H.02. Human Cognition and Behavior

Support: NIA 2RF1AG039103

Title: Age-invariant, overlapping pre- and post-stimulus subsequent memory effects in dorsal medial prefrontal cortex

Authors: *E. S. LIU[1], J. D. KOEN[2], M. D. RUGG[3];
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Abstract: Decline in episodic memory performance with increasing age has been attributed in large part to ineffective encoding. Here, we asked whether age differences in the neural correlates of episodic encoding are evident in *pre-stimulus subsequent memory effects* (preSMEs) - differences in neural activity preceding the onset of a study item that are predictive of later memory performance. It has been proposed that preSMEs reflect differential engagement of preparatory processing in anticipation of the upcoming study item. In light of evidence that older adults are, in general, less likely to engage proactive processing, we predicted that preSMEs would be attenuated in older adults relative to young participants. Healthy young and older adults (Ns=28) underwent fMRI while performing a study task requiring one of two judgments (size or location) on images of objects. A pre-stimulus cue signaling the nature of the study judgment was presented prior to the study item. The cue-stimulus interval was jittered to allow deconvolution of pre- and post- stimulus activity. In a subsequent test phase outside the scanner participants performed a recognition memory test for the objects and, for any object judged old, a source memory test for the study task. A 2 (Age group) x 3 (correct subsequent source judgment, correct item judgment only, item missed) ANOVA and follow-up analyses identified a region of dorsal medial prefrontal cortex (dmPFC) where the pre-stimulus BOLD signal varied inversely with memory strength: lowest for items subsequently attracting a correct source judgment, intermediate for item correct only, and greatest for subsequently missed. This 'negative' preSME did not differ in magnitude between the age groups. Post-stimulus SMEs were evident in numerous regions; importantly, these included the same dmPFC region that

manifest the aforementioned preSME. This post-stimulus effect was negative, consistent with prior reports of negative SMEs in this region. These findings suggest that negative SMEs in the dmPFC onset prior to the presentation of a study item, and hence that the region might play a role in preparatory processes that facilitate encoding. Contrary to our prediction, the findings provide no evidence that these processes differ according to age.

Disclosures: **E.S. Liu:** None. **J.D. Koen:** None. **M.D. Rugg:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 607.10/BB41

Topic: H.02. Human Cognition and Behavior

Title: A phenomenological model of power-law forgetting

Authors: *A. GEORGIOU, M. KATKOV, M. TSODYKS;
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Abstract: Persistence of information with time in the brain, or in other words memory, is a necessary condition for higher cognitive abilities. Due to the state of the world being in constant flux, with its inherent uncertainty, the ability to discard no longer relevant information is equally important. The process of forgetting, i.e the transient nature of memory, is hypothesized to be essential for adaptive behavior. A number of experiments under the realm of psychology and neuroscience over the past hundred years have showcased that forgetting occurs in a power-law manner, reflecting the fact that the probability that a piece of information is retained, is a decaying function of its age. Most theoretical models of memory however, utilizing forgetful learning rules, like memory palimpsests, treat forgetting as a linear process in time, with older memories being more likely to be forgotten than newer ones, which is not compatible with power-law retention. We have devised a phenomenological model that encapsulates the statistics of forgetting observed experimentally which we solved analytically. It is an implementation of retroactive interference, where newly acquired memories disrupt already stored ones, based on the salience of incoming items, formalized as a numerical value. When an element is commited, it acts on older memories, discarding those that have a lower value. We can expand this notion into n-dimensions considering multiple axes of importance for each element, requiring the above rule to be true in every axis for an item to be forgotten. An analytic solution exhibits power-law forgetting with the prefactor depending on the number of dimensions. Furthermore, we conducted two-alternative forced choice recognition experiments utilizing Amazon's mTurk platform, thus ascertaining the compatibility of our model to experimental data. Participants were presented with a stream of words sequentially, and at random points during the trial they were asked to select between a lure word and one of the first twenty five words presented, in order to

establish the relationship between memory recognition and its age. The results show a retention curve that is closely approximated by the model, posing it as a valid candidate of a forgetting mechanism.

Disclosures: **A. Georgiou:** None. **M. Katkov:** None. **M. Tsodyks:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

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Topic: H.02. Human Cognition and Behavior

Support: EU-H2020-FET
EU-M-GATE 765549
Foundation Adelis

Title: Free recall of common facts

Authors: ***M. KATKOV**, M. NAIM, M. V. TSODYKS;
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: A classical way of studying human episodic memory is free recall of randomly assembled words, where participants are presented with a list of words and are requested to report as many words as they could. Many experimental studies highlighted the main characteristics of this phenomenon: recency, higher probability to recall recently presented words; primacy, better recall of words in the beginning of list; contiguity, tendency to recall in temporal proximity words that were presented in temporal proximity. It was also observed that the number of words recalled depends sub-linear with the list length. In order to understand the generality of these phenomena to different types of information rather than single words, we performed recall experiments with lists of short sentences expressing unrelated common facts. We took advantage of the Amazon Mechanical Turk (R) platform, to perform experiments over the internet, with the pool of about 300 facts assembled specifically for this project. Interestingly, the number of facts recalled was similar to those of random words, for same list length. We also observed similar contiguity curve for facts and words. However, we observed that there was practically no recency effect in the recall of facts. Our results suggest that facts operate as units in free recall similar to words.

Disclosures: **M. Katkov:** None. **M. Naim:** None. **M.V. Tsodyks:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 607.12/BB43

Topic: H.02. Human Cognition and Behavior

Support: KL2TR000440

Title: Epilepsy patients with verbal memory deficits demonstrate differential transcript expression in the temporal lobe compared to those with intact memory

Authors: *R. M. BUSCH[1], L. YEHIA[1], M. SEYFI[1], I. BLUMCKE[2], B. HERMANN[3], I. NAJM[1], C. ENG[1];
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Abstract: Temporal lobe epilepsy (TLE) is the leading cause of seizure disorders in adults and is associated with a high risk for memory deficits. While a host of demographic and disease-related variables have been associated with episodic memory dysfunction in TLE, a substantial proportion of the variance in memory performance remains unexplained. The objective of this pilot study was to compare the brain transcriptome between patients with and without verbal memory impairments to identify genes and signaling networks important for episodic memory. We performed RNA-seq of total RNA extracted from brain tissues originating from 23 adults who underwent dominant temporal lobectomy for treatment of pharmacoresistant epilepsy. Patients were classified as having “reduced” or “intact” memory based on preoperative performance on measures of list learning and story recall. To control for potential effects of *APOE ε4* or *APOE ε2* on memory, only those homozygous for the *APOE ε3* allele were included. The two memory groups were well-matched on demographic and disease-related variables. Following standard quality control, we performed differential expression analysis using NOISeq-sim algorithm. We identified differentially expressed genes (DEGs) between the memory groups followed by pathway enrichment analyses using the clusterProfiler R package. Overall, we identified 135 unique DEGs between patients with and without memory impairments. The majority of DEGs (96 of 135; 71%) were underexpressed in the memory impaired group compared to the intact memory group. Gene ontology (GO) enrichment analyses identified multiple biological processes relevant to neuronal function, including cell growth, neuronal apoptosis, microtubule polymerization or depolymerization, and axonal transport of mitochondria. Similarly, GO cellular components were enriched for neurological and immune-related terms, including dendritic spine, neuron spine, neuron projection cytoplasm, axon cytoplasm, glial cell projection, and MHC protein complex. Our observations indicate that TLE-

associated memory function/dysfunction may be influenced by differences in gene expression profiles within the temporal lobe, particularly in genes implicated in neuronal-related pathways.

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Poster

607. Human Long-Term Memory: Encoding and Retrieval III

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 607.13/BB44

Topic: H.02. Human Cognition and Behavior

Support: CUNY Doctoral Student Research Grant

Title: Effects of HD-tDCS on item and associative encoding are modulated by individual differences in self-reported side effects of stimulation

Authors: *A. M. GAYNOR[1], E. F. CHUA[2,3];
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Abstract: Previous research has shown that the dorsolateral prefrontal cortex (DLPFC) plays a role in associative encoding, whereas the anterior prefrontal cortex (aPFC) is involved in the subjective confidence in one's own encoding success. It remains unknown whether these regions differ in their causal contributions to subjective and objective encoding for items as compared to associations. We applied 2mA of high-definition transcranial direct current stimulation (HD-tDCS) over the aPFC, DLPFC, and sham stimulation while subjects studied 100 word pairs. For each pair, subjects also made a Judgment of Learning (JOL), a memory monitoring judgment in which subjects judge their ability to accurately recognize each word pair at later test. Twenty-four hours later, subjects were tested on 150 pairs of words that were identified as "intact", "rearranged", or "new". Repeated measures ANOVAs on preliminary data (n=14) showed no effect of stimulation on the magnitude or accuracy of JOLs, and no significant effects on corrected associative or item recognition. Separate analyses of the side effects of stimulation (e.g. scalp tingling, burning sensations, and trouble concentrating) showed greater intensity of scalp sensations, but less trouble concentrating during aPFC stimulation compared to other stimulation conditions. To control for this, multilevel models with individual differences in head size, gender, age, and side effects of stimulation showed effects of stimulation on memory. Specifically, for associative memory, aPFC stimulation impaired associative encoding relative to sham ($p<0.01$) and DLPFC stimulation ($p<0.05$), whereas for item memory, both aPFC and DLPFC stimulation impaired encoding of individual items compared to sham ($p<0.001$). Scalp tingling, burning sensations, headache, and trouble concentrating during encoding also predicted

both associative and item recognition; greater intensity of these side effects was associated with poorer associative recognition performance under sham and DLPFC stimulation, but greater burning, tingling, and scalp pain were associated with better associative recognition following aPFC stimulation. For item recognition, greater intensity of side effects was associated with better memory for items across all stimulation conditions, but the correlation between side effects and recognition was strongest under aPFC stimulation. These results suggest HD-tDCS over the aPFC impaired encoding, but stimulation-related side effects may have induced a cognitive placebo effect whereby subjects' overall encoding under aPFC was similar to the DLPFC and sham sessions, perhaps due to increased arousal and attention.

Disclosures: A.M. Gaynor: None. **E.F. Chua:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

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Program #/Poster #: 607.14/BB45

Topic: H.02. Human Cognition and Behavior

Support: NRF-2019R1A2C1009674

Title: The subsequent memory effects of associative memory before and during memory encoding period of scalp EEG

Authors: *D. KIM[1], W. JEONG[3,4], J. KIM[2], C. CHUNG[1,3,4];
[1]Dept. of Brain and Cognitive Sci., [2]The Res. Inst. of Basic Sci., Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Dept. of Neurosurg., Seoul Natl. Univ. Hosp., Seoul, Korea, Republic of; [4]Neurosci. Res. Inst., Seoul Natl. Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: *Introduction:* The previous studies have shown that the success or failure of the memory can be predicted by the brain state either before or during memory encoding period. These brain states which called subsequent memory effects (SMEs) have been widely studied using fMRI modality. Those previous studies reported that neocortical brain areas (e.g., posterior parietal cortex, PPC) in addition to medial temporal areas contribute to successful episodic memory encoding. However, due to the low time resolution of fMRI, SMEs change over time can not be investigated. Here, we investigated the SMEs of the word and scene association task before or during the of the encoding period using scalp-EEG.
Methods: Eleven right-handed healthy subjects (4 females, 23 to 31 years old) were recruited. During the encoding period, the subjects were instructed to associate word-picture pairs by generating mental images. During the retrieval period, subjects were asked to recall the word cued by the scene presented. We investigated the differences in EEG activity during pre-stimulus period and encoding period between subsequently remembered and forgotten events through the

time-frequency analysis (alpha, beta and theta band).
Results: In the pre-stimulus period (-200~0 ms), there was stronger beta (14-30 Hz) power over electrodes in right PPC to subsequently remembered stimuli than to those forgotten. In the memory encoding period (200~400 ms), more increased theta (3-7 Hz) power over frontal midline and electrodes in right PPC was observed in remembered stimuli than forgotten stimuli.
Conclusions: In the present study, we found cortical contribution of successful episodic memory period using scalp-EEG. Interestingly, similar to the fMRI results, we also found the contribution of PPC on successful memory encoding process. Specifically, we found that beta power was increased before encoding period, which could reflect inhibition of task irrelevant information, and theta power was increased during encoding period, which is common feature of SMEs. In the future, our results could be used to prediction of memory success by utilizing SMEs according to the memory period, especially activities in PPC or midfrontal areas.

Disclosures: D. Kim: None. **W. Jeong:** None. **J. Kim:** None. **C. Chung:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

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Program #/Poster #: 607.15/BB46

Topic: H.02. Human Cognition and Behavior

Title: Contributions of semantic relatedness, distinctiveness, and emotion to enhanced emotional memory: An event-related potential study

Authors: V. C. ZARUBIN[1], T. K. PHILLIPS[2], E. G. ROBERTSON[2], *K. R. MICKLEY STEINMETZ[2];
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Abstract: Traditionally the enhanced emotional memory (EEM) effect has been explained by emotionality leading to enhanced processing for emotional stimuli. Some literature, however, suggests that the relative difference in memory between emotional and neutral stimuli may actually be due to an interruption in processing neutral stimuli when presented with emotional stimuli (Watts, Burrato, Brotherhood, Barnacle, & Schaeffer, 2014). Further, instead of emotion itself, confounding factors such as semantic relatedness or distinctiveness of emotional items may have a significant role in leading to these memory enhancements (Talmi, Luk, McGarry, & Moscovitch, 2007). The present study sought to examine whether the reduction in event related potential (ERP) differential memory (Dm) activity was best accounted for by emotion or by the inherent semantic category of emotional stimuli. To do so, ERPs were recorded while participants were presented with three types of images: negative images, semantically related neutral images, and unrelated neutral images. These images were presented in either mixed lists, composed of all three image types mixed together, or pure lists, composed of one type of image

per list. Immediate recall performance was used to bin images into remembered and forgotten categories for Dm analysis of ERPs. Behavioral results indicated that negative images were best recalled overall. Further, semantically related neutral images were better remembered than unrelated neutral images. ERP results help to explain this behavioral effect: negative and unrelated neutral in mixed lists had a stronger Dm effect than in pure lists, suggesting that an item's distinctiveness in mixed lists provides an advantage at encoding. In contrast, related neutral images, though recalled better than unrelated neutral images, showed a diminished Dm effect. Thus, while distinctiveness influences encoding, relatedness may be more likely to exert its influence at retrieval.

Disclosures: V.C. Zarubin: None. **K.R. Mickley Steinmetz:** None. **T.K. Phillips:** None. **E.G. Robertson:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 607.16/BB47

Topic: H.02. Human Cognition and Behavior

Support: 5K01MH111991-03
NARSAD Young Investigator Award

Title: Novelty influences coupling across multiple learning systems during post-task rest

Authors: *M. R. FAIN[1], I. O'SHEA[2], I. C. BALLARD[3], L. ELLMAN[1], V. P. MURTY[4]; [1]Temple Univ., Philadelphia, PA; [2]Northeastern Univ., Boston, PA; [3]Helen Wills Neurosci. Inst., Univ. of California, Berkeley, Berkeley, CA; [4]Psychology, Dr., Philadelphia, PA

Abstract: Fundamental to adaptive behavior is the ability to detect, learn about, and respond to change in the environment. Hippocampal novelty responses signal environmental change and predict neural and behavioral adjustments to it. Rodent work has shown that novelty can induce dopamine release (Lisman and Grace, 2005), a neuromodulatory system known to facilitate plasticity across multiple learning systems. Dopamine has been shown to enhance plasticity in both the procedural learning system centered on the dorsal striatum and the episodic learning system centered on the hippocampus (Shohamy and Adcock, 2010). However, the extent to which novelty facilitates interactions across these learning systems remains relatively unknown. Prior work suggests that the dorsal striatum and hippocampus are competitive during learning, thus proposing that novelty may facilitate an inverse relationship across these systems. Alternatively, novelty can simultaneously engage both the dorsal striatum and hippocampus, suggesting that novelty facilitates a positive relationship across these regions. To arbitrate between these hypotheses, we collected fMRI data during which participants completed a

resting-state scan, and then performed a target-detection task wherein participants were exposed to novel and previously familiarized trial-unique stimuli. Following this task, participants completed a post-novelty resting-state scan (N=12). We compared changes in functional coupling between the hippocampus and dorsal striatum during rest periods before and after exposure to novelty. We found a trend towards greater functional coupling between the hippocampus and dorsal striatum during post-novelty rest compared to pre-novelty rest ($p<0.06$). These preliminary findings suggest that there is a facilitation of information processing across the dorsal striatum and the hippocampus following exposure to novelty.

Disclosures: **M.R. Fain:** None. **I. O'Shea:** None. **I.C. Ballard:** None. **L. Ellman:** None. **V.P. Murty:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 607.17/BB48

Topic: H.02. Human Cognition and Behavior

Title: Differential effects of visuospatial interference on consolidation of emotional and neutral episodic-like memory in virtual reality

Authors: *S. FLASH, S. BARHOUM, J. DENGLER, K. SHAH, V. CASTILLO, G. HANSON GOTTHARD;
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Abstract: The working memory capacity theory of memory consolidation proposes that visuospatial interference tasks (VSI; e.g., Tetris) can disrupt memory consolidation by overloading working memory stores. Virtual reality (VR) was used to examine working memory capacity theory in the context of emotional and neutral information. VR is a valuable tool because it provides users with a highly immersive experience that produces more realistic episodic-like memories (Sauzeon et al., 2012). Experiment 1: Participants (n=68) consisted of undergraduate students from Muhlenberg College. Groups played either Job Simulator (n=40; emotionally-stimulating auto mechanic role playing game - PlayStation 4 VR system) or Venice (n=28; emotionally-neutral gondola tour in Venice during which a tour guide describes scenes along a canal - Oculus Rift VR system). Following the game, participants spent 10 minutes completing a visuospatial interference task (n=34; i.e., the computer game Tetris) or a control task (n=34; i.e., basic multiplication problems). Participants then completed a free recall test, a cued recall test, and a recognition test. Significant differences were observed for free recall [$F(3,64)=6.7$, $p=.001$, partial $\eta^2=.24$]. The Tetris/Job Simulator group had significantly lower free recall scores than Tetris/Venice ($p=.002$], Control/Job Simulator ($p=.006$), and Control/Venice ($p<.001$). No significant differences were observed between groups on cued

recall [F(3,64)=1.1, p>.05] or recognition [F(3,64)=0.1, p>.05].
Experiment 2: Participants (n=17) consisted of undergraduate students from Muhlenberg College. Groups played Ritchie's Plank Experience (n=17; highly emotionally-stimulating game in which participants ride an elevator to the top of a tall building and walk out onto a plank - Oculus Rift VR system). Following the game, participants spent 10 minutes completing a VSI task (n=8; i.e., the computer game Tetris) or a control task (n=9; i.e., basic multiplication problems). Participants then completed a free recall test, a cued recall test, and a recognition test. Tetris produced marginally significant reductions in free recall [t(15)=-2.02, p=.06, d=.97] and statistically significant declines in recognition [t(15)=-2.8, p=.014, d=1.34]. No differences were observed for cued recall [t(15)=-.3, p>.05]. The present studies demonstrated that a VSI task (i.e., Tetris) was able to decrease free recall of emotional episodic-like memory but not neutral episodic-like memory. Less impairments were seen in tasks that provided cues (e.g., cued recall), which may support a retrieval failure interpretation (Gisquet-Verrier et al., 2015).

Disclosures: S. Flash: None. **S. Barhoum:** None. **J. Dengler:** None. **K. Shah:** None. **V. Castillo:** None. **G. Hanson Gotthard:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 607.18/BB49

Topic: H.02. Human Cognition and Behavior

Title: Oscillatory activity supports contextual binding in young and old adults

Authors: *A. E. KARLSSON, M. C. SANDER;
Ctr. for Lifespan Psychology, Max-Planck Inst. For Human Develop., Berlin, Germany

Abstract: Reinstatement of the learning context during retrieval boosts memory performance. Although old adults benefit from context reinstatement, they have more difficulties retrieving the specific item-context association as compared to young adults. To better understand these age differences, we investigated the neural mechanisms of memory formation for item and context information in young (n=49, 20-30 years) and old (n=43, 65-75 years) adults. Participants were familiarized with pictures of objects and outdoor scenes in a pre-learning fMRI session. Then, while EEG data was recorded, participants performed an item-context binding task during which they imagined using the presented object in the context depicted by an outdoor scene shown as background. Subsequently, all objects were presented again in a post-learning fMRI session. Finally, in a surprise memory test, participants discriminated between old and new objects. Old objects were either presented on the same background as during the learning phase or on a different background. New items were presented either on an old or a new background. Participants had to judge whether the item was old or new followed by a judgment on whether

the item-context pairing was old or new. We computed corrected recognition scores to assess the effect of context reinstatement on item retrieval. Item memory performance did not differ between age groups, and both groups benefited from context reinstatement. However, as predicted, pair memory was reduced in old compared to young adults. Time-frequency analysis of the EEG data was performed to investigate the neural underpinnings of contextual memory formation. A positive subsequent memory effect (SME) was found in the theta band between 0-600 ms and a negative SME in the alpha band between 0-3000 ms. Whereas the theta SME may reflect the associative strength between an item and its context, alpha band SME may indicate the depth of elaboration contributing to successful memory formation. Accordingly, only the theta SME varied by later context reinstatement. These effects were larger in older than in younger adults. We are currently relating the behavioral context effects with the neural SME and learning-related changes in neural patterns of item representations in the hippocampus, as measured with fMRI. Thus, we will provide novel insights into the neural substrates of contextual binding in young and old adults.

Disclosures: **A.E. Karlsson:** None. **M.C. Sander:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 607.19/BB50

Topic: H.02. Human Cognition and Behavior

Title: Reward motivation during encoding influences free recall accuracy and dynamics

Authors: *E. A. EBERTS[1], B. KATERMAN[1], S. DUBROW[2], V. P. MURTY[1];
[1]Psychology, Temple Univ., Philadelphia, PA; [2]Psychology, Univ. of Oregon, Eugene, OR

Abstract: Reward motivation reliably influences memory encoding to benefit the storage of high value information in long-term memory (Murty & Adcock, 2017). Previous investigations of reward memory have mostly focused on accuracy, but the influence of reward on memory organization remains unclear. There are two contexts by which information is typically organized: temporal (associations formed during a learning episode for items studied nearby in time) and semantic (long-standing associations between word meanings). This investigation aimed to characterize how reward motivation influences free recall accuracy as well as the use of temporal and semantic contexts for memory organization. In the current study, 59 participants learned pure word lists that were associated with either high or low reward for successful memory. Memory was tested using a free recall paradigm immediately and after 24 hours. Here, we report the 24-hour data. Results show better long-term recall for high value versus low value words ($p < .01$), suggesting that individuals have greater access to valuable information during retrieval. There was also a trend towards greater temporal clustering among high value words (p

= .095), suggesting that individuals re-instate the original encoding experience to structure the retrieval of valuable information. Interestingly, there was no effect of reward on semantic clustering (p = .69). These findings extend prior models of reward memory to include how reward changes the structure of memory organization. In future studies, we will use a mixed list design in order to determine whether individuals may also use reward value to organize memories (i.e., cluster information based on high and low reward, rather than temporal context).

Disclosures: **E.A. Eberts:** None. **B. Katerman:** None. **S. Dubrow:** None. **V.P. Murty:** None.

Poster

607. Human Long-Term Memory: Encoding and Retrieval III

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 607.20/BB51

Topic: H.02. Human Cognition and Behavior

Title: Heart (EKG) and brain (ERP) activity as predictors of subsequent memory for emotional images

Authors: *T. J. BUNGE[1], P. G. BOLTON SWAFFORD[1], D. P. AGUILLARD[1], V. C. ZARUBIN[2], C. M. MARTSBERGER[1], K. R. MICKLEY STEINMETZ[1];
[1]Wofford Col., Spartanburg, SC; [2]Univ. of California, Davis, Sacramento, CA

Abstract: Negative information is often remembered better than neutral information. However, it is difficult to determine if this is solely due to the emotional nature of negative stimuli, as results are often confounded by negative stimuli being more interrelated and more distinctive than neutral comparison images. To investigate differences in emotional response systems in the brain and the sympathetic nervous system, heart rate and event related potentials (ERPs) were recorded while participants viewed three types of images: negative images, semantically related neutral images, and unrelated neutral images. These images were presented in either mixed lists, composed of all three image types mixed together, or pure lists, composed of one image type per list. Participants completed immediate recall tests following the presentation of each list. Participants remembered negative images more often than both related and unrelated neutral images. Related neutral images were better remembered than unrelated neutral images. For mixed lists, heart rate increased significantly more in response to negative images than for either type of neutral image. Notably there was no heart rate increase at all for related neutral images. For pure lists there were relatively few differences in heart rate between emotion categories. When investigating the ERP data, subsequent memory effects (Dm) were not found for related neutral images. This suggests that both emotion and distinctiveness (mixed lists) can boost sympathetic response and encoding activity. However, the memory boost found for related neutral stimuli relative to unrelated neutral stimuli can likely be attributed to processes at retrieval.

Disclosures: **T.J. Bunge:** None. **P.G. Bolton Swafford:** None. **D.P. Aguillard:** None. **V.C. Zarubin:** None. **C.M. Martsberger:** None. **K.R. Mickley Steinmetz:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 608.01/BB52

Topic: H.02. Human Cognition and Behavior

Support: NIBIB R01EB022864
ONR MURI N00014-16-1-2832
ONR DURIP N00014-17-1-2304

Title: Neural implementation of behavioral models of working memory tasks

Authors: *Z. TIGANJ, N. A. CRUZADO, M. W. HOWARD;
Dept. of Psychological and Brain Sci., Boston Univ., Boston, MA

Abstract: Constrained by results from classic behavioral experiments we provide a neural-level cognitive architecture for modeling behavior in working memory tasks. We propose a canonical microcircuit that can be used as a building block for working memory, decision making and cognitive control. We show that this type of cognitive architecture can account for results in behavioral experiments such as judgment of recency, probe recognition and delayed-match-to-sample. In addition, the neural dynamics generated by the cognitive architecture provides a good match with neurophysiological data from rodents and monkeys. For instance, it generates cells tuned to a particular amount of elapsed time (time cells), to a particular position in space (place cells) and to a particular amount of accumulated evidence.

Disclosures: **Z. Tiganj:** None. **N.A. Cruzado:** None. **M.W. Howard:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

Location: Hall A

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Program #/Poster #: 608.02/BB53

Topic: H.02. Human Cognition and Behavior

Support: NIH F32 MH119797-01

Title: Pseudo-reward processing during human reinforcement learning

Authors: *S. D. MCDOUGLE, A. G. E. COLLINS;
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Abstract: Human reinforcement learning (RL) theory is built around two primary psychological variables - a value function and the reward prediction error that updates it. In human RL experiments, rewards themselves are often defined a priori, via explicit cash incentives, “points” exchanged for money, or subject-rated appetitive stimuli (e.g., food preferences). Because of this, a key variable of RL, the reward function, is usually pre-specified, and the value function is then estimated. However, in the real world, humans often need to specify their own reward functions. For instance, when learning how to make a cappuccino, one should be incentivized to achieve the correct coarseness when grinding the beans, even though this particular step is abstracted from the primary rewards of the task (e.g., caffeine). Here, we ask how abstract “pseudo-rewards” and concrete primary rewards are leveraged during RL, and if they are similarly processed in the brain. Human subjects performed a probabilistic learning task while undergoing fMRI. In this task, subjects had to learn which of two arbitrary choice stimuli was more likely to yield reward. Two conditions were intermixed during learning: pseudo-reward and primary-reward. In the pseudo-reward condition, correct trials were cued by arbitrary fractal stimuli that were specified every trial. In the primary-reward conditions, money-like points were given after correct trials, unambiguously signaling rewards. Subjects performed well in the task in both conditions, though expressed a slower learning rate in the pseudo-reward condition. Moreover, their performance on an independent working memory task correlated positively with their performance in the pseudo-reward task. We discuss preliminary cortical and subcortical imaging results related to these findings, and propose that working memory is critical for flexibly setting a reward function during learning, allowing RL to operate over arbitrary, novel stimuli in the environment.

Disclosures: S.D. McDougle: None. **A.G.E. Collins:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

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Program #/Poster #: 608.03/BB54

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant 1P01HD080679
Wellcome Trust Senior Investigator Award WT106931MA

Title: The neural link between subjective value and decision entropy

Authors: *S. BOBADILLA SUAREZ[1], O. GUEST[1], B. C. LOVE[1,2];
[1]Univ. Col. London, London, United Kingdom; [2]The Alan Turing Inst., London, United Kingdom

Abstract: A number of brain regions, such as ventromedial prefrontal cortex (vmPFC), are associated with value-based choice. Recently, signals related to decision confidence have been found to accompany value signals in vmPFC. Here, we find that these seemingly ancillary confidence signals are in fact the primary drivers of activity in a number of so-called value areas. We analyzed fMRI data from a mixed (containing gains and losses) gambling task in which participants either accepted or rejected a gamble on each trial. We fit a cognitive model to each individual's behavioral data, which allowed us to assess the subjective value (a weighted combination of possible gains and losses) and decision entropy (akin to inverse confidence) on each trial. Entropy peaks when the fitted model predicts there is a 50% chance that a participant would accept a gamble and is minimal when there is a 0% or 100% chance of acceptance. Using the trial-by-trial value and entropy estimates of the cognitive model, we were able to characterize fMRI activity related to choice. We found entropy signals to be stronger and more widespread throughout the brain than value signals. Value and entropy signals were not independent of one another, but correlated such that voxels that showed a positive effect for value also tended to show a positive effect for entropy. Likewise, voxels that showed a negative effect for one signal also tended to show a negative effect for the other signal. The intricate link between subjective value and decision entropy suggests that both quantities are required for full characterization of brain activity when making choices under risk.

Disclosures: S. Bobadilla Suarez: None. **O. Guest:** None. **B.C. Love:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 608.04/BB55

Topic: H.02. Human Cognition and Behavior

Title: Theta phase synchronization underlays intuitive calculation in an arithmetic task

Authors: *A. OKUWA[1], A. FUNASE[1], H. NAKATANI[2], I. TAKUMI[1];
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Abstract: [Purpose]In cognitive science research, we have been devoted to study on experts who have an expertise and high performance. Calculation experts can solve the arithmetic problem quickly with "intuitive calculation". "Intuitive calculation" enables calculation experts to understand the pattern of the problem quickly underlaying cognitive expertise. Therefore they

make an answer in short response time without actual calculating process. Neuroimaging study find the calculation expert's superior cognition is sustained by right prefrontal and medial temporal activity, however their functional connectivity remains unrevealed. Here, We analyze EEG phase synchronization to investigate the functional connectivity in understanding the pattern of the problem. In this research, We aim to reveal the functional connectivity underlaying calculation expert's quick solving the problem.[Experiments]We carry out Factorization task as mental arithmetic task. In each trial, subjects factor an arithmetic equation. Each trials consists of 3 phases as following. 1) participants fixate a cross shown in the center of the display. 2) participants factor a quadratic equation presented after fixation as quickly as possible and push the button when they come up with an answer. 3) participants answer that solution orally and take 5 [sec] rest. Participants totally repeat the trial 180 times and take a short break per 90 trials in the experiment. We measure the response time to solve the problem between the stimulation and button-push in each trial. We focus on the expert's brain activity within 1[sec] of perception. We record the EEG signals and focus on Fz, T8 and Pz electrodes to identify global brain connectivity in front and temporal-parietal. We conduct the time-frequency analysis and phase synchronization analysis to evaluate the functional connectivity. [Results and Discussion]From results, we obtain distinctive brain activity and functional connectivity related to quick solving the problem. Transient periods of time-frequency amplitude in the theta band is shown in Fz and T8 electrodes in short latency of 300[ms]. Subsequent to front-temporal activity, Time-frequency amplitude in Pz electrode is shown in long latency of 700[ms]. Theta band amplitude featured above is larger in short response time within 1[sec] than in long response. Furthermore, theta phase synchronization appears in front-temporal and front-parietal concurrently with task relevant brain activity. Functional connectivity between frontal and temporal-parietal in theta band is related to calculation expert's quick solving the arithmetic problem.

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Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

Location: Hall A

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Topic: H.02. Human Cognition and Behavior

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Title: Temporal expectation drives proactive preparation in simple response tasks

Authors: ***M. WANG**[1], H. ZHANG[1,2,3];
[1]Sch. of Psychological and Cognitive Sci. and Beijing Key Lab. of Behavior and Mental Hea,

[2]PKU-IDG/McGovern Inst. for Brain Res., [3]Peking-Tsinghua Ctr. for Life Sci., Peking Univ., Beijing, China

Abstract: In a simple response task, subjects are required to respond as fast as possible to the onset of an unambiguous target. Previous studies suggest that simple response tasks are not simple at all but reflect the temporal predictions of the brain. In particular, it is widely believed that the response time (RT) at a specific SOA (time from trial start to target onset) is determined by the hazard rate of the target at the moment. Though hazard rate has proved to be an effective predictor of RT, the instantaneousness of hazard rate is inconsistent with the cumulative motor preparation observed in neural data. Here we proposed a new computational model to account for the RT patterns in simple response tasks, which assumes that sensorimotor preparation is proactive and cumulative, taking into account the probabilistic expectation for all future moments. We designed a behavioral experiment where our model and the hazard rate theory would lead to distinct predictions. Each trial started with a centered gray disk. Subjects (N=14) were asked to press mouse button as soon as the disk briefly turned green. There were three possible SOAs: 500, 1170, and 2720 ms. We varied the probabilities of different SOAs across seven blocks of 147 trials, which were 1:1:1 for the first block, and were 1:2:4, 1:4:2, 2:1:4, 2:4:1, 4:1:2, and 4:2:1 in the following six blocks, with block order randomized for each subject. Different blocks would lead to different temporal expectations and we found that subjects' RTs varied with SOA ($F(2, 273) = 19.40$, $p < 0.0001$) , block ($F(6, 273) = 9.42$, $p < 0.0001$) and their interaction ($F(12, 273) = 1.80$, $p = 0.049$). We further compared RTs between conditions of the same SOA and hazard rate. Had RT been determined merely by hazard rate, these RTs would be equal. However, at SOA=1.17, RTs were significantly longer for 1:2:4 than for 4:1:2 (363 vs. 324 ms, $t(13) = 5.28$, $p < 0.001$), and significantly longer for 1:4:2 than for 4:2:1 (339 vs. 315 ms, $t(13) = 4.93$, $p < 0.001$). In two follow-up experiments, we replaced the stimulus with a concentric sinusoidal grating that contracted towards its center, where subjects were asked to press button as soon as the contracting speed turned faster. The first follow-up experiment (N=7) had the same design as the original experiment except for not including 1:1:1 block and the second experiment (N=6) only included 1:2:4 and 4:1:2 blocks. The significant RT difference between 1:2:4 and 4:1:2 at SOA=1.17 was replicated in both experiments ($t(6) = 2.93$, $p = 0.013$ and $t(5) = 3.71$, $p = 0.010$). These RT patterns violate the predictions of the hazard rate theory but are well predicted by our model. Model comparison analysis provided converging support for our model.

Disclosures: M. Wang: None. **H. Zhang:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 608.06/BB57

Topic: H.02. Human Cognition and Behavior

Title: Behavioral modeling and temporal dynamics of intertemporal choice

Authors: *W. YI, Q. LIU, B. M. TURNER;
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Abstract: Intertemporal choice is decision making about preference related to two dimensions of information: time delay and reward. This decision can be changed as time goes by. We investigated the temporal dynamics of intertemporal choice with an electroencephalogram (EEG) in this study. To identify the interaction of delay and reward information, we developed the Multialternative Decision Field Theory (MDFT) model of intertemporal choice under the Bayesian modeling framework. Specifically, intertemporal choice can be assumed to have the accumulation processes of reward and delay information, and this accumulation can include information loss (leakage) and competition (lateral inhibition) among the intertemporal choice options. We compared several candidate models and selected the best model based on the information criteria. In addition to the MDFT model, an EEG can be used for its temporal dynamics of intertemporal choice. The brain activity of the EEG data can reflect the traces of intertemporal choice related to different brain areas. Based on these activity patterns, the functional connectivity of the EEG data can also reveal the inter-relationship among the different brain areas of intertemporal choice decision.

Disclosures: **W. Yi:** None. **Q. Liu:** None. **B.M. Turner:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 608.07/BB58

Topic: H.02. Human Cognition and Behavior

Title: Cognitive basis of reasoning: A flexible analogical access (FAA) model

Authors: *N. C. CATANZARITE, K. N. DUNBAR;
Univ. of Maryland, College Park, MD

Abstract: Identifying relations between our current knowledge and new situations is an essential component of learning, but the cognitive processes that underlie relational reasoning are unclear. We conducted three experiments with a total of 189 undergraduate students to investigate the reasoning strategies used to identify categorical and analogical relations. Participants completed an information encoding task, then an information retrieval task. In Experiment 1, we found that reasoning strategies remain consistent across time. A week-long lag between the encoding and retrieval tasks decreased the number of relations participants were able to identify, but did not

change the types of relations they identified. In Experiment 2, we found that the framing of the questions asked during the retrieval task influence the type of reasoning strategy participants will use. Questions that target memory facilitate access to categorical relations, while questions about relationships facilitate access to analogical relations. In Experiment 3, participants were asked multiple types of questions in counterbalanced orders. Surprisingly, regardless of question order, participants identified mostly categorical relations in response to surface-level questions, and analogical relations in response to causal questions. This was intriguing because even after demonstrating cognitive access to analogical relations, participants proceeded to access only categorical relations in response to subsequent questions. Overall, these experiments indicate that reasoning strategy does not change over time (one week), and that the type of relations accessed by a particular question does not necessarily reflect the type of relations available. Rather, participants retrieve information about a subset of relations that are consistent with the framing of the retrieval questions. We propose the Flexible Analogical Access (FAA) model to interpret these findings and argue that this model can account for a wide variety of findings in the Analogical Reasoning literature. Currently, we are using fNIRS to investigate the neural mechanisms underlying these reasoning strategies and aim to determine their time course of activation.

Disclosures: **N.C. Catanzarite:** None. **K.N. Dunbar:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 608.08/BB59

Topic: H.02. Human Cognition and Behavior

Support: SNU Grant 200-20170098

Title: Predicting trial-wise choices from multi-modal data in a new environment

Authors: *H. PARK, J. YANG, W.-Y. AHN;
Dept. of Psychology, Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: A hallmark of a good model is to make accurate predictions to new conditions. To maximize prediction accuracy, it is critical to understand neurocognitive mechanisms underlying choice behavior and incorporate them into a quantitative model. While computational modeling of behavior data has greatly advanced our understanding of cognitive processes underlying our decision making, it is still challenging to make accurate predictions of choice behavior in a new environment using computational modeling and behavioral data alone. Here, we tested the hypothesis that incorporating multi-modal data such as eye movements and facial expressions into quantitative models will increase prediction accuracy in a new environment. In the current

study, participants performed description-based decision-making tasks for two consecutive days. Eye movements and facial expressions were recorded in real time while participants performed the tasks. We used the data of the first day to build a model that make use of all multi-modal data, and assessed the prediction accuracy of the model on the choice data of the second day. Our preliminary results demonstrated that incorporating fixation time, pupil dilation, and facial expressions into a computational model significantly improved the prediction accuracy compared to a model that uses choice data alone. These results highlight that facial expressions and eye movements provide useful information regarding our decision making and may help us make better predictions of others' behaviors.

Disclosures: H. Park: None. **J. Yang:** None. **W. Ahn:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 608.09/DP12/BB60

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: H.02. Human Cognition and Behavior

Support: NIH Grant 1R01MH115557-01

Title: Dynamics of evidence accumulation in a visual motion direction discrimination task containing change-points

Authors: *A. E. RADILLO, J. I. GOLD;
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Abstract: Judgments about noisy time-varying stimuli require the temporal integration of sensory information. It is known that the rate at which a stimulus undergoes abrupt, unsignaled state changes (or change-points) should and does influence the timescale of this integration. In particular, there is typically a negative correlation between the frequency of change-points in a stimulus and the timescale of sensory evidence integration. However, the exact temporal dynamics of evidence integration around the time of a real or expected change-point is not known, leaving open the more general question of how our brains implement information integration in our ever-changing world. To better understand this process, we set up a human psychophysical experiment in which we asked each subject to report the final direction of motion of a random-dot kinematogram. The dots stimulus contained a single change-point in the direction of coherent motion on some randomly chosen trials. To assess the time dynamics of evidence integration, we varied the viewing duration between 100-400 msec in steps of 100 msec, while fixing the single change-point time at 200 msec. The probability of a change-point

occurring on any given trial longer than 200 msec was manipulated across blocks, between 0.1-0.9. We hypothesize that the probability of a change-point modulates the dynamics of the accrued evidence according to the normative model. More precisely, we expect subjects to behave as perfect integrators before and after the change-point. However, around the expected time of a possible change-point and on trials in which the sensory evidence is weak, we expect the dynamics change in a manner that is governed primarily by the instructed probability of a change-point, as opposed to whether or not it actually occurred. To assess the time course of the accrued evidence around this time, we use a reverse-kernel analysis on the motion energy of the dots kinematograms. The results will allow us to better constrain future theoretical and neuronal models of human adaptive decision-making in realistic, dynamic environments.

Disclosures: **A.E. Radillo:** None. **J.I. Gold:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

Location: Hall A

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Program #/Poster #: 608.10/BB61

Topic: H.02. Human Cognition and Behavior

Support: Natural Sciences and Engineering Research Council of Canada Gradaute Fellowship (PGSD3-471313-2015; M.P.)

Title: Individual decision-making underlying the tragedy of the commons

Authors: ***M. CHAWLA**[1], M. R. PIVA[2], S. AHAMMAD[1], R. JIA[2], I. LEVY[3], S. W. CHANG[4]; [1]Dept. of Psychology, [2]Interdepartmental Neurosci. Program, [3]Departments of Comparative Medicine, Neurosci. and Psychology, [4]Departments of Psychology and Neuroscience, Kavli Inst. for Neurosci., Yale Univ., New Haven, CT

Abstract: Introduction: The tragedy of the commons is an economic theory (Hardin, 1968) that predicts the overuse and eventual depletion of shared resources. Development of a computerized paradigm amenable to behavioral modeling and simulation analyses could allow for exploration of whether resources will be overused in a given group of individuals and allow for the rapid testing of behavioral interventions designed to reduce instances of resource overuse. **Methods:** Using a newly developed group decision-making task, we studied how participants made decisions to utilize shared resources for the potential to receive a larger amount of money or conserve shared resources for a smaller amount of money. Eighty participants (53F, mean age=26.5, sd=7.6, range=18-55) completed the task along with questionnaires relating to social attitudes online. Participant choices in the task were modeled to conceptualize subjective value as a function of monetary reward and resource availability to extrapolate sensitivity to resource availability for each participant (parameter *k*). Simulation analyses via bootstrapping were

performed to examine the effect of individual differences in decision-making on task outcomes. **Results:** Behavioral modeling indicated that a parabolic function best fit participants' responses (BIC: linear=3000, exponential=3241, hyperbolic=3373, parabolic=2572). Simulation analyses revealed that higher reward levels increased resource overuse more than diminished amounts of resources available. Simulation analyses further revealed that participants who utilized resources more often earned more than those who chose to conserve resources, although this effect was reversed when participants who chose to use more resources were placed in a group together. Furthermore, as additional people who chose to use more resources were placed in a single group, average group earnings catastrophically decreased following the point at which 30% of a given group was comprised of such individuals. Finally, self-reported antisocial attitudes correlated with sensitivity to resource availability (k) across participants (r=-0.348, P=0.004). **Conclusion:** Subjective value was substantially affected by shared resource availability only when the amount of resources available was exceptionally low, suggesting that participants may have been more likely to overuse middling amounts of resources. Participants with higher measures of antisocial attitudes were less sensitive in their subjective valuation to diminished resources, in turn resulting in resource overuse particularly in groups in which at least 30% of group members displayed these characteristics.

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Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 608.11/BB62

Topic: H.02. Human Cognition and Behavior

Support: NIMH Pre-Doctoral IRTA Fellowship

Title: A combination of perceptual and reward information predicts choice and individual differences in optimality

Authors: *M. GHANE[1,2], S. A. JAPEE[1], J. A. RICHEY[2], L. G. UNGERLEIDER[1];
[1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Dept. of Psychology, Virginia Tech., Blacksburg, VA

Abstract: Background: Several psychiatric conditions are affected by co-occurring difficulties in perceptual and reward-based decision-making (PDM; RDM). PDM and RDM are often studied separately, either by manipulating uncertainty about what a stimulus is, or what it is worth. However, in the real-world, uncertainty in these two domains often co-occurs. The current study tested the hypothesis that decisions are best modeled using combined sensory and reward

information rather than either alone. It also aimed to determine whether a two-parameter model of decision-making could help identify individual differences in behavior. **Methods:** Nine adults completed two versions of a combined noisy target search and probabilistic reward task. In task 1 we manipulated perceptual uncertainty (PU) across trials (dynamic), and reward uncertainty (RU) between runs (stable); vice versa in task 2. On each trial, participants viewed two targets (face/house) and two distractors (cars) and were instructed to select one of the four images to maximize reward. Probabilistic contingencies and relative target visibility were known. We performed a 2 (Task) x 5 (RU Levels) x 5 (PU Levels) repeated measures ANOVA predicting target selection percentages to first test whether PU and RU interacted in the context of choice. We then used logistic regression to test the degree to which PU, RU, or a combination best classified individual subject choice. Single parameter models were compared with the two-parameter model using a difference in log-likelihood ratios. **Results:** ANOVA results revealed a significant interaction between PU and RU ($F(16,128) = 11.701$, $p < .001$, $\eta_p^2 = .594$). Participants selected high RU targets more often if they were easier to detect (greater in task 2) and high PU targets more when reward was more likely (greater in task 1). The two-parameter model fit data better in all subjects compared to either single parameter model ($MDiff_{Per}$=-58.23; $MDiff_{Rew}$ = -166.34). There was evidence for individual differences in sensory or reward-based choice biases and degree of optimal integration ($SD_{MDiffPer}$=57.50; $SD_{MDiffRew}$=73.44). **Conclusions:** Overall, decision relevant uncertainty, independent of PU or RU domain, modulated choice behavior. Participants were more biased by perceptual or reward information when uncertainty in the other domain was high, and task structure moderated these effects. Our unique approach also allowed us to identify individual differences in optimal integration of PU and RU. Ongoing fMRI studies will examine whether shared or distinct neural substrates underlie estimation of choice relevant PU and RU in perceptual and reward biases during decision making.

Disclosures: **M. Ghane:** None. **S.A. Japee:** None. **J.A. Richey:** None. **L.G. Ungerleider:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 608.12/BB63

Topic: H.02. Human Cognition and Behavior

Title: Model comparison with multimodal data: Bayesian inference on integrated models of behavioural and imaging data

Authors: *D. CUSTOVIC[1], B. NIKOLIC[3], C. CLOPATH[2], A. HAMPSHIRE[1];
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[3]Astrophysics Group, Cavendish Lab., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Introduction
Theoretical models in cognitive neuroscience make predictions across multiple data modalities, e.g. behavioural and imaging data. Testing these models thus requires a unified approach to inference from multimodal data: a successful inference approach must be able to concurrently fit models to multiple data sets and to discriminate between models on their explanatory power across data sets while taking model complexity into account.
These requirements can be met by modern Bayesian inference algorithms. Bayesian inference (BI) provides a rigorous mathematical basis for the notion of model comparison; the basic insight of BI is that the extent to which the data favours one model over another can be stated as the ratio of their *Bayesian evidences*, a principled metric of goodness-of-fit robust to overfitting. Our chosen BI algorithm, MultiNest, provides an efficient means to simultaneously fit model parameters and calculate model evidence. For many models, the shape of the likelihood function is unknown, motivating the use of a more computationally expensive approach over faster approximation methods.
We present two studies showing how BI can be successfully applied to problems in cognitive neuroscience.
Methods
Study 1: Behavioural data was gathered on 18 subjects performing the simple reaction time task. We considered four variants of the drift diffusion model to explain SRT performance, including one with collapsing bounds (CB). Log-likelihood functions were built for each model and used within MultiNest to find, for each subject and model, the best-fit parameters and Bayesian evidence. The models were compared for their performance against the data at the best-fit parameters, and the quantitative conclusion reached through Bayesian analysis compared with the models' performances at their best-fit parameters.
Study 2: We extend the methodology to fit two models of a learning curves task to imaging and behavioural data simultaneously, to uncover the roles of different ROIs, especially the LFC, in the task learning process.
Results
Study 1 finds the data decisively favours (by Bayes factor 80) a CB DDM. Comparison of model predictions at best-fit parameters with the empirical data finds the CB model is capable of explaining numerous effects in the data which the others cannot.
Study 2 gives proof-of-principle that models can be fit to multimodal data and compared within a unified framework. We show that including a hyperparameter to adjust the weighting of each data set allows us to account for the relative information content in each data set. We show that this unified approach provides tighter constraints than considering the two data sets separately.

Disclosures: D. Custovic: None. **B. Nikolic:** None. **C. Clopath:** None. **A. Hampshire:** None.

Poster

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Program #/Poster #: 608.13/BB64

Topic: H.02. Human Cognition and Behavior

Support: NIH P20 DA022539
NIH R01 DA020726
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Title: Modafinil effects on inhibitory control in methamphetamine-dependent individuals: A Bayesian model-based fMRI study

Authors: *H. WANG[1], D. GHAHREMANI[1], D. GUO[4], A. J. YU[4], *E. D. LONDON[1,2,3]; [1]Psychiatry and Biobehavioral Sci., [2]Mol. and Med. Pharmacol., [3]Brain Res. Inst., UCLA, Los Angeles, CA; [4]Cognitive Sci., Univ. of California San Diego, La Jolla, CA

Abstract: Methamphetamine (MA) is one of the most widely used illicit drugs worldwide, partially due to its low cost and long-lasting psychoactive effects (Panenka et al., 2013). Chronic use of MA is associated with prefrontal cortical dysfunction and cognitive impairment, especially with respect to features of inhibitory control that could influence the maintenance of addiction. Modafinil, a medication that is used to treat narcolepsy, has been shown to improve cognitive performance in a number of clinical populations (Minzenberg & Carter, 2008), including MA-dependent individuals (Ghahremani et al., 2011). We conducted a randomized, double-blind, placebo-controlled study on the acute effects of modafinil (200 mg, 2 hours before testing) on motor response inhibition and related neural activity in 18 MA-dependent individuals. Previous work indicated lower prediction error-related neural activation in MA-dependent individuals than in healthy control subjects performing the Stop Signal Task (SST; Harlé et al., 2016). We used the SST and fMRI to evaluate whether modafinil enhances prediction error-related neural activation in this clinical population. We estimated prediction error parameters by characterizing the effects of sequential task performance using a Bayesian Dynamic Belief Model (DBM), which describes the expectation of a stop trial (i.e., P(stop)) incorporating prior belief and trial history. We included trial-wise signed prediction error (SPE) and unsigned prediction error (UPE), derived from DBM, as parametric modulators in fMRI analyses. Consistent with the assumptions of the model, P(stop) was linearly positively correlated with RT in non-stop trials (Go RT) in both drug conditions; and modafinil reduced Go RT (478 ms vs. 494 ms after placebo; $p < 0.001$). Modafinil modulated SPE-related activation more than placebo in left precentral gyrus and inferior frontal gyrus, as measured with fMRI (whole-brain, cluster

corrected at $P < 0.05$, height threshold of $Z > 3.1$). The results present an initial model-based account of the effect of modafinil on response inhibition by MA-dependent individuals. Such a model-based approach may unveil subtle effects of modafinil, with implications for treatment of MA Use Disorder and potentially other psychiatric diseases.

Disclosures: H. Wang: None. **D. Ghahremani:** None. **D. Guo:** None. **A.J. Yu:** None. **E.D. London:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

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Title: Bounded rationality and temporally extended actions shape optimal perceptual decisions

Authors: *J. R. CASTIÑEIRAS, A. RENART;
Champalimaud Res., Champalimaud Fndn., Lisbon, Portugal

Abstract: Adaptive behavior in a perceptual decision making (PDM) task involves a trade-off between the performance deficit of responding too soon and the cost of time associated to gathering evidence. The optimal solution to this problem has been understood using the Partially Observable Markov Decision Process framework (POMDP). However, these kinds of policies assume perfectly rational agents and therefore ignore constraints that real agents have to confront. Here, we generalize ideas from optimal control theory to derive optimal policies that solve a categorical PDM task in the presence of two generic kinds of such constraints.
One is a “cost of control”, which penalizes policies that deviate from the agent’s default actions. In particular, we consider the effect of impulsivity, a spontaneous tendency to respond (consistent with the concept of exploration). The other cost is derived from the fact that the actions which communicate the agent’s choices and trigger the offset of the stimulus are extended in time (e.g. a nose poke, or an arm movement). This implies that since the initiation of an action until the moment that the stimulus stops, there is a certain period that we term "execution delay" in which the agent’s beliefs are subject to change. We show that the optimal policy in this setting involves a separation between a first commitment to act, and a final revision of that action, in which it could be maintained or switched to the alternative option.

We provide semi-analytical solutions for the probability that the agent will choose an option at a given time with a given belief, deriving predictions on measurable observables: choice, reaction time (RT) and decision confidence. We show that when the cost of control or the execution delay are significant, the behavior of decision confidence departs from the POMDP solution and resembles predictions of signal detection theory. Moreover, these different regimes also lead to distinct profiles on the distributions of anticipatory responses and "lapses".
Overall, our results clarify the link between the observed phenomenology of decision confidence and different notions of optimality, and also provide a more general notion of normative behavior that includes both task contingencies as well as unavoidable costs faced by real organisms.

Disclosures: J.R. Castiñeiras: None. **A. Renart:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

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Topic: H.02. Human Cognition and Behavior

Support: NSF Grant GG011240
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Title: Uncertainty-based arbitration between incremental and episodic control over decisions

Authors: *J. NICHOLAS[1], N. D. DAW[2], D. SHOHAMY[1];
[1]Columbia Univ., New York, NY; [2]Princeton Univ., Princeton, NJ

Abstract: Decisions between two familiar options can be made by consulting an average value built over many experiences or by retrieving value from a single past episode. However, it remains unknown how these two strategies trade-off. Here we tested the hypothesis that uncertainty modulates the relative contribution of incremental vs. episodic influences on choice. In Experiment 1, participants (n=100) made a series of choices for possible reward. Feedback was provided after each choice in order to promote learning about the value of two cues: incremental (card decks with average value) and episodic (unique objects on each card in a deck). Incremental cue outcomes came from either a certain or an uncertain distribution centered around the same average value. We found that participants were more likely to use episodic cues to guide choices when the incremental cue's value was less certain. Moreover, we found that the interaction between uncertainty and episodic choice was more pronounced early in learning. This result suggests that ambiguity about value plays an important role in adjudicating between incremental and episodic control. Experiment 2 tested this hypothesis directly by manipulating the volatility of the choice environment. Participants (n=160) in two groups completed a similar

task where each deck's average value switched between high and low. One group completed the task in an environment with fewer switches (stable) than the other (volatile). We measured the effects of a switch on choices. Because ambiguity about the decks is greatest following a switch, we predicted that volatility would increase the use of episodic cues both within (as a function of distance from switch) and between participants (predicting that the volatile group should be more sensitive to the value of episodic cues). We found that the high volatility group showed poorer learning overall for both cues. In the stable condition we also found that the effect of episodic choice was greater as distance from the switch increased, suggesting that resolving incremental ambiguity takes precedence over using episodes. Together, these results suggest a trade-off between incremental and episodic control that is governed by uncertainty, shedding light on when episodes are used for decisions.

Disclosures: J. Nicholas: None. **N.D. Daw:** None. **D. Shohamy:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 608.16/BB67

Topic: H.02. Human Cognition and Behavior

Title: Dopamine and serotonin in reward and addiction

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[1]Dept. of Nuclear Med. and PET Ctr., Aarhus, Denmark; [2]Univ. of Cambridge, Cambridge, United Kingdom; [3]Aarhus Univ. Hosp., Aarhus, Denmark

Abstract: Addiction as a phenomenon has existed for centuries in the forms of substance use and behaviour, and is demarcated by impulsivity and compulsivity, leading to clinical symptoms of tolerance and withdrawal. In numerous western countries such as the U.S., addiction is one of the costliest public health problems, and present technological advances have paved the way for new addictive phenomena, which rely on behaviour rather than drugs of abuse. These addictive processes are primarily guided by the neurotransmitters of dopamine (DA) and serotonin (5-HT), which play crucial roles in aspects of reward processing in the human brain, where overconsumption can lead to addiction. It is therefore of the highest relevance to assess more precisely the underlying mechanistic neurobiological aspects of reward processing, and assess addictive disorders in order to improve their options for treatment. In the present PhD project the roles of DA and 5-HT in reward processing, and the neural properties of gambling disorder (GD) and compulsive sexual behaviour disorder (CSBD) have been examined. The experiments were carried out in a between-subjects double blinded design and contained testing of more than 200 subjects, including healthy volunteers (HV) and GD subjects, and CSBD subjects; both psychiatric patient groups with profound deficits in impulsivity and compulsivity. This was done

in order to isolate the neural and behavioural correlates of both increasing DA and depleting 5-HT to investigate: 1) how this affected neural activity in a task-based fMRI experiment on different forms of rewards 2) cognitive components of impulsivity and compulsivity through behavioural testing 3) how these two points relate to GD and CSBD patient groups 4) a connectome-based diffusion tensor imaging (DTI) sequence assessing structural neural networks.

Disclosures: C. Schmidt: None. **V. Voon:** None. **A. Moller:** None.

Poster

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Topic: H.02. Human Cognition and Behavior

Support: DFG-SFB 940/2-B7

Title: How do monetary gains and losses affect the arbitration between reinforcement-learning strategies in adolescents and adults?

Authors: *F. BOLENZ[1], B. EPPINGER[2];
[1]Technische Univ. Dresden, Dresden, Germany; [2]Concordia Univ., Montreal, QC, Canada

Abstract: Motivated behavior undergoes substantial changes during adolescence. Recent findings suggest that adolescents show a strong asymmetry in the neural processing of monetary gains and losses, but it is unclear whether these developmental asymmetries in value processing also affect higher-order decision mechanisms, such as the arbitration between different reinforcement-learning strategies. We investigated developmental asymmetries in the arbitration between model-free and model-based reinforcement learning. Adolescents (12-17 y) and adults (18-25 y) performed a sequential decision-making task and across trials, the magnitude of outcomes was manipulated which lead to different pay-offs of the model-based strategy. Furthermore, during some blocks of the task, outcomes were framed as gains while during others, outcomes were framed as losses. Replicating previous findings, we found that in blocks with gains, reliance on model-based reinforcement learning was increased in trials with amplified rewards. In blocks with losses, we observed a reduced adaptation of reinforcement-learning strategies. However, we did not find developmental differences in the effect of gains and losses on the arbitration of reinforcement-learning strategies. Interestingly, this is in contrast with the effects of outcome valence in a risk-preference task in the same sample. Our findings show that monetary gains and losses differ in how they affect the arbitration of reinforcement-learning strategies with gains leading to a stronger adaptation to different reward magnitudes. However, we do not find support for the idea of a developmental asymmetry in the value-based engagement in different reinforcement-learning strategies.

Disclosures: **F. Bolenz:** None. **B. Eppinger:** None.

Poster

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Program #/Poster #: 608.18/BB69

Topic: H.02. Human Cognition and Behavior

Support: NIDA Grant DA038063

Title: Evidence accumulation and optimal stopping in stochastic choice

Authors: ***S. F. BUCHER**[1], P. W. GLIMCHER[2];
[2]Ctr. for Neural Sci., [1]New York Univ., New York, NY

Abstract: Drift-diffusion models (DDM) have had empirical success in fitting both behavior and electrophysiological recordings during binary choice tasks. They model response times along with choice probabilities and permit insights into the processes from which (perceptual or value-based) decisions originate. In the recent theoretical literature, the DDM has been shown to arise as the solution to a subset of narrowly defined optimal stopping problems. This literature assumes that evidence accumulates according to an (unobserved) underlying stochastic process with a drift that depends on the stimulus, but usually neither on the state of the accumulator nor on time. We present a behavioral experiment designed to visualize the "drifting particle" of the DDM by measuring directly how choice accuracy evolves with time. This permits more direct inference on the form of the underlying stochastic process than do traditional approaches, allowing us to better differentiate between competing models of evidence accumulation. In each of 360 trials, subjects are briefly shown 100 small circles, some red and some blue, and are asked whether the majority of these are red or blue. What is systematically varied is the duration for which the circles are visible prior to onset of a visual mask. Three treatments are examined: unpredictable-time-of-offset, unpredictable-time-of-onset, and free-response. The free-response trials, in which subjects may take as long as they like, correspond to the standard reaction time version of a DDM-style experiment. Finally, separate blocks of trials also systematically manipulate the prior probability that the correct response is red, allowing us to visualize the time-varying effect of prior probability on the decision variable. On each trial, after subjects choose "red" or "blue", we elicit their probabilistic beliefs (or confidence) that their preceding choice was correct. As expected and previously demonstrated, the accuracy of choices increases as a function of the time during which the dots are displayed. Shifting prior probabilities have large early influences on the decision variable, which rapidly decay. Reported confidence is linearly correlated with the accuracy of the decisions, and provides further empirical restrictions on how the underlying stochastic process modeled by the DDM evolves with time. This experimental

methodology thus promises empirical insights that permit us to refine bounded accumulation models in a way that is not possible when relying on decisions and response times alone.

Disclosures: S.F. Bucher: None. **P.W. Glimcher:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

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Program #/Poster #: 608.19/BB70

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant 1U01NS103799-01

Title: Relating human substantia nigra neural activity to eye movement

Authors: A. G. RAMAYYA[1], *B. J. MCSHANE[1], L. Y. BUCH[1], M. DONELEY-FLETCHER[1], L. DING[2], J. I. GOLD[3], G. H. BALTUCH[1];
[1]Pennsylvania Hosp., Philadelphia, PA; [2]Dept. of Neurosci., Univ. of Pennsylvania, Philadelphia, PA; [3]Dept Neurosci, Univ. Pennsylvania, Philadelphia, PA

Abstract: Introduction: The ability to direct one's gaze appropriately based on incoming sensory information is essential to survive and thrive in our dynamic and uncertain world. Impairments in the ability to select eye movements is disrupted in diverse conditions such as schizophrenia, traumatic brain injury and Autism. Animal studies have shown that the Substantia Nigra, Pars Reticulata (SNr), an output nucleus of the basal ganglia (BG), acts as a gating mechanism that suppresses unwanted eye movements but allows wanted ones. However, the function of this nucleus during human eye movements has not been studied in detail.
Methods: We performed intra-operative studies in patients undergoing deep brain stimulation (DBS) for Parkinson's disease. These studies combined single-unit recording from SNr and extra-occulography (EOG) to measure horizontal and vertical eye movements on both visual- and memory-guided saccade tasks.
Results: We recruited 22 patients. Intra-operative studies were completed for 14 of these patients. The average patient age was 65 +/- 12.2 years. We identified 11 neurons from SNr in 7 patients. We observed a mean firing rate of 18 Hz (range: 5.1-37.3 spikes/second) and a mean waveform duration of 2.06 ms (range: 1.64 - 2.52), which likely includes both dopamine and GABA neurons (Ramayya et al, 2014). Preliminary analyses identified firing rate modulation the 500 ms interval prior to saccade onset in several units.
Conclusions: We report preliminary results relating human SNr neurons to eye movements. Identifying pauses in SNr activity in the moments leading up to human eye movements would support the hypothesis that human SNr neurons act as a gating mechanism to select appropriate eye movements during decision-making.

Disclosures: **A.G. Ramayya:** None. **B.J. McShane:** None. **L.Y. Buch:** None. **M. Doneley-Fletcher:** None. **L. Ding:** None. **J.I. Gold:** None. **G.H. Baltuch:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

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Topic: H.02. Human Cognition and Behavior

Support: N00014-16-1-2251

Title: Differences between learners and non-learners during visual category learning

Authors: ***B. REUVENI**, B. FEINSTEIN, P. J. REBER;
Psychology, Northwestern Univ., Evanston, IL

Abstract: The development of expertise in complex decision-making tasks relies on multiple strategies including implicit statistical learning, and effortful explicit rule discovery as well as successfully incorporating feedback. To study this development, we use fMRI and a visual category learning paradigm that first teaches participants to sort 2D sinewave gratings that vary on spatial frequency (line thickness) and orientation (tilt) according to a simple rule based on line thickness. We then gradually expose the true category structure, that requires both line thickness and tilt. This is done via online model-driven adaptive stimulus selection aimed at facilitating a transition from one strategy to the other by actively disconfirming unidimensional rules and confirming a more complex two-dimensional one. The model, PINNACLE 2.0 (Nomura & Reber, 2012; Reuveni & Reber, *in prep*), is based on memory systems theory and provides a framework for understanding the roles of implicit / explicit memory and their interplay during learning. Prior work has demonstrated the success of this relatively simple model in accounting for participant behavior using 3 relevant strategies based on stimulus features (i.e. line thickness, tilt, or a combination of both). In the current study, a large subset of participants (19/32) fail to adapt to the changing task demands and remain at chance performance after an initial period of successful learning. In contrast, participants who do adapt show an initial dip in performance as task demands change followed by a gradual improvement throughout 400 trials. Neuroimaging analysis contrasting learners vs. non-learners showed greater activity in medial cingulate as well as in the precuneous for learners suggesting that even though learners perform less errors, they are more responsive to error signals and evidence accumulation.

Disclosures: **B. Reuveni:** None. **B. Feinstein:** None. **P.J. Reber:** None.

Poster

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Program #/Poster #: 608.21/BB72

Topic: H.02. Human Cognition and Behavior

Title: The role of perceptual uncertainty in value learning and naturalistic stimulus categorization

Authors: *A. GEANA[1], W. MAHAPHANIT[1], M. J. FRANK[2];
[1]Brown Univ., Providence, RI; [2]Brown Univ., Carney Inst. for Brain Sci., Providence, RI

Abstract: To successfully navigate our daily environment, humans (as well as non-human organisms) rely on the crucial skill of selecting perceptual information into relevant categories (e.g. 'things that are edible', 'things that are dangerous' etc.). This categorization process entails extracting relevant information from an often noisy environment, and using that information to make decisions about category boundaries (e.g. 'is this four-legged furry animal the type that wil try to eat me?')—decisions which later play into higher-level behavioral decisions (e.g. 'should I run or can I pet the four-legged furry animal?'). There has been a growing emphasis in the field of computer vision on integrating categorization algorithms into learning and decision-making studies, and recent advances have included creating complex perceptual models to classify image stimuli in a way that correponds to observed findings from human psychophysics and neural data (Sofer, Crouzet, & Serre, 2015), thus tying neural evidence for perceptual categorization to decision-making behavior. In the current study, we used a logistic regression classifier with L2 regularization to categorize naturalistic stimuli (man-made or natural scenes) and obtain their respective distances from a perceptual decision boundary line (Sofer al., 2015), and used the resulting stimulus set to test the extent to which humans integrate perceptual uncertainty into their value learning process. We tested Amazon Mechanical Turk participants on a complex two-phase task that combines facets of reinforcement learning and memory encoding (Jang et al. 2018). We captured the contribution of perceptual uncertainty with a mixed reinforcement learning model that uses a POMDP to infer underlying perceptual belief states, and found preliminary evidence for a role of perceptual uncertainty in value computations at the learning level, with more uncertain stimuli contributing less to overall value learning.

Disclosures: A. Geana: None. **W. Mahaphanit:** None. **M.J. Frank:** None.

Poster

608. Human Decision-Making and Reasoning: Cognition and Computations II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 608.22/BB73

Topic: H.02. Human Cognition and Behavior

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The Sloan Foundation
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Title: Reward structure regulates belief update strategy during hierarchical reasoning

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Abstract: A hallmark of intelligence is the ability to represent uncertain and dynamic environments in terms of a hierarchy of states, and update beliefs about those states using decision outcomes. This belief update process, however, depends critically on the nature of reward contingencies. For example, when reward is contingent upon committing to a specific path along the hierarchy, the belief update process has to take into account the specific path taken. In contrast, when reward depends only on the endpoint of the hierarchy, the update process has to consider all the paths that are consistent with that endpoint.
To investigate the computational principles of such high-level reasoning, we trained monkeys to perform two variants of a hierarchical decision-making task with distinct reward contingencies. In task one, monkeys made two sequential decisions corresponding to two levels of hierarchy in a decision tree, and received reward if both decisions were correct. Task 2 was governed by the same hierarchical structure but monkeys only reported their final decision, and received feedback based on that decision. We used these tasks to address two interrelated questions: (1) is the belief update process consistent with an optimal probabilistic model that takes reward contingencies into account? (2) can the sensitivity of the belief update process to reward contingencies be implemented by a vector-space evidence integration model?
According to an ideal observer model, monkeys should adopt two different reasoning strategies for the two tasks. For task 1, the expected reward has to be evaluated through conditionalization; i.e., “what is the probability of reward for my second decision given my first decision?” For task 2, in contrast, it has to be evaluated through marginalization; i.e., “what is the probability of

reward for my second decision considering the two possible choices I could have made for the first decision?"
The behavior was consistent with the predictions of the ideal observer: monkeys' responses conformed to the conditionalization strategy in task 1 and the marginalization strategy in task 2. Currently, we are developing vector-space models that can capture the belief update process in terms of outcome-dependent evidence accumulation. Preliminary work suggests that these two belief update strategies can be implemented by representing the integrated evidence in two different forms: graded evidence for marginalization and binary evidence for conditionalization.

Disclosures: M. Sarafyazd: None. **M. Jazayeri:** None.

Poster

609. Decision Making II

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

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Simons Foundation/ CSHL Interdisciplinary Scholars Program

Title: Inhibitory selectivity and choice performance in a circuit model of perceptual decision making

Authors: *J. P. ROACH, A. K. CHURCHLAND, T. A. ENGEL;
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Abstract: Cortical circuits perform computations to generate appropriate behaviors based upon diverse sensory inputs an example of which are perceptual decision-making tasks. The classical circuit model of decision-making focuses solely on the effects of recurrent excitation, treating inhibitory neurons as agnostic facilitators of competition between excitatory subpopulations. Inspired by recent experimental results reporting highly selective inputs to and firing by inhibitory neurons within cortical circuits, we've developed a mean-field firing rate model of a cortical decision-making circuit which parameterizes selectivity in connection strengths between subgroups within the excitatory and inhibitory populations. Analyzing this model, we've found that in order to produce network selectivity for a single choice outcome excitatory-excitatory selectivity (recurrent excitation) must always be high while excitatory-inhibitory selectivity can be varied over a wider range, as long as inhibitory selectivity is changed as well. Specifically, for every decrease in excitatory-inhibitory selectivity, there must be a corresponding increase in inhibitory selectivity. Additionally, this model reproduces the attractor-based decision-making dynamics previously demonstrated by non-selective inhibition models. The updated model

shows that selective inhibition does not disrupt overall network choice selectivity and predicts that perturbations to excitatory selectivity will disrupt decision-making behaviors more than perturbations to inhibitory selectivity. To extend our present findings, we implemented inhibitory selectivity into a full spiking network model which can validate the results of the mean-filed model and allow for more direct comparison with experimental results. From this work we can make an inference as to the circuit structures which support reliable perceptual decision making with equal excitatory and inhibitory selectivity, providing greater insight into the role of inhibition in cortical computation.

Disclosures: **J.P. Roach:** None. **A.K. Churchland:** None. **T.A. Engel:** None.

Poster

609. Decision Making II

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Program #/Poster #: 609.02/BB75

Topic: H.02. Human Cognition and Behavior

Support: 15/CDA/3591

Title: A neurocognitive architecture for audio-visual signal detection

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Abstract: We currently know very little about how we respond to multiple signals that occur at the same time. For example, a rock tumbling down a steep slope could be detected by either our sight or hearing, and we often respond faster to the presence of two such co-occurring signals than we would to those signals in isolation. However, despite extensive research, we still do not know whether the signals are processed entirely by separate parallel channels, or whether processing converges to a common channel. Many alternative models of the evidence accumulation process that produces our responses to such sensory signals can fit behavioural data. Here we used a human EEG signature of the process ("CPP") along with behavioural data to distinguish between potential architectures, where using behavioural data alone could not. We asked participants to report periods of coherency in otherwise incoherent auditory and visual stimuli while we recorded EEG. In half of the blocks participants were asked to report either visual or auditory events, or their co-occurrence [redundant detection]. In the other half the participants were asked to only report the co-occurrence of auditory and visual events [conjunctive detection].We found that a model consisting of separate unimodal evidence accumulators that converge to a common later stage could be used to explain the data from the redundant detection task, while data from a model consisting of separate unimodal evidence

accumulators that have gated access to a common later stage explained the data from the conjunctive detection task. In both cases the models were fit to behavioural data and then used to simulate CPPs. However, some commonly proposed alternative models failed to explain our data. We then extended our search for viable models by jointly fitting models to both behavioral and EEG data, allowing us to search through larger parameter sets. Overall, our research demonstrates the usefulness of the CPP in combination with behaviour in determining the neurocognitive architectures that underlie simple perceptual tasks.

Disclosures: **J.M. Egan:** None. **S. Kelly:** None. **R.G. O'Connell:** None.

Poster

609. Decision Making II

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Program #/Poster #: 609.03/BB76

Topic: H.02. Human Cognition and Behavior

Support: Wellcome 203147/Z/16/Z
MRC MC_UU_12024/5

Title: Neural activity in the human subthalamic nucleus during stochastic decision making depends on presented evidence

Authors: Z. E. PATAI[1,2], T. FOLTYNIE[2], P. LIMOUSIN[2], M. I. HARIZ[2], L. ZRINZO[2], R. BOGACZ[1], *V. LITVAK[2];
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Abstract: During decision-making, humans often accumulate noisy information and only commit to making a choice after sufficient evidence has been integrated. How and where the brain determines if the evidence is sufficient is still largely unknown. One candidate region implicated in this process is the subthalamic nucleus (STN), where the activity has been shown to modulate how high this evidence criterion, or the decision threshold, is set. To date, however, no study has investigated how the responses in the STN depend on the continual unfolding of evidence over time. To understand how the neural activity in STN changes during the evidence accumulation, we used an expanded judgement task, in which evidence is presented at discrete moments in time. Here we report on recordings of the STN in 15 Parkinson's patients (14 male, mean age: 59, range 47-71) while they performed an expanded judgment task. During each trial, patients were presented with a series of images of a mouse facing either left or right ('cue'). The cues were continuously presented until the patient responded with a prediction as to the probable direction in which the mouse would run (left or right). The two directions were equally likely across trials and within a trial the mouse faced in the correct direction with a probability of 0.7.

All but two patients were able to perform this task above chance (mean accuracy= 0.69±0.2 s.d.), and varied on the number of stimuli they observed before making a response (5.44±1.9 s.d.). Based on the hypothesized role of beta oscillations in inhibiting impulsivity during conflict, we analyzed induced responses in bilateral STN, locked to the cue images. We found that the power of beta oscillations in the STN was modulated by the visual cues. Specifically, these changes were dependent on the sequence of stimuli presented: we found increased beta power when two sequential cues were the same (e.g. L cue followed by L cue). Moreover, this increase for 'same cues' was only present on trials in which patients correctly guessed the running direction of the mouse, underscoring the notion that these beta power differences were task-relevant. Finally, we also examined button press-locked beta, but found no effect of choice correctness, despite patients receiving immediate feedback, highlighting that the effects seen during the cue periods are distinct from movement- and feedback- related beta changes. Although the STN is traditionally considered to be primarily a motor structure, these results suggest that beta power in the STN is responsive to sequential changes in evidence, which is consistent with the role of STN in modulating decision processes according to regularities in the presented evidence.

Disclosures: **Z.E. Patai:** None. **T. Foltynie:** None. **P. Limousin:** None. **M.I. Hariz:** None. **L. Zrinzo:** None. **R. Bogacz:** None. **V. Litvak:** None.

Poster

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Title: Choice history biases subsequent evidence accumulation

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Abstract: Perceptual choices depend not only on the current sensory input, but also on the behavioral context. An important contextual factor is the history of one's own choices. Choice history often strongly biases perceptual decisions, and leaves traces in the activity of brain regions involved in decision processing. Yet, it remains unknown how such history signals shape the dynamics of later decision formation. Models of perceptual choice construe decision formation as the accumulation of sensory evidence towards decision bounds. In this framework, it is commonly assumed that choice history signals shift the starting point of accumulation towards the bound reflecting the previous choice. We here present results that challenge this idea.

We fit bounded-accumulation decision models to behavioral data from multiple perceptual choice tasks (different task protocols and sensory modalities), and estimated bias parameters that depended on observers' previous choices. Individual history biases in overt behavior were consistently explained by a history-dependent change in the evidence accumulation, rather than in its starting point. This was true irrespective of the outcome (correct or incorrect) of the previous choice. The effect of choice history on drift bias was long-lasting, decaying over approximately 3 past trials. Lastly, we fit a leaky accumulator (Ornstein-Uhlenbeck) model, revealing that choice history biases the input to the evidence accumulation process.

Choice history signals thus seem to bias the interpretation of current sensory input, akin to shifting endogenous attention towards (or away from) the previously selected interpretation.

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Poster

609. Decision Making II

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Program #/Poster #: 609.05/BB78

Topic: H.02. Human Cognition and Behavior

Support: New York State ECRIP Fellowship

Title: Probing sensory evidence accumulation and decision-related signals using human intracranial EEG

Authors: *S. BICKEL[1,3], N. MARKOWITZ[2], J. L. HERRERO[2], E. ESPINAL[1], S. GHERMAN[1], R. G. O'CONNELL[4], A. D. MEHTA[2], S. KELLY[5];
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Abstract: The brain continuously receives noisy sensory signals which need to be evaluated prior to leading to specific actions. However, the neuronal cascade in the human brain from

perceived sensory evidence to specific actions remain poorly understood. Recordings in non-human primates identified specific brain regions, such as the lateral intraparietal area (LIP), which participate in such decision-making processes, reflecting the accumulation of sensory evidence towards a decision bound. Similarly, scalp EEG recordings in humans identified signals building up over widespread central-posterior regions during sensory evidence accumulation. However, to our knowledge, the exact anatomical location of the generators of these complex signals have not yet been identified in the human brain. Intracranial EEG (iEEG) recordings in presurgical epilepsy patients may provide the opportunity to fill this gap as this approach allows to record directly from potential target sources with high spatial and temporal resolution. In this study, we recorded two sensory evidence-based decision-making experiments in patients implanted with depth electrodes to identify the local sources of these evidence accumulation processes and investigate its temporal dynamics across brain regions. In task one, subjects viewed two patches of randomly moving dots with embedded coherent motion and were asked to respond with different key presses depending on the direction of the coherent motion. In an auditory adaptation of this task, a mixture of tones was presented with the emerging dominance of tones of either high or low pitch, which again have to be discriminated by the subject. Indeed, we found specific brain regions that showed a ramping up of activity mirroring accumulating sensory evidence, reminiscent of signals found with scalp EEG. This study provides preliminary evidence of the feasibility and complementary value of iEEG to scalp EEG and invasive animal studies to investigate the neural underpinnings of perceptual decision making.

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Poster

609. Decision Making II

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Program #/Poster #: 609.06/BB79

Topic: H.02. Human Cognition and Behavior

Support: NEI R01 EY024554

Title: Evidence accumulation in abstract decisions cued by varying perceptual information

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Abstract: Perceptual decision making is thought to depend on the accumulation of sensory evidence in the intraparietal sulcus (IPS), independent of the specific motor effector. However, whether similarly general mechanisms apply to evidence supporting abstract decisions is

unknown. Under a general accumulator framework, evidence used to drive both concrete (1st order) and abstract (2nd order) stimulus-response (S-R) relationships should accumulate in the same area of IPS. In contrast, progressively higher-order policy requires progressively more anterior regions of the lateral frontal cortex, each of which is most strongly connected to different parietal regions. Under a network-based hypothesis, evidence used to drive concrete (1st order) and abstract (2nd order) S-R relationships should thus accumulate within different areas of IPS. To evaluate these competing hypotheses, we designed a task in which the coherence of a perceptually graded stimulus (motion, color, or shape) and the level of policy abstraction (1st or 2nd order) were independently varied. Following training to ensure stable performance, subjects each completed 5 fMRI sessions, for 660 total trials. Within a trial, subjects viewed 3 separate, sequentially presented stimuli - dot motion (up/down), dot color (blue/gray), and shape (circle/triangle) - in pseudorandomized order before making a button press. Prior to each run, subjects were informed that one stimulus (e.g. color) would represent the 2nd order cue. Based on the 2nd order percept for each trial (e.g. blue/gray color), subjects then made a button press response based upon one of the other features (the relevant feature - e.g. motion) while ignoring the third (the irrelevant feature - e.g. shape). Behavioral results indicate that subjects benefit from higher coherence, utilize abstract information, and attend less to irrelevant stimuli, as predicted. Preliminary imaging results show greater activity in anterior frontal cortex including pre-PMd, a region implicated in 2nd order abstract decisions, when subjects view a 2nd order versus 1st order stimulus. Select bilateral IPS regions show greater activation in this comparison as well. In a univariate contrast of 1st order relevant versus irrelevant cues, greater activity in motor planning regions such as supplementary and premotor cortex, as well as higher order visual areas in lateral occipital gyrus, is seen. Further work with greater subject numbers will seek to confirm or refute these initial imaging findings.

Disclosures: M.L. Newton: None. **A.S. Kayser:** None.

Poster

609. Decision Making II

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Title: Neural representations of number across semantic, phonological, visual, and manual formats

Authors: *G. E. KOCH, R. LIU, M. E. LIBERTUS, J. A. FIEZ, M. N. COUTANCHE; Psychology, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Five fingers held up in the air can convey the same information as the symbol “5” drawn on a chalkboard, but how does our brain represent these different visual forms so that we understand the meaning of the number *five* in both cases? Four constituents have been implicated as being involved in adult numerical processing: semantic, visual, manual, and phonological, however, all four constituents have rarely been studied simultaneously using a single paradigm. We have developed a novel paradigm to identify and investigate the four constituents of the number processing network. We collected functional magnetic resonance imaging (fMRI) data from 18 adult participants while they completed our novel paradigm, as well as a traditional paradigm that has been used previously to study numerical processing in adults and children (Cantlon & Li, 2013; Emerson & Cantlon, 2015). Our novel paradigm uses a 2-by-2 factorial design, in which participants view one of two stimulus types indicating a quantity from 1 to 9: Arabic numerals or hands. Orthogonally, participants complete one of two tasks: deciding if the shown quantity is greater than another number (e.g., “greater than 3?”) or if the quantity contains a long vowel sound (i.e. long *e* in “three”). In the traditional paradigm, participants decide whether pairs of numbers, faces, shapes, and words are the same or different (e.g., same number of dots as a shown numeral). Collecting data from the same participants with both paradigms afforded us the opportunity to identify neural regions sensitive to numbers resulting from each paradigm separately, and to also directly compare paradigms and evaluate overlapping regions. Univariate analyses targeting numerical processing reveal highly overlapping activation patterns for both paradigms in the intraparietal sulcus, with additional activation in the medial frontal gyrus and insular cortex for our novel paradigm. Orthogonal multivariate analyses utilizing machine learning classifiers for the novel paradigm suggest that neural representations reflecting differences between semantic (numerical) and phonological processing can be successfully detected within the regions identified through the univariate approach. Additionally, underlying differences in numerical and phonological processing are robust enough to generalize across stimulus types (i.e. training on numerals and testing on hands). Our findings indicate that within brain regions sensitive to numbers, the underlying neural representations pertaining to numerical processing are invariant to visually-presented form.

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Poster

609. Decision Making II

Location: Hall A

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Program #/Poster #: 609.08/BB81

Topic: H.02. Human Cognition and Behavior

Title: Influence of repetitive transcranial magnetic stimulation of the posterior medial frontal cortex on the behavioral and electrophysiological measures of cognitive dissonance

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Abstract: Choosing between two similarly valued alternatives is a complex behavior. Multiple studies have shown that making such kind of difficult choice leads to the devaluation of the rejected alternative (Brehm, 1956). This choice-induced preference change (CIPC) is one of the main observable effects of cognitive dissonance (CD) that occurs as a reaction to inconsistency (Festinger, 1957). Temporal dynamics and neuronal mechanisms of the CD and subsequent CIPC are still not fully understood. Neuroimaging studies revealed probable crucial brain regions, including posterior medial frontal cortex (pMFC). An activity of this region is associated with performance monitoring and detection of cognitive conflicts (Debener et al., 2005) and expressed in the generation of electrophysiological error-related negativity component (ERN). Modern CD theories assume the role of the pMFC is linked with the detection of dissonance in difficult choices.
Latest studies of our research group were dedicated to the possibility of CIPC modulation using transcranial direct current stimulation (tDCS) of the pMFC. One of the previous studies (Colosio et al., 2018) showed that cathodal (inhibitory) tDCS has a small decreasing effect on CIPC comparatively to the spurious stimulation (sham) ($t(16) = -3.29$, $p = .002$, Cohen's $d = .29$). However, the application of the anodal (excitatory) tDCS did not show a significant result ($t(17) = -1.08$, $p = .15$). The ongoing study is aimed to check the effect of the stimulation of the pMFC in more robust conditions and using a more focused stimulation protocol.
We suppose to modulate both behavioral (CIPC) and electrophysiological (ERN amplitude) measures of the CD using transcranial magnetic stimulation (TMS). Here we use 20-40 s of the theta burst stimulation (TBS) before performing the difficult choices between two alternatives. For the checking duration and depth of the stimulation effect, we carry out additional control study using the same TBS protocol of the inferior part of the primary motor cortex with the registration of the motor evoked potential (MEP). Obtaining the deflection in CIPC and ERN under the TBS will allow to link the activity of the pMFC and CD processes more reliably. More importantly, through the observation of MEP amplitude damping and adjusting duration of stimulation, we may be able to clarify does CIPC occur already on the decisional stage of choice or after it as mostly considered before. It also can give us an opportunity to go further in the specification of the temporal neurodynamics of the CD using online TMS.

Disclosures: E. Rybina: None. **A. Shestakova:** None. **V. Klucharev:** None.

Poster

609. Decision Making II

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Program #/Poster #: 609.09/BB82

Topic: H.02. Human Cognition and Behavior

Title: Reinforcer devaluation in humans using task delays as reinforcers

Authors: *H. LIN, S. ZIMMERMAN, C. LONG, C. L. PICKENS;
Kansas State Univ., Manhattan, KS

Abstract: Reinforcer devaluation refers to tasks in which a cue predicts an outcome in a first phase, the value of the outcome is decreased subsequently, and there is then a test of whether participants spontaneously decrease their responding associated with that outcome. This task is common in non-human animals, but less common in humans. One possible reason why devaluation tasks are rare in humans is that the standard devaluation task tends to use tangible reinforcers (ex: foods) or physically aversive stimuli (ex: shocks) as the outcomes, and it is more difficult to use these outcomes with human participants. Our present experiment was meant to determine whether shorter task delays (that made task end sooner) would be reinforcing, and whether this reinforcing value would be sensitive to devaluation. Undergraduate students were given cue exposure phases alternating with response phases. In the cue exposure phases, the participants were exposed to black shapes (spade, club, heart, diamond) associated with delays that were longer (18-second) or shorter (0.5-second) than the intermediate delay of 8 seconds (associated with a circle shape). In the response phases, the participants were presented with different colored squares (yellow, green, blue, red). Responses during presentations of the different colored squares earned a shape (ex: responses during the yellow square earned the spade and a 0.5-second delay, responses during the red square earned the diamond shape and an 18-second delay). Withholding responses during the shapes always earned the circle shape and an 8-second delay. In the final cue exposure phase, the value of one of the card suit shapes that previously predicted a short delay was decreased/devalued by now having it predict a longer delay (ex: the spade shape went from being associated with a 0.5-second delay to being associated with an 18-second delay). In the subsequent response phase (which functioned as an extinction test, as responses always led to the circle shape and 8-second delay), responses to the colored square that predicted the devalued shape were decreased compared to responses to another colored square that continued to predict a shape associated with a 0.5-second delay. This suggests that task delays changes can act as reinforcers to support responding, and these reinforcers are sensitive to devaluation.

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Poster

609. Decision Making II

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Support: JSPS KAKENHI 16H06570

Title: Neuro - computational process for deciding with predicting others' decision

Authors: *N. MA[1], N. HARASAWA[1], K. UENO[2], N. ICHINOHE[4], M. HARUNO[5], K. CHENG[3,2], H. NAKAHARA[1];
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Abstract: In social life, humans are often required to consider others' decisions to make better decisions. A question of the neuro-computational process is poorly understood: how does the prediction about others' decisions contributes to one's own better decision-making? We addressed this issue by tracking the corresponding brain signals in human fMRI in relation to behavior which helped us dissociate them. We devised a novel behavioral task in human fMRI, combined with computational modeling. In our task, there is a main trial together with two types of control trial, self and other trials. In the main trial, the subject was required to make a choice from two options while predicting others' choice of two options, because the subject received outcomes differently, dependent upon the choice of others. In self and other trials, we separately examined each of two elementary processes in the main trial, making self value-based decisions and predicting others' decisions, respectively. In behavior, we found that the subject made choices in the main trial, combining two possible decision values (DVs), each of which would be generated by having two different prediction of others' choice, and weighting them with the predictions. Using model-based analyses, we examined the BOLD signals, in contrast with those by the DVs in the self trial and predicted-others' DVs in the other trial. First, we found that the self DV had significant activations in the medial prefrontal cortex (mPFC) for both main and self trials, while the others' DV had significant activations in the right temporoparietal junction (rTPJ) for both main and other trials. Second, to probe integration process of predicting others' decision to decisions, we introduced an intermediate variable called effectivity, which quantified how much the prediction contributed to the decisions in the main trials. We found the effectivity correlated with significant activations of the right anterior insula (rAI) and left dorsolateral prefrontal cortex (ldlPFC). Finally, using connectivity (psychophysiological interaction) analysis, we found that the rTPJ responses had significant impacts on the mPFC responses, but only mediated through rAI in the main trials, whereas there was direct impact of the rTPJ on the mPFC responses in the other trials. Taken together, these findings suggest that the additional neuro-computational processes are recruited to integrate the prediction about others' decisions for making one's own better decisions.

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Poster

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Title: Phasic arousal suppresses suboptimal decision biases in mice and humans

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Abstract: Decisions under uncertainty entail an accumulation of ambiguous evidence supporting different choice alternatives. The brain's arousal systems are rapidly recruited during such decisions. But how do the rapid ("phasic") arousal boosts affect decision-making? We here established a principle of the function of phasic arousal in decision-making, which generalizes across species (humans and mice) and behavioral tasks (from perceptual to memory-based and numerical decisions): suppressing maladaptive biases in the accumulation of evidence leading up to choice. We exploited that pupil dilation indexes cortical arousal state as well as response of the noradrenergic locus coeruleus in humans, monkeys and mice.
We recorded the pupil diameter of 20 humans and 5 mice during a difficult auditory go/no-go detection task. Humans responded with a button press, mice by licking for sugar water reward. In addition, 15 human subjects performed a forced-choice decision task based on identical stimuli under systematic manipulations of target probabilities, 54 human subjects performed a memory-based decision task, and 37 human subjects performed a basic laboratory task model of value-based stock market decisions.
In mice and humans, task-evoked pupil responses occurred early during decision formation, even on trials without any motor response, and predicted a suppression of a suboptimal conservative choice bias. Drift diffusion modeling revealed that the bias reduction was due to a selective interaction with the evidence accumulation process, rather than a shift in starting point. We showed that, within the same subjects, phasic arousal flexibly reduces both conservative and

liberal accumulation biases in a context-dependent manner. The same pupil-linked suppression of evidence accumulation bias also when evidence is accumulated from memory. Finally, by comparing a leaky selective integration model to other accumulation-to-bound models, we found a similar reduction in evidence accumulation bias towards risk-seeking, a higher-level form of human bias widely known in behavioral economics.
Our findings point to a precise, yet broadly generalized, role for global arousal state of the brain in decision making in the face of uncertainty. Our results indicate that pupil-linked phasic arousal suppresses choice biases in evidence accumulation across species and across domains of decision-making, ranging from decisions based on low-level perceptual evidence, to evidence sampled from memory, to high-level numerical evidence. In conclusion, phasic arousal calibrates a key computation during decision-making.

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Poster

609. Decision Making II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 609.12/BB85

Topic: H.02. Human Cognition and Behavior

Support: National Key R&D Program 2017YFC0803400

Title: Helping or punishing: The influence of testosterone and acute stress

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Abstract: Humans display an intriguing propensity to help the victims of social norm violations or punish the violators. The acute stress have been implicated in modulating various social behaviors including trust, risk-taking. However, it is still elusive how stress influence the third-party altruistic decision, especially when people face the conflict of self-interest and others' interests. To address this question, the participants were exposed to either a physical stressor (CPT, Cold Pressor Test) or a (TSST, Trier Social Stress Test) or a accordant control condition , and then completed an economic decision making task in which they could use MUs from their own endowment to either punish a norm violator or help a victim. After the decision making task, the participants was also asked to finish an analogous scenario task. Across both studies, the participants in stress group had a significant increase in cortisol, but the influence of different stressors on third-party decision making are inconsistent. After a psychosocial stress, participants showed more prosocial behaviors. Specifically, stressed participants transferred more MUs to the

victims in the economic decision task when the transgression is more severe, and were more likely to help the victims in scenario task than the control group. On the contrary, after a physical stress, participants prefer to punish the violators and decrease the tendency to help the victims, moreover, for the scenario task, most participants are prone to help the victims, physical stress has no significant impact.
As the previous studies found that testosterone can promote punish perpetrators. To explore the increased punishing behavior after physical stress, we focus on the dual-hormone effect in the CPT study. As a result, for individuals who showed higher basal testosterone was prior to punish violators, for those who has a lower basal testosterone trends to help victims, but this only occurs when the individuals are not under stress conditions. In the stress condition, the helping behavior of lower basal testosterone individual was suppressed, but the punishing behavior of higher basal testosterone was enhanced. This is consistent with previous findings about dual-hormone effect.

Keywords
Acute stress, CPT, TSST, Testosterone, dual-hormone, Third-party intervention.

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Poster

609. Decision Making II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 609.13/CC1

Topic: H.02. Human Cognition and Behavior

Support: Grant-in-Aid for Scientific Research from the Japanese government (18H03612)

Title: The neural correlate of legal judgment: Do legal expertise and a trust in the law make a difference ?

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Abstract: The neural correlate of the legal judgment of ordinary people has been underexplored, although the lay-judge system is an important part of the court system in many countries, including Japan, Korea, the United States, and the United Kingdom. On campus, we recruited two groups of participants: students on campus who are not specialized in law and law students who had just passed the national bar exams. We also recruited lawyers who have had experience in legal practice. The novelty of our approach is examining the difference in brain activation between legal professionals and lay people. In addition, we examined the difference in rsfMRI between legal professionals and lay people. Inside an MRI machine, participants were asked to read vignettes about criminal procedure cases and make legal judgments. With close cooperation from legal specialists, five murder cases were used to examine the effect of the repentance of the

defendant on the judgment of an appropriate punishment. We focused on the brain activity that is associated with legal judgment when a defendant does or does not show repentance. We examined whether and to what extent legal expertise and one's attitude toward the legal system make a difference in a participant's neural correlates when he/she makes legal judgments. Differential activation was found between those with and without legal expertise in the default mode network, i.e., the dorsal anterior cingulate cortex, the caudate nucleus, and the insula. The results also indicate that the strength of support for the legal system dissociates brain activation when non-law students made a legal judgment, but did not when law students and lawyers made a judgment. Overall, the neural correlates suggest that both legal expertise and a trust in the law make a difference in the brain activity.

Disclosures: **T. Asamizuya:** None. **H. Saito:** None. **S. Ota:** None. **J. Kato:** None.

Poster

609. Decision Making II

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 609.14/CC2

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant DA038063

Title: Trait level influences on political preference shifts differ between Democratic- and Republican-supported laws

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Abstract: Unlike value-based decisions, it is unclear if political decisions are made using a principled evaluation of alternatives. Scholars long considered political preferences to be a privileged class of decision-making, much like religious beliefs, that defy logical thought processes. Since the mid-20th century, political science has tried to make sense of this behavior, first using normative economic and later decision theoretic models. Competing schools of thought disagree on the influence of trait political awareness—one's tendency to keep up with politics—as compared to partisanship or in-group identification on voters' preference malleability . Using a novel psychophysical task that orthogonalizes partisanship and political information, we employed a neuroeconomic approach to examine how political information alters preferences. Two behavioral studies, one online and another in the lab, made preference ratings on real proposed laws that have appeared before US Congress. Subjects first reported their preferences based solely on a synopsis of the law, and later reevaluated those preferences after learning about the percent of members of Congress in each party who voted in favor of the

law. Laws' true congressional support were unrelated to their perceived partisanship (i.e., the true levels of support for each bill were completely uncorrelated with participants' estimates of that support). Partisanship predicted preference alignment with the in-group for members of both parties. However, desire for social esteem only predicted alignment with Democrat-favored laws and degree of self-regarding preference only did so for Republican-favored laws. A third study employs a version of this task adapted for functional neuroimaging to pinpoint the neural locus of political preference representation in the brain. While previous studies reported a common neural representation for differing goods types and personal preferences, it is still unclear whether political preferences lie on this same axis.

Disclosures: B.B. Lu: None. **J. Zimmermann:** None. **J.J. Van Bavel:** None. **P.W. Glimcher:** None.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.01/CC3

Topic: H.03. Schizophrenia

Title: Inhibition of fast glycine re-uptake restores deficits in mismatch negativity caused by depletion of GluA1 from parvalbumin interneurons

Authors: *R. SPRENGEL[1], M. ZONOUZI[2], V. MACK[2], H. ROSENBROCK[2], **N. SCHUELERT**[2];
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Abstract: Mismatch negativity (MMN) is an auditory event-related potential that provides an index of automatic context-dependent information processing that can be measured in humans and in animal models. Cognitive impairment in schizophrenia is linked to robust abnormalities in the generation of MMN. It has been suggested that cognitive dysfunction might arise from an aberrant interplay of inhibitory parvalbumin (PV) and somatostatin (SOM) positive interneurons with pyramidal cells, leading to an excitation-to-inhibition imbalance and abnormal sensory processing revealed by reduced MMN. In this exploratory study we investigated the impact of Cre-mediated selective depletion of the AMPA-type glutamate receptor subunit 1 (GluA1) from PV positive interneurons in mice on cortical network oscillations and auditory event-related potentials. Previous studies have shown that the lack of GluA1 expression in PV interneurons reduces the excitatory input onto PV positive interneurons leading to neurophysiological abnormalities and cognitive impairment. We have performed wireless EEG recordings from implanted epidural electrodes above the primary auditory cortex and the medial prefrontal cortex of adult of $GluA1^{PVCre-/-}$ and control mice. Our results indicate that GluA1 in PV-positive

interneurons is dispensable for the generation of basal and auditory evoked high frequency oscillations in cortical areas. In contrast, the PV specific depletion of the AMPA receptor subunit GluA1 led to impaired MMN, reminiscent of a cortical processing deficit observed in Schizophrenia. The effect on MMN might indicate a lack of separation between sensory information caused by a lower excitatory input to PV neurons. This effect could be rescued by the GlyT Inhibitor Bitopertin highlighting the impact of NMDA receptor signalling on sensory processing and intact MMN. Thorough histological studies are currently performed to gain more insight to potential changes in cortical network assembly caused by depletion of GluA1 from PV interneurons. Thus $GluA1^{PVCre-/-}$ mouse might represent a suitable model to investigate pathological mechanisms related to insufficient recruitment of PV interneurons and pathological sensory processing.

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Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.02/CC4

Topic: H.03. Schizophrenia

Title: Neuroprotective effect of ethyl acetate fraction of terminalia macroptera leaf against ketamine-induced schizophrenia related behaviour in mice

Authors: *O. O. SUNDAY[1], L. IOR[2];
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Abstract: It has been hypothesized that oxidative imbalance and alterations in nitrergic signaling play a role in the neurobiology of schizophrenia. The leaf of *Terminalia macroptera* has been reported to possess a number of psychopharmacological activities by traditional herbalists in Northern Nigeria. The present study was carried out to investigate the protective effects of ethyl acetate fraction of *T. macroptera* in an experimental model of ketamine-induced schizophrenia related behaviour in mice. Schizophrenia related behavior was induced by administering sub anaesthetic dose of Ketamine (30 mg/kg) daily for seven days. The effect of the Ethyl Acetate fraction of methanolic extract of *T. macroptera* (100, 200 or 400mg/kg) were compared with the effect of a standard atypical antipsychotic, risperidone (0.5 mg/kg). Behavioral effects monitored include: locomotor activity, stereotype behaviour, immobility duration and memory retention. The effect of test agents on catalepsy in mice was also accessed in wood block test, using haloperidol 1 mg/kg and risperidone 0.5 mg/kg as reference drugs. *T. macroptera* at the dose of 100 - 400 mg/kg significantly ($P \leq 0.05$) reduced ketamine-induced hyperactivity, immobility and memory deficit. The efficacy of Ethyl Acetate fraction of the extract (at the doses used) was

comparable to that of risperidone. The extract did not produce extrapyramidal side effects, as evidenced by decreased descent latency in the wood block catalepsy test in mice. The study revealed that ethyl acetate fraction of *T. macroptera* ameliorate schizophrenia related symptoms in mice, underscoring its antischizophrenic profile. Our findings support the folkloric use of extract of *T. macroptera*.

Disclosures: O.O. Sunday: None. **L. Ior:** None.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.03/CC5

Topic: H.03. Schizophrenia

Support: GACR grant 17-04047S
AZV grant 17-30833A
RVO grant 67985823
MEYS grant LM2015062
EPTRI Grant 777554

Title: *In-vivo* optogenetic stimulation of prefrontal PV+ interneurons has a recovering role in a rat model of schizophrenia-like cognitive inflexibility

Authors: *E. PATRONO[1], K. HRUZOVA[1], J. CHVOJKA[2], H. BROZKA[1], D. RADOSTOVA[1], J. SVOBODA[1], P. JIRUSKA[2], A. STUCHLIK[1];
[1]Dept. of Neurophysiol. of Memory, [2]Dept. of Developmental Epileptology, Inst. Of Physiol. CAS, Prague, Czech Republic

Abstract: Cognitive flexibility is an ability to adjust a response based on changed conditions and is disrupted in schizophrenia-like psychosis. Parvalbumin-positive (PV+) interneurons into the medial prefrontal cortex (mPFC) have a critical role in flexibility, and poor function of mPFC-PV+ interneuron is linked to schizophrenia. The aims of the study were 1) to create a new model of acute cognitive inflexibility using systemic injections of MK-801, an NMDA receptor antagonist, and measure it by an Attentional Set-Shifting Task (ASST); 2) to investigate the therapeutical role of mPFC-PV+ interneurons in the acute model of cognitive inflexibility, using in-vivo optogenetics PV+ stimulation in channelrhodopsin-2 (ChR2) transfected rats; 3) to validate the in-vivo optogenetics behavioral outcomes, to check the viral transfection, and the optical stimulation proficiency onto mPFC-PV+ cells. In the ASST, rats learned to dig/retrieve food reward from a cup, after a two dimension-operant-association - relevant (odor) and irrelevant (digging medium). Reversal learning (RL-odor switch) and extra-dimensional shift (EDS-relevancy switch) sessions measured the cognitive flexibility in the rat. AAV-containing-

ChR2 transfections and optic fiber implant were stereotaxically applied into the rat mPFC, unilaterally, 2 weeks before assessing ASST. Immunohistochemistry was performed on transfected/implanted rats previously performing ASST. An in-vitro Opto-Electrophysiology method was used on transfected/implanted rats of the same group. Results showed that acute MK-801 during RL and EDS induced cognitive inflexibility compared to the saline. Moreover, mPFC-PV+ optogenetic stimulation recovers the ability to switch odor and/or medium relevancy. Finally, by immunohistochemistry, AAV-ChR2 transfection occurred in Pre- and Infra-Limbic Cortex; by in-vitro Opto-Electrophysiology, a blue LED light was able to induce a firing activity on transfected brain slices, in Pre- and Infra-Limbic Cortex. We observed that enhancing the inhibitory activity of PV+ interneurons in mPFC is a new experimental therapeutic opportunity to rescue cognitive flexibility in schizophrenia-like psychosis. Moreover, we elaborated a new complex method to validate the behavioral outcomes from in-vivo optogenetics experiments. This work was supported by GACR grant 17-04047S and AZV grant 17-30833A. Institutional support for IPHYS provided by RVO: 67985823. Additional support from MEYS (LM2015062) Czech-BioImaging and H2020 INFRADEV-01-2017 project ID-EPTRI (European Paediatric Translational Research Infrastructure - EPTRI Grant Agreement 777554).

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Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.04/CC6

Topic: H.03. Schizophrenia

Title: The NMDA receptor antagonist ketamine exerts biphasic effects on mismatch negativity in the rat

Authors: *S. KANTOR[1], B. LAURSEN[2], N. UPTON[1], J. F. BASTLUND[3];
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Abstract: Background: Mismatch negativity (MMN) is a component of event-related potentials recorded in the scalp EEG. MMN is diminished in many neuropsychiatric disorders including schizophrenia. Antagonists of the N-Methyl-D-aspartate (NMDA) receptor, such as ketamine, mimic symptoms of schizophrenia and disrupt MMN in healthy volunteers. MMN can be measured in rodents as well. To examine the back-translational potential of the MMN assay, we tested whether ketamine could impair MMN in the rat similar to humans.
Methods: 24 adult (200-250 g) male CD rats (Charles River, UK) were surgically implanted with telemetry transmitters (HD-S02; DSI, USA) for fronto-parietal EEG and EMG recordings.

MMN was elicited in awake, freely-behaving rats by an auditory oddball paradigm in which a deviant ('oddball'; DEV) tone occurred randomly within a sequence of identical tones ('standards', STD). Components of the auditory evoked potential (AEP) were measured in difference (DIF) waves that were generated by subtracting STD waves from DEV waves. After establishing the baseline MMN, the rats were treated with ketamine (3, 10 and 30 mg/kg, s.c.) or its vehicle (saline, 5 ml/kg) in a cross-over design with 3-4 days washout between the treatments. The MMN protocol was started immediately after the treatment and the data recorded between 20-80 min post-treatment was used for analysis. In addition to analysing MMN, we also performed a spectral analysis of the EEG.
Results: We found that high dose of ketamine (30 mg/kg) significantly reduced the amplitude of AEP in DIF waves compared to vehicle treatment, thereby demonstrating impaired MMN in the rats. Specifically, we found that ketamine (30 mg/kg) reduced the absolute distance between N1-P2 peaks (10.5 ± 1.1 μV vs. 7.3 ± 0.5 μV) as well as the area under N1 peak (30-60 ms; -70.3 ± 11.2 μV^2 vs. -31.0 ± 5.3 μV^2) in DIF waves. In contrast, the low dose of ketamine (3 mg/kg) improved some components of the AEP including the sum of all values in the 20-50 ms region of N1 in DIF waves (-7.7 ± 8.411.2 μV^2 vs. -31.4 ± 7.3 μV^2). Besides altering MMN, ketamine also increased EEG gamma (30-100 Hz) oscillations in the rats in a dose-dependent manner.
Conclusion: We have shown that rats have a clear electrophysiological correlate of the clinical MMN and that can be impaired by high dose ketamine treatment. Our data also suggest that low doses of ketamine may have beneficial effects on MMN that is in contrast with the detrimental effect caused by high doses of the drug. Overall these data demonstrate that MMN may be a valuable translational tool for testing therapeutics targeting neuropsychiatric disorders including schizophrenia.

Disclosures: S. Kantor: A. Employment/Salary (full or part-time):; Transpharmation Ltd. **B. Laursen:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **N. Upton:** A. Employment/Salary (full or part-time):; Transpharmation Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Transpharmation Ltd. **J.F. Bastlund:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); H. Lundbeck A/S.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.05/CC7

Topic: H.03. Schizophrenia

Title: GPR52 agonists represent a novel approach to treat unmet medical need in schizophrenia

Authors: A. J. GROTTICK[1], B. GRAYSON[2], G. PODDA[2], N. IDRIS[2], J. C. NEILL[2], ***S. HOBSON**[3];
[1]Beacon Discovery Inc., San Diego, CA; [2]Div. of Pharm. and Optometry, Univ. of Manchester, Manchester, United Kingdom; [3]CNS Dis. Res., BI Pharma Gmbh & Co. KG, Biberach a.d. Riss, Germany

Abstract: GPR52 is an orphan G-protein coupled receptor that is selectively expressed in brain. In the cortex, it co-localizes with dopamine D1 receptors (D1R) on glutamatergic neurons. Deficiencies in D1R activation are associated with both cognitive impairments associated with schizophrenia (CIAS) and negative symptoms. In contrast, in the striatum, GPR52 co-localizes almost exclusively with dopamine D2 receptors, where inhibition mediates antipsychotic efficacy. Based on GPR52's expression pattern and Gs functional coupling, agonists would be predicted to functionally resemble D1 agonists in cortical areas and to resemble D2 receptor antagonists in the striatum, thus holding the potential to provide a novel treatment for the three core symptom domains associated with schizophrenia. To assess for antipsychotic potential, a GPR52 agonist was tested in an amphetamine-induced hyperlocomotion model. The efficacy of a GPR52 agonist for CIAS and sociability, an aspect of negative symptoms, was assessed in the sub-chronic phencyclidine (scPCP) model for schizophrenia, known to induce long-lasting cognitive and social behaviour deficits, in addition to a reduction in parvalbumin-positive GABAergic interneurons in hippocampus and pre-frontal cortex. In the scPCP model, rats were tested in the attentional set shifting task (ASST) for executive function and the social interaction (SI) test for sociability, respectively, following treatment with a GPR52 agonist. GPR52 agonists were efficacious in these animal models assessing the three main symptom domains associated with schizophrenia. Efficacy in ASST and SI demonstrate both pro-cognitive efficacy and restoration of an aspect of negative symptoms, in a well-established model inducing behavioral and neuropathological deficits associated with schizophrenia. Furthermore, GPR52 agonists reduced psychostimulant-induced hyperlocomotion, an effect associated with antipsychotic efficacy. Taken together, these data demonstrate the potential of this innovative mechanism to simultaneously treat the three core symptoms domains associated with schizophrenia.

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Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.06/CC8

Topic: H.03. Schizophrenia

Support: BDD GmbH

Title: Rapid augmentation of antipsychotic drugs by sodium nitroprusside. Behavioral assessment and effect on brain dopaminergic transmission in rats

Authors: *J. TITULAER[1,2], A. MALMERFELT[1], M. MARCUS[1], A. PERRONE[3], G. ALKEN[3], J. P. LOWRY[4], T. H. SVENSSON[1];
[1]Karolinska Institutet, Stockholm, Sweden; [2]Dept. of Pharmaceut. Biosci., Uppsala Univ., Uppsala, Sweden; [3]BDD Berolina Drug Devolopment, Berlin, Germany; [4]Maynooth Univ., Maynooth, Ireland

Abstract: Background
Recently, a single injection of the nitric oxide donor sodium nitroprusside (SNP) was found to induce a rapid (within 4 hours) and sustained (several weeks) antipsychotic effect in treatment-resistant schizophrenic patients [1]. Moreover, SNP was shown to generate both rapid and persisting changes in brain synaptic plasticity, including enhanced excitatory postsynaptic current responses and spine morphology in layer V pyramidal cells in rat medial prefrontal cortex (mPFC) brain slices [2]. Here, we have studied the antipsychotic-like effect of SNP in combination with risperidone (RISP) in rats.
Methods
We used the conditioned avoidance response (CAR) test to investigate the antipsychotic-like efficacy, as well as in vivo microdialysis and NO selective amperometry in freely moving animals to measure neurotransmitter efflux in the mPFC and the nucleus accumbens (NAc). All experiments were approved by the local animal ethics committee, Stockholm North, and the Karolinska Institutet, Sweden.
Results
Addition of SNP to RISP dramatically enhanced the antipsychotic-like effect of RISP in the CAR test. In the mPFC, addition of SNP significantly enhanced the risperidone-induced dopamine output, whereas there was no difference in the NAc in risperidone-induced dopamine output after SNP was added. Furthermore, we found that SNP resulted in a strong and immediate but short-lasting increase of NO levels in the mPFC and the NAc.
Conclusions
The present preclinical results support the clinical observation that a single injection of SNP can rapidly and dramatically augment the clinical efficacy of antipsychotic drugs in schizophrenia. SNP selectively increased risperidone-induced prefrontal dopamine release, while not increasing risperidone-induced dopamine release in the NAc. Therefore, the antipsychotic effect of SNP seems to be achieved by enhanced prefrontal dopamine output. Based on these findings it could be expected that SNP improves cognition as D1 receptors in the prefrontal cortex play a crucial role in cognition. Our results were obtained using a low dose of SNP and a low dose of RISP, indicating that both drugs could be administered in a lower dose in patients, reducing the risk of side effects.
References
1.
Hallak, J. E. C. *et al.* (2013) ‘Rapid Improvement of Acute Schizophrenia Symptoms After Intravenous Sodium Nitroprusside: A Randomized, Double-blind, Placebo-Controlled Trial.’, *JAMA psychiatry*, 70(7), pp. 668-676.

2.
Liu, R.-J. *et al.* (2015) 'Effects of the Rapidly-Acting Antipsychotic Agent Sodium Nitroprusside (SNP) on Synaptic Spine Function and Morphology in Medial Prefrontal Cortex', *ACNP 54th annual meeting*, (3), pp. 1-3.

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Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.07/CC9

Topic: H.03. Schizophrenia

Title: Discovery of TAK-041: A potent and selective GPR139 agonist for the treatment of negative symptoms associated with schizophrenia

Authors: *R. HODGSON[1], J. ATIENZA[2], H. REICHARD[2], V. MULLIGAN[3], J. CILIA[3], H. MONENSCHEIN[2], D. COLLIA[3], J. RAY[4], N. L. BRICE[5], G. KILPATRICK[3], M. CARLTON[3], S. HITCHCOCK[2], G. CORBETT[3], H. H. SCHIFFER[6];
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Abstract: Individuals with schizophrenia frequently have residual motivational and social deficits, in addition to cognitive impairment, which are thought to relate to abnormalities in midbrain dopamine activity. The habenula is a well conserved paired structure, which is part of the reward pathway and functions with dopamine neurons in the ventral tegmental area to mediate reward related signals, specifically aversive and negative stimuli (Hikosaka, 2010); pathology in the habenula contributes to schizophrenia (Sandyk, 1992; Caputo *et al*., 1998; Shepard et al., 2006). Despite many studies on the habenula, its precise function remains unclear. Here we describe functional consequences of regulation of GPR139, an orphan *G protein-coupled receptor* (GPCR) that is specifically expressed in the CNS and enriched in the habenula (Matsuo *et al*., 2005) in mouse models of schizophrenia. Specific expression of mouse GPR139 in the habenula was evaluated using BacTrap and confirmed by immunohistochemistry.

GPR139-/- mice were generated by removal of a 736bp region encoding the seven-transmembrane domain. We expressed full length GPR139 in CHO cells and screened a 600K compound library using a calcium assay to identify small molecule agonist. Hits were identified and physical properties optimized to produce the GPR139 agonist molecule TAK-041 suitable for *in vivo* evaluation. Using BacTRAP we observed enriched expression of GPR139 in substance P positive cells of the medial habenula. This expression was confirmed with immunohistochemistry. To determine if GPR139 regulates the hypothesized role of the habenula in learning, motivation, and social behavior, GPR139 -/- animals inbred on a 129/SvEv background were generated and phenotyped. These animals appeared normal and performed comparably to wild-type animals in a range of standard tasks. However, they were significantly impaired in models that reflect aspects of negative symptoms such as progressive ratio, a measure of motivation, and nest-building, a model of self-neglect. Furthermore, these animals showed deficits in the novel object recognition model of working memory. The small molecule GPR139 agonist TAK-041 was observed to reverse deficits in models of schizophrenia, including cognition in a subchronic PCP-impaired attentional set-shifting paradigm (Birrell and Brown, 2000) and impaired social interaction in the Poly(I:C) maternal immune activation model (Bitanihirwe *et al*., 2010). These data further support the hypothesis that the habenula plays an important role in schizophrenia, and that selective GPR139 agonists may be a beneficial treatment for the disease.

Disclosures: **R. Hodgson:** A. Employment/Salary (full or part-time):; Takeda Pharmaceuticals. **J. Atienza:** A. Employment/Salary (full or part-time):; Takeda Pharmaceuticals. **H. Reichard:** A. Employment/Salary (full or part-time):; Takeda Pharmaceuticals. **V. Mulligan:** A. Employment/Salary (full or part-time):; Takeda Pharmaceuticals. **J. Cilia:** A. Employment/Salary (full or part-time):; Takeda Pharmaceuticals. **H. Monenschein:** A. Employment/Salary (full or part-time):; Takeda Pharmaceuticals. **D. Collia:** A. Employment/Salary (full or part-time):; Takeda Pharmaceuticals. **J. Ray:** A. Employment/Salary (full or part-time):; Takeda Pharmaceuticals. **N.L. Brice:** None. **G. Kilpatrick:** A. Employment/Salary (full or part-time):; Takeda Pharmaceuticals. **M. Carlton:** A. Employment/Salary (full or part-time):; Takeda Pharmaceuticals. **S. Hitchcock:** A. Employment/Salary (full or part-time):; Takeda Pharmaceuticals. **G. Corbett:** A. Employment/Salary (full or part-time):; Takeda Pharmaceuticals. **H.H. Schiffer:** A. Employment/Salary (full or part-time):; Takeda Pharmaceuticals.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.08/CC10

Topic: H.03. Schizophrenia

Support: Fapesp Grant 2014/16634-1

Title: Acute restraint stress differently alters prepulse inhibition of the acoustic startle reflex and social interaction in male wistar rats. The role of the inferior colliculus in the modulation of these responses

Authors: *R. SILVA, P. SILVA, A. WERDER, R. DE OLIVEIRA, J. SIMOES, D. ORTOLANI, I. CESPEDES, R. SPADARI, M. B. VIANA;
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Abstract: Stress plays a role in many psychiatric disorders that are characterized by deficits in prepulse inhibition,PPI. PPI impairment is observed in schizophrenic patients and serves as an index of attention deficit. These deficits may be linked to impairments in sensorimotor gating a mechanism that enables normal individuals to suppress irrelevant information which allows the hierarchical organization of the most relevant information. The inferior colliculus, IC, is a critical structure of the auditory pathway mediating acoustic PPI. One of the main negative symptoms of schizophrenia is social withdrawal. Social behavior can be measured in rodents by the interaction between animal pairs, being a component of the pair considered a reference for the test. The aim of this study was to investigate the effect of exposure of male wistar rats, 250-280 g, to restraint stress, RS, in PPI, social interaction, SI, and corticosterone levels, CL. Analysis of fos protein immunoreactivity, fos-ir, was used to map areas activated by exposure of rats to RS for 15 min, in an acrylic restraining cylinder, previously to the tests. For the PPI test, 18 rats were divided in 2 groups N=9 per group: nonstressed, and stressed. The stressed rats showed a significant increase in PPI response observed in all three prepulse intensities levels compared to nonstressed controls. A possible explanation would be that RS exposure alters processing of external stimuli enhancing attention and thereby influences the effectiveness of a prepulse to inhibit startle responding. For SI test, 40 rats were divided in 4 groups N=10 per group: vehicle-nonstressed; vehicle-stressed; clozapine-nonstressed, and clozapine-stressed. Prior to RS the animals received intraperitoneal injection of vehicle or clozapine, 5 mg/kg.The vehicle/stressed group showed a significant decrease in SI duration in comparison to the other groups probably due to an increase in anxiety levels. Pretreatment with clozapine, prior to RS, was effective in blocking anxiety, facilitating SI behavior in the clozapine/stressed group showing an anxiolytic effect. Measurement of CL showed a significant increase in vehicle/stressed animals. Analysis of fos-ir showed that, among all the analyzed areas, the IC presented the highest mean of activation in the stressed animals. In conclusion, our results confirm that exposure to stressful events is considered an important risk factor in the pathophysiology of schizophrenia triggering physiological, behavioral and emotional changes. Moreover, although the IC is classically related to auditory pathways it seems to be also involved in the elaboration of emotional responses.

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Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.09/CC11

Topic: H.03. Schizophrenia

Title: SUVN-1702012 a multimodal molecule demonstrating separation between antipsychotic and motor side effects

Authors: *A. K. SHINDE, **J. TADIPARTHI**, J. FERNANDES, R. MEDAPATI, A. VYURU, S. PETLU, V. MEKALA, R. SUBRAMANIAN, S. EDULA, M. SRIRANGAVARAM, R. ABRAHAM, P. ACHANTA, J. THENTU, N. MUDDANA, R. NIROGI;
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Abstract: There is an unmet medical need in the treatment of psychotic patients due to treatment resistance or debilitating side effects. SUVN-1702012 is a multimodal lead molecule having affinity for 5-HT/dopamine receptors and proposed for the treatment of psychosis. *In-vitro* pharmacological properties of SUVN-1702012 were evaluated in radioligand binding assay. The pharmacokinetic profile and brain penetration of SUVN-1702012 was evaluated in rodents. SUVN-1702012 reversed head twitches induced by 1-(2, 5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) and hyperlocomotion induced by amphetamine. The doses, at which significant effect was observed in the above assays did not cause motor in-coordination, assessed using the rotarod test. SUVN-1702012 did not induce catalepsy and the time taken to correct the posture was similar to that of vehicle. SUVN-1702012 did not have propensity to induced tardive dyskinesia at the tested doses. Non-radiolabeled assay was used to assess the occupancy of test compound at 5-HT2a, 5-HT1a and D2 receptors in rats. From the current research we conclude that SUVN-1702012 has therapeutic potential to reverse psychosis without inducing debilitating side effects associated with antipsychotics

Disclosures: **A.K. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **J. Tadiparthi:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **J. Fernandes:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Medapati:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **A. Vyuru:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **S. Petlu:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **V. Mekala:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Subramanian:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **S. Edula:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **M. Srirangavaram:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Abraham:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **P. Achanta:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **J. Thentu:** A. Employment/Salary

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Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.10/CC12

Topic: H.03. Schizophrenia

Support: NCN OPUS 12

Title: Nasal respiration drives high frequency oscillations after ketamine in the rat olfactory bulb

Authors: *J. J. WROBEL[1], W. SREDNIAWA[1,2], D. K. WOJCIK[1], M. J. HUNT[1];
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Abstract: Subanesthetic doses of ketamine are used to model schizophrenia in humans and experimental animals. Abberant high frequency oscillations (HFO) 130-180 Hz have been reported in various rodent brain regions following ketamine administration, however the mechanisms underlying the generation of this activity remain unclear. We have shown recently that the rat olfactory bulb (OB) is an important generator of HFO, post ketamine, indicating that sensory input may drive this activity. In this study we recorded local field potentials in the OB and nasal respiration using thermocouples, in freely moving rats. We found that ketamine 20 mg/kg, at a dose that increased locomotion (measured by beam breaks), increased the amount of fast exploratory sniffing behaviour. Post ketamine, HFO in the OB were modulated by a slower 2-12 Hz oscillation that was coupled to nasal respiration on a cycle-by-cycle basis. Unilateral naris blockade attenuated ketamine-induced increases in HFO power on the ipsilateral, but not contralateral side. Bilateral naris blockade produced more complex effects on ketamine-induced HFO, with both reductions in HFO frequency and power observed. Notably, following bilateral naris blockade we also observed a significant reduction in ketamine-induced locomotion, not present after unilateral blockade. Together, these findings show that nasal respiration drives and underlies the coupling of HFO, post ketamine, to lower frequencies. We speculate that the presence of HFO, after ketamine, leads to abnormal processing of olfactory information which contributes to behavioural hyperactivity in rodents.

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Poster

610. Schizophrenia Models and Drug Development

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Program #/Poster #: 610.11/CC13

Topic: H.03. Schizophrenia

Support: Brain Korea 21 PLUS Project for Medical Science, Yonsei University

Title: Obsessive-compulsive disorder-like behaviors in clozapine-treated mice

Authors: *S. KANG, H. NOH, C. KIM;
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Abstract: Clozapine is an atypical antipsychotic drug, which has been used as an effective treatment for schizophrenia. However, their wide range of pharmacological actions to multiple receptors can give rise to various adverse effects. Several clinical studies have reported obsessive-compulsive disorder (OCD) symptoms in schizophrenic patients with chronic pharmacotherapy of clozapine. So far, the relationship between OCD and schizophrenia remains complex, and possible explanations as to why OCD is frequently associated with schizophrenia have been proposed including that OCD is a subgroup of schizophrenia or unmasked by treatment in schizophrenia or induced *de-novo* as one of the aversive effects of treatment. To find out the effects of clozapine on the emergence of OCD symptoms, using mice model of clozapine administration was required. Therefore, we used C57BL6/J wild-type (WT) adult mice to investigate whether clozapine induces *de-novo* onset of OCD-like behaviors. The mice were administered with either clozapine or placebo for 28 weeks, starting from 12-week-old. They were regularly implanted every 60 days with subcutaneous pellets, which release clozapine 0.06 mg/day for 60 days. Behavioral analysis of grooming time and grooming bouts was conducted using video recording at the age of 15, 20, 30 and 40 weeks. Here, we showed that clozapine-treated mice significantly increase repetitive self-grooming behavior after 18 weeks of clozapine treatment. Previous studies reported that genetic deletion of SAP90/PSD95-associated protein 3 (SAPAP3 also known as DLGAP3) induced OCD-like behavior in mice; furthermore, there are significant associations between clozapine-induced OCD symptoms and genetic variants of DLGAP3 in schizophrenic patients. Hence, we wanted to further analyze clozapine-induced OCD-like behavior using DLGAP3 heterozygous knock-out (HET) mice. We observed that clozapine-treated DLGAP3 HET mice also significantly increased self-grooming behaviors, and moreover, it was triggered at an earlier time point compared to the WT mice. Together, these findings highlight that chronic clozapine treatment induces *de-novo* OCD-like symptoms in mice model, suggesting that clozapine might induce OCD-like symptoms in schizophrenic patients irrespective of the brain pathology and the course of schizophrenia.

Disclosures: **S. Kang:** None. **H. Noh:** None. **C. Kim:** None.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

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Topic: H.03. Schizophrenia

Support: Ministry of Science and Technology in Taiwan 104-2918-I-002-016
Ministry of Science and Technology in Taiwan 105-2410-H-002-228
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Ministry of Science and Technology in Taiwan 107-2911-I-002-510 (France-Taiwan Orchid Program)

Title: Therapeutic potential and underlying mechanism of sarcosine (N-methylglycine) in N-methyl-D-aspartate (NMDA) receptor hypofunction models of schizophrenia

Authors: *J.-C. PEI[1], W.-L. HUNG[1], B.-X. LIN[1], M.-H. SHIH[1], L.-Y. LU[1], D.-Z. LUO[1], H.-C. TAI[1], V. STUDER[2,3], M.-Y. MIN[1], W.-S. LAI[1];
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Abstract: Compelling animal and clinical studies support the N-methyl-d-aspartate receptor (NMDAR) hypofunction hypothesis of schizophrenia and suggest promising pharmacological agents to ameliorate negative and cognitive symptoms of schizophrenia. Sarcosine, a glycine transporter-1 inhibitor, was found to improve schizophrenic symptoms in add-on and monotherapy clinical studies. It is imperative to evaluate the therapeutic effect of sarcosine in animal models, which provide indispensable tools for testing drug effects in detail and elucidating the underlying mechanisms. In this study, a series of 7 experiments was conducted to investigate the therapeutic effect of sarcosine in the amelioration of schizophrenia-related behavioral deficits and the underlying mechanism in pharmacological (i.e., MK-801-induced) and genetic (i.e., serine racemase-null mutant ($SR^{-/-}$) mice) NMDAR hypofunction models of schizophrenia. In Experiments 1, our results indicated that the acute administration of 500/1000 mg/kg sarcosine (i.p.) had no adverse effects on motor function and serum biochemical responses. In Experiments 2-4, sarcosine significantly alleviated MK-801-induced (0.2 mg/kg) brain abnormalities and behavioral deficits in MK-801-induced and $SR^{-/-}$ mouse models of NMDAR hypofunction. In Experiment 5, the injection of sarcosine enhanced CSF levels of glycine and serine in rat brain. In Experiments 6-7, we show for the first time that sarcosine facilitated NMDAR-mediated hippocampal field excitatory postsynaptic potentials (fEPSPs) and

influenced the movement of surface NMDARs at extrasynaptic sites. Collectively, sarcosine effectively regulated surface trafficking of NMDARs, NMDAR-evoked electrophysiological activity, brain glycine levels, and MK-801-induced abnormalities in the brain, which contributed to the amelioration of schizophrenia-related behavioral and cognitive deficits in NMDAR hypofunction models of schizophrenia.

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Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

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Topic: H.03. Schizophrenia

Support: NIH Grant MH092638
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Title: Disruption of CA1 sharp-wave ripples by the nonbenzodiazepine hypnotic eszopiclone

Authors: L. A. BECKER[1], H. PENAGOS[2], D. S. MANOACH[3], M. A. WILSON[2], *C. VARELA[4];
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Abstract: Sleep-dependent memory consolidation relies on the coordination of hippocampal, thalamic and neocortical activity. Hippocampal sharp wave ripples (SWRs), which correspond to the reactivation of memory representations, are correlated with neocortical slow oscillations and thalamocortical spindles, and this coordination is thought to facilitate the transfer of memory traces from the hippocampus to neocortex during sleep. Neuropsychiatric disorders such as schizophrenia show disrupted sleep oscillations, which correlate with cognitive impairment. Compounds that enhance these oscillations could therefore have value for the treatment of cognitive deficits in schizophrenia. One candidate is *eszopiclone* (ESZ), a nonbenzodiazepine sedative hypnotic that is used to treat insomnia. We sought to characterize the single-cell and circuit-level effects of ESZ on coordinated sleep oscillations.
We used multi-tetrode implants in male Long-Evans rats (n = 3) to record local field potentials (LFPs) and single units from CA1 in the hippocampus, the retrosplenial cortex and the thalamus. The rats were also implanted with an intraperitoneal infusion cannula for drug delivery.
We recorded from these three brain regions for > 3 hours/recording session in 3 rats. We used

two controls: we compared two ESZ (10 mg/kg) and two vehicle infusions per rat; we also recorded one hour before infusion to obtain a within-session baseline. We find that cell firing in the retrosplenial cortex and in CA1 decreases after ESZ compared to vehicle, and the effect is strongest in CA1 (up to 40 % decrease in firing). To study sleep population dynamics, we detected sleep events from the filtered LFPs: K-complexes in retrosplenial cortex (KCs, which mark the down-states of the slow oscillation), and SWRs in CA1. We observed a reduction in the number of SWRs after ESZ, and no substantial change in the rate of KCs. Lastly, spectral analyses show a decrease in power in the CA1 100-275 Hz band, confirming a disruption of CA1 SWRs.
The results suggest that ESZ may have an adverse effect on hippocampus-dependent memory due to an impairment of CA1 SWRs. These results may explain its failure to improve sleep-dependent memory consolidation in humans; they also validate a rodent preparation that can be used to evaluate the effect of drugs on the oscillations that are key for memory consolidation, prior to clinical trials to improve memory in schizophrenia and other disorders.

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Poster

610. Schizophrenia Models and Drug Development

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Program #/Poster #: 610.14/CC16

Topic: H.03. Schizophrenia

Support: CONACyT (No. 385511)

Title: Cerebrolisyn treatment improves behavioral deficits and neuronal changes in a prenatal immune challenge

Authors: *G. TELLEZ[1], F. DE LA CRUZ[1], G. FLORES[2];
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Abstract: Cerebrolysin (CBL) is a neuropeptide mixture that is known to stimulate the activation of neurotrophic factors (Ubhi et al., 2015), increase neuronal survival in a transgenic mouse model of Alzheimer disease (Rockenstein et al., 2015) and ameliorate neuronal changes in limbic regions and behavioral deficits (Vazquez-Roque et al 2012, 2014) in an animal model of schizophrenia.
Also, it was observed that CBL treatment improves cognitive deficits in schizophrenic patients (Xiao et al., 2012). The prenatal immune challenge using lipopolysaccharide (LPS), a potent immune activator. It is based on the fact that maternal infections during pregnancy can result in

behavioral and neuronal dysfunctions in the adult offspring, which are associated with schizophrenia-related behavior in rodents. Currently, the main objective of schizophrenia treatment is based on counteracting the positive symptoms. However, other aspects of the pathology also need to be addressed. In the present report, we evaluate the effect of chronic CBL treatment at post-pubertal age on behavior and neuronal morphology changes induced by LPS prenatal exposure in rats. Open field and social interaction tests were performed. Golgi-Cox staining method was used to analyze neuronal morphology in the prefrontal cortex and basolateral amygdala. In a previous study, we found a significant increase in motor activity and a decrease in social interaction in LPS offspring. Also, we reported hypertrophy in the prefrontal cortex and basolateral amygdala. We observed that the CBL treatment ameliorate motor activity and social interaction. The morphological analysis of the prefrontal cortex and basolateral amygdala showed atrophy in the animal exposed to LPS that was restored by the CBL treatment. Our result suggests that CBL ameliorate the behavioral dysfunction and morphological alterations caused by the prenatal immune challenge. (Supported by: CONACyT grants (No. 385511) to GTM).

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Poster

610. Schizophrenia Models and Drug Development

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Topic: H.03. Schizophrenia

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Grant #: 304332/2016-0 Abreu-Villaça (PI) 04/2017 - 03/2021 National Research Council (CNPq) / Brasilia, Brazil

Title: Nicotine pre-exposure alters PCP-induced hyperlocomotion in adolescent C57BL/6 mice: The impact of the dopaminergic system

Authors: *A. C. DUTRA-TAVARES[1], V. H. DUARTE-PINHEIRO[2], J. O. SILVA[2], A. BANDEIRA-MARTINS[2], C. C. FILGUEIRAS[2], A. C. MANHAES[2], Y. ABREU-VILLAÇA[2]; [1]Physiological Sci., Univ. Do Estado Do Rio De Janeiro, Rio de Janeiro, Brazil; [2]Physiological Sci., State Univ. of Rio de Janeiro, Rio de Janeiro, Brazil

Abstract: The prevalence of tobacco use is much higher in schizophrenic patients than in individuals that do not develop this disorder. Recently, epidemiological data has shown that

tobacco use often precedes the first psychotic event. Notwithstanding, there is a lack of experimental studies that investigate the impact of previous exposure to nicotine in schizophrenia models. Considering that hyperactivity is a positive symptom of schizophrenia that can be induced in the rodent phencyclidine (PCP) model of this disease, this work aimed to evaluate the effects of nicotine (NIC) pre- and concomitant exposure on PCP-induced hyperlocomotion. Given the established role the dopaminergic system in locomotor activity, we further investigated whether raclopride (RAC), a D2 antagonist, mediates PCP and nicotine effects. To do this C57BL6 mice were exposed to nicotine (24mg/kg/day) or deionized water through osmotic minipumps (1002 model, Alzet) from postnatal day (PN) 37 to PN50. From PN41 to PN43, mice were habituated to an open field arena (60min/day) and to subcutaneous injections. Subsequently, for 7 consecutive days (acquisition period, PN44-PN50), both nicotine-exposed and control mice were submitted to daily open field sessions divided into 3 blocks: 1) 10 min of testing to assess baseline ambulation, 2) raclopride (0.25mg/kg, s.c.) or saline injection followed by 10 min of testing and 3) PCP (2.5mg/kg, s.c.) followed by a 40-min ambulation assessment in the open field. All mice received PCP injections, accordingly, there were four groups: CTRL, n=6; RAC, n=7; NIC, n=8; NIC-RAC, n =7). Ambulation reduced throughout the sessions blocks of the habituation phase. Comparisons between open field blocks 1 and 3 indicated that PCP induced hyperlocomotion throughout acquisition phase. Although in the first acquisition day nicotine reduced PCP-induced hyperlocomotion, with repeated PCP administration a potentialization of PCP-induced hyperlocomotion effect by chronic nicotine was observed. Concerning raclopride effects, this drug decreased PCP effects during acquisition phase. Newsworthy, nicotine increased raclopride inhibitory effect on PCP-induced hyperlocomotion. These results suggest that previous exposure to nicotine can magnify PCP effects, an established pharmacological animal model of schizophrenia, corroborating the shared vulnerability theory of schizophrenia-nicotine dependence comorbid association. Finally, the reduced locomotor activity in mice exposed to raclopride indicate that both PCP and nicotine hyperlocomotor effects are mediated, at least in part, by the activity of the dopaminergic system.

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Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.16/CC18

Topic: H.03. Schizophrenia

Title: Serpentine and AJC-61 effects on cognitive deficit, locomotor activity and social interaction in phencyclidine (PCP)-treated mice and other behaviors are blocked by the 5-HT_{2C} receptor antagonist, SB242084

Authors: *H. Y. MELTZER[1], K. SCHEIDT[2], A. J. CSAKAI[2], J. MCCORVY[3], L. RAJAGOPAL[4], M. HUANG[5];
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Abstract: 5-HT_{2C} agonists have considerable therapeutic potential. The 5-HT_{2C} agonist, vabicaserin, WAY 163909, was effective in preclinical models of antipsychotic activity and in treating acutely psychotic schizophrenia patients. Another 5-HT_{2C} agonist, lorcaserin, is approved but only for weight loss. Weight gain due to antipsychotic drugs (APDs) is due, in part, to 5-HT_{2C}R antagonism. An APD with minimal weight gain and facilitation of weight loss would be highly desirable. We have found that the alkaloids, alstonine, a natural product, and its isomer, serpentine, have 5-HT_{2C}R agonist-like effects. These include inhibition of LMA due to phencyclidine (PCP), an NMDAR uncompetitive antagonist, an indication of antipsychotic activity. This effect is blocked by the neutral 5-HT_{2C} antagonist, SB242084. Based on the structure of these natural products, we have synthesized a series of 9*H*-pyrido[3,4-*b*]indol-6-ols and extensively characterized one of them, AJC-61, in a variety of behavioral assays and microdialysis. Like other 5-HT_{2C} agonists, serpentine and AJC-61 inhibit the release of DA in PFC and dSTR of awake freely moving mice, in an SB242084 dependent manner. Serpentine and AJC-61 restored novel object recognition and reversal learning in mice treated with PCP for 7 days, followed by withdrawal. Both AJC-61 and serpentine restored social interaction in scPCP mice. Thus, AJC-61 has promise as a treatment for cognitive impairment, positive and negative symptoms. AJC-61 restored NOR in 20 month old mice and was also active in the forced swim, marble burying and nestlet shredding tests, indications of efficacy as an antidepressant and OCD. AJC-61 inhibited the increases in cortical glutamate, and other neurotransmitters, following PCP. AJC-61 has only weak affinity for the 5-HT_{2C} and had even lower affinity for D_2, 5-HT_{2A} or other GPCRs, and had little activity in cell-based assays for 5-HT_{2C} activity. AJC-61 or other compounds in this series are being investigated for several clinical indications, including schizophrenia. Supported by donations from the Weisman and Price families and a grant from the Center for Life Processes, Northwestern University.

Disclosures: H.Y. Meltzer: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NIDA, Acadia, •Sumitomo Dainippon Pharma , Sunovion, Eli Lilly, Lundbeck. **K. Scheidt:** None. **A.J. Csakai:** None. **J. McCorvy:** None. **L. Rajagopal:** None. **M. Huang:** None.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.17/CC19

Topic: H.03. Schizophrenia

Support: NRSA NIMH F31MH109238
NIMH R01 MH077779

Title: Schizophrenia-like cognitive control failure after NMDAR blockade reflects disrupted interactions between prefrontal cortex and MD thalamus

Authors: *A. L. DENICOLA[1,2], M.-Y. PARK[1,2], D. A. CROWE[3,2], M. V. CHAFEE[1,2]; [1]Neurosci., Univ. of Minnesota, Minneapolis, MN; [2]Brain Sci. Ctr., Veterans Affairs Hosp., Minneapolis, MN; [3]Biol., Augsburg Univ., Minneapolis, MN

Abstract: Cognitive control deficits are a hallmark of schizophrenia. Our lab studies cognitive deficits in a model of schizophrenia using the Dot-Pattern Expectancy Task (DPX). This task consists of a cue stimulus, a delay period, a probe stimulus and then a response. The response is determined by the combination of the cue and probe: A-cue followed by an X- probe requires a target response and all other cue-probe combinations (AY, BX, and BY) require a nontarget response. Trials are presented in two different set types, balanced (25% of each trial type) and prepotent (69% AX, 12.5% AY and BX, and 6% BY). Patients with schizophrenia perform worse on BX trials due to potential deficits in working memory, context processing, and habitual response inhibition. Brain regions associated with cognitive control and have been found to be hypoactive in patients with schizophrenia include the dorsolateral prefrontal cortex (PFC) and the mediodorsal nucleus of the thalamus (MDT). We have developed a monkey model of schizophrenia by injecting of Ketamine or Phencyclidine (PC), resulting in a BX error during acute drug exposure. Using this model we explored the role of the PFC and MDT during performance of the DPX task. We recorded in both brain regions simultaneously using 32-channel linear silicone electrode arrays, allowing for tetrode-like recording of spike data.
We found that MD contained the full complement of neural signals present in PFC during the task, including 'switch' neurons maximally activated by B-cues during the cue period and the AY cue-probe sequence during the probe period. These neurons appear to encode the likelihood of having to override the prepotent 'target' response in the task based on the stimuli shown and therefore reflect cognitive control. Interestingly, we found that response related activity (both numbers of neuron and signal strength) was strongly enriched in the MD thalamus in comparison to PFC. In addition, we found that the habitual 'target' motor response was much more strongly encoded in MD than PFC, which appeared principally engaged to override this response. Finally, blocking NMDAR using PCP significantly reduced cognitive control signals in both PFC and

MD, but PFC signals were particularly weakened by NMDAR blockade under conditions of increased cognitive control load. These data suggest that, when the network is not working properly, as in the schizophrenia-like state caused by NMDAR synaptic failure, BX errors emerge due to the inability of the PFC to inform the MDT to inhibit the prepotent response.

Disclosures: **A.L. DeNicola:** None. **M. Park:** None. **D.A. Crowe:** None. **M.V. Chafee:** None.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.18/CC20

Topic: H.03. Schizophrenia

Support: 1R01MH107491

Title: Disrupting NMDAR synaptic transmission changes causal relationships between cell and network level physiological signals in the prefrontal-parietal network

Authors: E. KUMMERFELD[1], S. MA[2], ***D. A. CROWE**[3], R. K. BLACKMAN[4], M. V. CHAFEE[5];
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Abstract: A crucial challenge in the biology of neuropsychiatric disease is understanding the relationship between changes in brain function at the cell level, (such as are caused by synaptic failure or genetic mutation,) and changes in brain function at the network level, (such as are detectabledetectible with human neuroimaging techniques and are related to information processing for behavior). To understand these relationships, we applied dynamic causal discoverymodeling to time series of neural data at the cell level (spike trains of individual neurons) and the network level (oscillatory power in local field potential recordings) obtained from monkey prefrontal and parietal cortex during the performance of a task measuring cognitive control failure in schizophrenia. We contrasted causal relationships between these variables (a) , under control conditions, and (b) following systemic blockade of NMDAR synaptic transmission in monkeys we have shown mimics the cognitive control error pattern of patients.
We found that dynamic causal discoverymodeling detected causal relationships between neural signals at the cell level (cell-to-cell based on spike timing), the network level (LFP-to-LFP at different brain sites based on modulation of oscillatory power), and across levels (LFP-to-cell and vice versa). Fitting causal models to neural data recorded under controlbaseline conditions and following NMDAR blockade revealed the contribution of NMDAR synaptic transmission to network dynamics. Blocking NMDAR produced opposite changes in prefrontal and parietal

neural dynamics. Both cell-to-cell and LFP-to-LFP causal interactions were weaker in prefrontal cortex and stronger in parietal cortex following NMDAR blockade. Finally, we found interactions between LFP and cell spiking were strongest in different frequency bands in parietal cortex (primarily theta band) and prefrontal cortex (delta band), and differentially aeffected by NMDAR blockade. These results provide evidence that prefrontal and parietal network dynamics are differentially dependent on NMDAR synaptic mechanisms and that dynamic causal discoverymodeling can capture interactions between brain signals at different levels of physical scale (cell and network). Thisthat could make it possible to infer the state of cell-to-cell interactions in the human brain based on network signals that can be measured in humans.

Disclosures: D.A. Crowe: None. **M.V. Chafee:** None. **E. Kummerfeld:** None. **S. Ma:** None. **R.K. Blackman:** None.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.19/CC21

Topic: H.03. Schizophrenia

Support: Allergan L. C.
donations from the Weisman family

Title: Administration of rapastinel on multiple dose schedule enhances its antidepressant and cognitive enhancing properties: Evidence for a 5-HT_{1A} dependent mechanism of action

Authors: *M. HUANG[1], L. RAJAGOPAL[1], A. M. ELZOKAKY[1], C. A. RYAN[1], P. BANERJEE[2], H. Y. MELTZER[1];
[1]Psychiatry and Behavior Sci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL;
[2]Allergan Plc., New Jersey, NJ

Abstract: Rapastinel, an NMDAR positive modulator, has shown antidepressant and cognitive enhancing actions in rodent models, with inconclusive results as adjunctive treatment in depressed patients. We reported that rapastinel 1.0 mg/kg, but not 0.3 mg/kg, significantly reversed the deficit in novel object recognition (NOR) in mice administered the NMDA receptor antagonist, phencyclidine (PCP), for one week (sub-chronic PCP, sc-PCP), suggesting possible efficacy in treating cognitive impairment in schizophrenia and other psychotic spectrum disorders. We have now examined the ability of rapastinel administered subcu at various schedules to restore NOR and mobility in the forced swimming test (FST), a test of antidepressant action, in sc-PCP-treated mice, as well as the role of 5-HT_{1A} agonism in its mechanism of action. We now report that administration of rapastinel at 8 hr intervals on a bid schedule for 3 or 5 days at doses up to 30 mg/kg in sc-PCP mice restored NOR and improved

mobility in the FST, not evident with lower single doses or bid doses for 1 or 2 days. For example, rapastinel (1 mg/kg, subcu bid for 3 days) restored NOR for 9 weeks, while 5 days bid treatment restored NOR for 17 weeks. Rapastinel (10 mg/kg, subcu bid for 3 days) increased mobility in FST for 7 weeks in scPCP mice. This suggests rapastinel has the ability to stimulate neuroplasticity and a link between cognitive impairment and depression based upon shared mechanisms of synaptic dysfunction. Using microdialysis in freely moving mice, we found that rapastinel (3 and 10 mg/kg, subcu) increased efflux of cortical 5-HT, along with dopamine, norepinephrine, acetylcholine, but not glutamate, which might contribute to its cognitive enhancing and antidepressant actions. Pretreatment with the 5-HT_{1A} antagonist, WAY100635, blocked the effect of rapastinel in NOR in wildtype mice and FST in mice which had received both sc-PCP and chronic unpredictable stress, a model of treatment resistant depression. These data suggest that bid schedule with rapastinel may trigger synaptic plasticity. Whether this type of repeated administration will enhance clinical efficacy of rapastinel requires clinical testing.

Disclosures: **M. Huang:** None. **L. Rajagopal:** None. **A.M. Elzokaky:** None. **C.A. Ryan:** None. **P. Banerjee:** A. Employment/Salary (full or part-time):; employee. **H.Y. Meltzer:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research grant. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); receipt of drugs. F. Consulting Fees (e.g., advisory boards); consulting.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.20/CC22

Topic: H.03. Schizophrenia

Title: Bumetanide rescue of phencyclidine-induced deficits in cognition, positive and negative symptoms in mice implicates NKCC1/KCC2-mediated changes in GABAA function in the pathophysiology and treatment of schizophrenia

Authors: *L. RAJAGOPAL[1], H. R. KIM[2], M. MARTINA[3], H. Y. MELTZER[4]; [1]Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [2]Dept. of Physiol., Northwestern Univ., Chicago, IL; [3]Northwestern Univ. Med. Sch., Chicago, IL; [4]Northwestern Univ. Sch. of Med., Chicago, IL

Abstract: GABA is the major inhibitory neurotransmitter in the developing and adult brain but in the earliest weeks of life, and in various pathological conditions, it is excitatory, and helps to shape neurocircuitry and neuroplasticity. Whether GABA neurons are excitatory or inhibitory is a function of their chloride content, with high intracellular chloride leading to excitatory

GABAergic activity. The ratio of the activity of two membrane transport proteins which transport sodium, potassium, and chloride ions across the cell membrane, NKCC1 and KCC2, enabling chloride to enter the cell or be extruded, respectively, determines whether stimulation of $GABA_A$ receptors will be depolarizing or hyperpolarizing. Bumetanide is an inhibitor of NKCC1 and can convert $GABA_A$ currents from excitatory to inhibitory. We have found that after one week administration of the NMDAR inhibitor, phencyclidine (PCP), to rodents, a widely studied model of schizophrenia, bumetanide acutely rescued the deficit in novel object recognition, executive function, and working memory produced by PCP treatment. Five days treatment with bumetanide to PCP mice followed by withdrawal restored NOR for up to four weeks with a lesser effect each week. Bumetanide also acutely improved the scPCP-induced deficit in negative symptoms and inhibited amphetamine- and PCP- induced locomotor activity, two distinct models of positive symptoms. Sub-effective doses of bumetanide and the selective GABAA agonist, Gaboxadol, acutely restored NOR in PCP mice. Bumetanide was also effective to alter PCP-induced changes in locomotor activity and social interaction indicating that all major dimensions of schizophrenia may be sensitive to this mechanism. We subsequently found that scPCP in 20 week old mice increases NKCC1, without altering the level of KCC2, in the PLC sub-region of the PFC (Kim et al. this meeting). Formal clinical trials of bumetanide are required to test its efficacy as a treatment for schizophrenia.

Disclosures: L. Rajagopal: None. **H.R. Kim:** None. **M. Martina:** None. **H.Y. Meltzer:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NIDA, REPROOF Sumitomo Dainippon Pharma Co., Ltd, Acadia, Allergan, Eli Lilly, Sunovion, Takeda.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.21/CC23

Topic: H.03. Schizophrenia

Title: Increased NKCC1 expression in mPFC pyramidal cells of the subchronic phencyclidine (scPCP) mouse model of schizophrenia causes a depolarizing shift of $GABA_A$ current reversal potential and mediates cognitive impairment

Authors: H. KIM, L. RAJAGOPAL, H. Y. MELTZER, *M. MARTINA;
Northwestern Univ. Med. Sch., Chicago, IL

Abstract: Cognitive deficits are the major determinants of functional outcome in schizophrenia. Current atypical antipsychotic drugs (APDs) only partially address these deficits and only in some patients. Previous studies suggested that alteration of GABAergic inhibition in the medial prefrontal cortex (mPFC) is critical for cognitive deficits in schizophrenic patients. However,

there is a longstanding debate on the role of altered GABA, and how the mPFC networks of dorsal/ventral (prelimbic cortex; PLC, infralimbic cortex; ILC) subdivisions are affected in schizophrenia remains unclear. We utilized mice withdrawn from subchronic treatment (7 days 10mg/kg bid) with the NMDAR uncompetitive antagonist, phencyclidine (PCP), an established model for cognitive deficits in schizophrenia, to investigate the role of GABAergic signaling in the mPFC. Ex-vivo whole-cell patch clamp recordings in acute slices showed that scPCP treatment caused increased excitability of pyramidal neurons in the ILC, but not PLC, without apparent differences in the frequency of $GABA_A$-mediated synaptic currents. We then performed gramicidin perforated patch clamp recordings in acute PFC slices to record electrical signals while keeping intact the intracellular chloride concentration. We found that the reversal potential of the $GABA_A$ current in ILC pyramidal neurons from scPCP mice was depolarized compared to the control (vehicle-treated) group. Next, we used quantitative *in situ* hybridization to examine the expression level of the ion cotransporters controlling intracellular chloride concentration and found that the expression of the sodium-potassium-chloride cotransporter NKCC1 was selectively increased in the ILC of the scPCP mice, suggesting a possible molecular basis for the impaired neuroplasticity and the vulnerability to excitotoxic damage to the ILC. We, therefore, tested the effect of bumetanide, a relatively selective NKCC1 inhibitor, in acute slices and found that it normalized the reversal potential of the $GABA_A$ current in scPCP mice. Additionally, behavioral analysis showed that bumetanide treatment *in vivo* rescued the cognitive impairment of these mice (Rajagopal et al. this meeting).

Disclosures: H. Kim: None. **L. Rajagopal:** None. **H.Y. Meltzer:** None. **M. Martina:** None.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.22/CC24

Topic: H.03. Schizophrenia

Support: Linea 2 - Piano ricerca dipartimentale

Title: Epistatic interaction between dopamine D3 receptor and dysbindin modulates cortical functions and behavior related to schizophrenia in human and mice

Authors: *S. SALOMONE[1], G. LEGGIO[1], S. A. TORRISI[1], F. DRAGO[1], F. PAPALEO[2]; [1]Univ. of Catania, Catania, Italy; [2]Fondazione Inst. Italiano Di Tecnologia, Genova, Italy

Abstract: Dopamine D2-like receptors, including D2R, D3R and D4R subtypes, have been implicated in schizophrenia neuropathology and its therapeutic treatments. However, it is still unknown whether intracellular trafficking of the D2R-like family might play a role in the pathology onset and therapy efficacy. Here we focused on dysbindin-1, a protein implicated in

D2R-like intracellular trafficking, and D3R expression and activity. We first analyzed the genotype of schizophrenic patients (CATIE). Those patients exhibiting concomitant reduced function of both D3R and dysbindin-1 showed better executive and working memory functions (Wisconsin Card Sorting Test and Working Memory performances). Based on these data we hypothesized an interaction between these genes in humans and tested this interaction in mice, by generating a mouse line with concomitant hypofunction of both Dys and D3R genes ($D3^{+/-}$ *$Dys^{+/-}$). These double mutants showed an improvement in PFC-dependent working memory abilities, compared to single D3R+/- and Dys+/- and their wild-type +/+ littermates, as assessed in experimental behavioral paradigms, such as the Temporal Order Recognition (TOR), the working memory discrete paired-trial variable-delay T-maze task, the startle/prepulse inhibition (PPI), the social interaction, locomotors activity. Furthermore, the double mutant showed a rescue in PFC neuronal excitability and extracellular dopamine levels, that were changed in the Dys+/-. No epistatic effects were detected on positive and negative symptoms in humans (PANSS) and in their mouse equivalent (sensorimotor gating, locomotor functions and social behavior). These behavioral differences are consistent with a genetic-driven D2/D3 receptor unbalance in the PFC, but not in the striatum, which may serve as target for pro-cognitive treatments in schizophrenia, in the context of genetic-based precision medicine.

Disclosures: S. Salomone: None. **G. Leggio:** None. **S.A. Torrisi:** None. **F. Drago:** None. **F. Papaleo:** None.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.23/CC25

Topic: H.03. Schizophrenia

Support: The Watanabe Foundation

Title: NLRP3 may not be related to the pathological specific features of schizophrenia

Authors: *N. KAJITANI[1], T. YAMAUCHI[1,9], M. IWATA[2], A. MIURA[3], T. YAMANASHI[4], N. KAMIYA[5], K. TSUNETOMI[4], M. NAGATA[6], A. SHIBUSHITA[1], R. MATSUO[7], T. NISHIGUCHI[8], K. WATANABE[10], K. KANEKO[11];
[1]Tottori Univ., Yonago, Japan; [2]Tottori Univ., Yonago, Tottori, Japan; [3]Tottori Univ., Yonago/Tottori, Japan; [4]Tottori Univ., Tottori, Japan; [5]Tottori Univ., Tottori-Prefecture, Yonago-City, Japan; [6]Tottori Univ., Yonago-Shi, Japan; [7]Devision of Neuropsychiatry, Tottori Univ., Yonago-Shi, Tottori-Ken, Japan; [8]Tottori Univ., Yonago-Shi Tottori, Japan; [9]Dept. of Psychiatry, Nara Med. Univ., Nara, Japan; [10]Watanabe Hosp., Tottori, Japan; [11]Fac Med. Tottori Univ., Yonago, Japan

Abstract: In recent years, it has been suggested that inflammation is involved in the pathophysiology of various psychiatric disorders such as major depressive disorder, bipolar disorder, and schizophrenia. It has been demonstrated that schizophrenia patients show high blood levels of inflammatory cytokines. Previously, we had revealed that stress causes inflammation in the brain, and that NLRP3 is a critical molecule that causes inflammation. In preclinical studies, we showed that stress activated NLRP3 and increased pro-inflammatory cytokine levels in brain. Moreover, pro-inflammatory cytokines did not increase under stressful conditions if NLRP3 was inhibited. Also, in clinical trials by another group, NLRP3 was increased in major depressive disorder patients, and antidepressant treatment reduced NLRP3. We can conclude NLRP3 seems to play an important role in the pathophysiology of psychiatric disorders in terms of inflammation. Here, we investigated whether NLRP3 is involved in the pathophysiology of schizophrenia on a small number of patients as a preliminary study. The study consisted of a schizophrenia group of 7 patients with initial or relapsed phase, compared with 7 healthy subjects. There was no difference between the mean age and gender ratio of the schizophrenia group and the healthy group. Some patients in the schizophrenia group were taking antipsychotic drugs. Blood samples were collected, and the concentration of NLRP3 in monocytes and plasma was examined by western blotting. The results showed that there was no significant difference in NLRP3 concentration between schizophrenic and healthy group. In addition, when comparing before and 2 months after the treatment, there was no correlation between the PANSS score and the concentration of NLRP3. To our knowledge, two reports have examined NLRP3 in schizophrenia so far, and it has been reported that there is no difference between schizophrenic and healthy individuals. Although the sample size was small, our data showed similar results. In addition, it was found that the PANSS score and the levels of NLRP3 did not correlate in the same patient in spite of the treatment. These findings suggest that there may be no relationship between schizophrenia and NLRP3. Activation of IL-1β is known to be regulated by NLRP3, but elevated levels of pro-inflammatory cytokines such as IL-1β in schizophrenia may be controlled by other factors. Since this study was conducted in a small group, further large-scale investigation is needed. The study was approved by the Ethics Committee of the Faculty of Medicine of Tottori University, Tottori, Japan.

Disclosures: **N. Kajitani:** None. **T. Yamauchi:** None. **M. Iwata:** None. **A. Miura:** None. **T. Yamanashi:** None. **N. Kamiya:** None. **K. Tsunetomi:** None. **M. Nagata:** None. **A. Shibushita:** None. **R. Matsuo:** None. **T. Nishiguchi:** None. **K. Watanabe:** None. **K. Kaneko:** None.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.24/CC26

Topic: H.03. Schizophrenia

Title: Vesicle trafficking mechanisms in BLOC-1 deficiencies

Authors: R. DZVURUMI, S. HATCHER, A. LOMBARDO, R. THOMPSON, A. WAGNER, S. CORDERO ROMERO, ***J. L. LARIMORE**;
Agnes Scott Col., Atlanta, GA

Abstract: Dysbindin is a subunit of the octomeric biogensis of lysosme related organelles complex 1 (BLOC-1) which regulates vesicle trafficking from the early endosome to the lysosome, and, in neurons, to the axon terminal. Dysbindin has been implicated in several neurodevelopmental disorders including Rett syndrome (RTT) and schizophrenia (SZ). Endosomal proteins have been identified in genomic studies in both disorders, suggesting a common molecular mechanism between these neurodevelopmental disorders. This study explores the levels of key endosomal and secretory pathway proteins in coronal brain sections from Mecp2 null mice and BLOC-1 deficient mice to determine if trafficking proteins are altered in the dentate gyrus. Further characterization of vesicle trafficking protein levels in the dentate gyrus is necessary to better understand how the endosomal pathway regulates proper neuronal development in the hippocampus.

Disclosures: R. Dzvurumi: None. **S. Hatcher:** None. **A. Lombardo:** None. **R. Thompson:** None. **A. Wagner:** None. **S. Cordero Romero:** None. **J.L. Larimore:** None.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.25/CC27

Topic: H.03. Schizophrenia

Support: FAPESP
CNPq
CAPES

Title: Ndel1 neuropeptidase activity as a potential biomarker of early and late stages of schizophrenia

Authors: *M. F. H. HAYASHI;
Unifesp, São Paulo, Brazil

Abstract: Aim: We have showed reduced Ndel1 enzyme activity in patients with chronic schizophrenia (SCZ), and only a subtle *NDEL1* mRNA increases in antipsychotic-naïve first-episode psychosis (FEP) individuals compared to matched healthy controls (HC). Aiming to refine the evaluation of Ndel1 enzyme activity in early stages of psychosis, we compared 4 groups composed by (1) subjects at ultra-high-risk (UHR) for psychosis, (2) antipsychotic-naïve

FEP individuals (assessed in three moments, at baseline (FEP-0), and after 2 months (FEP-2M) and one year (FEP-1Y) of treatment with risperidone), (3) chronic SCZ patients, and (4) HC volunteers.
Methods: Blood samples were collected from all subjects into heparin vacuum tubes for plasma preparation. Ndel1 enzyme activity was measured essentially by measuring the hydrolysis of a FRET substrate at 37ºC.
Results: There was no significant difference in Ndel1 enzyme activity between UHR and HC, but this activity was significantly lower in FEP compared to HC. Conversely, Ndel1 activity in HC groups was higher than in FEP even before (FEP-0) or after the treatment with risperidone (FEP-2M and FEP-1Y). Progressive decrease of Ndel1 activity and significant symptomatic improvement were observed with this treatment. In addition, a positive correlation was observed for Ndel1 activity with clinical symptoms amelioration, as assessed by PANSS or GAF scores, although this correlation was not observed for chronic SCZ.
Conclusion: We show here that even under maintenance of the treatment with antipsychotics, the Ndel1 activity does not return to the levels determined at pre-morbid stage UHR or to those found in HC.
Financial support by FAPESP, CNPq and CAPES.

Disclosures: M.F.H. Hayashi: None.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.26/CC28

Topic: H.03. Schizophrenia

Support: Department of Psychiatry (UAB)

Title: mTOR complex specific abnormalities in schizophrenia brain

Authors: *R. CHADHA[1,2], J. H. MEADOR-WOODRUFF[1];
[1]Dept. of Psychiatry, [2]GBS, Neurosci. theme, Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Cognitive deficits are observed in a majority of schizophrenia (SZ) patients. The AKT-mTOR pathway is an important signaling cascade associated with cognitive dysfunction. This pathway is tightly regulated by differential phosphorylation of key proteins. AKT is a serine-threonine kinase which regulates cell survival, proliferation and growth and requires phosphorylation at S473 and T308 for complete activation. Prior literature suggests reduced expression of AKT in SZ. mTOR is a kinase that forms 2 distinct complexes- mTORC1 and mTORC2. mTORC1 consists of mTOR, Raptor, GβL, PRAS40 and Deptor proteins. It facilitates

ribosome biogenesis and protein translation and acts downstream of AKT. mTORC2 consists of mTOR, Rictor, GβL, Protor, mSin1 and Deptor proteins. It plays an important role in actin dynamics and acts upstream of AKT. mTOR is phosphorylated at S2448 and S2481 sites for activation in both complexes. Abnormalities in the mTOR complexes can contribute to dysregulated protein synthesis and actin dynamics, both of which which have been implicated in SZ. Previously, we found decreased levels of AKT and GβL protein expression in SZ brain. Phosphorylated forms of AKT (S473), mTOR (S2448) and S6RP (S235/236 and 240/244) were also found to be reduced. Therefore, in this study, we investigated if there are mTOR complex specific deficits in SZ. We used postmortem dorsolateral prefrontal cortex (DLPFC) from 22 matched pairs of SZ and comparison subjects. The DLPFC plays an important role in cognitive functioning and has widespread evidence in support of its role in SZ. We co-immunoprecipitated mTORC1 using Raptor and mTORC2 using Rictor proteins, to determine the structural and functional integrity of each complex. Using western blot analysis, we measured protein expression of raptor, rictor and mTOR, as well as phosphorylation of mTOR in both complexes. To assess the relative abundance of mTOR complexes, we co-immunoprecipitated mTOR and measured the ratio of raptor to rictor. Our findings suggest that the AKT-mTOR signaling pathway is downregulated in SZ DLPFC. Given the importance of this pathway in synaptic plasticity via its regulation of protein synthesis and cytoskeletal organization, these abnormalities may represent a mechanism underlying cognitive dysfunction in SZ.

Disclosures: R. Chadha: None. **J.H. Meador-Woodruff:** None.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.27/CC29

Topic: H.03. Schizophrenia

Support: USPHS grant P50-MH103222

Title: Treatment of pregnant rats with N-acetylcysteine does not alter kynurenic acid levels in the fetal brain

Authors: *K. V. SATHYASAIKUMAR, M. A. R. THOMAS, R. SCHWARCZ;
MPRC, Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Elevated brain kynurenic acid (KYNA) levels are implicated in the pathophysiology of schizophrenia. In rats, prenatal treatment with KYNA's immediate bioprecursor kynurenine leads to elevated brain KYNA levels and to cognitive deficits reminiscent of schizophrenia in adulthood (Pocivavsek et al., 2014). KYNA synthesis from kynurenine occurs mainly through irreversible enzymatic transamination by kynurenine aminotransferases (KATs). In the brain of

adult rats, KAT II is the principal enzyme responsible for the neosynthesis of rapidly mobilizable KYNA and therefore constitutes an attractive target for pro-cognitive interventions (Schwarcz et al., 2012). We recently demonstrated that N-acetylcysteine (NAC) inhibits KAT II activity in liver and brain tissue homogenates in rats and humans (Sathyasaikumar et al., SfN 2018), and therefore suggested that this effect may play a critical role in the pro-cognitive effects of the compound seen in humans (Steullet et al., 2016). In further support of this hypothesis, we also showed that NAC reduces *de novo* production of KYNA in the medial prefrontal cortex of unanesthetized adult rats treated with kynurenine *in vivo*. As NAC crosses the placenta in humans (Horowitz et al., 1997), and in view of the developmental etiology of schizophrenia, we now designed a follow-up study to examine the effects of *prenatal* treatment with NAC on KYNA levels and neosynthesis in *fetal* brain and liver as well as in the dam. To this end, we fed pregnant rats with kynurenine alone (100 mg/day in chow; N=4), NAC alone (350 mg/day in chow; N=2), or kynurenine + NAC (100 mg/day + 350 mg/day in chow; N=4) from embryonic day (ED)15 until ED20. Control rats (N=3) received normal chow. Tissues were collected from dams and fetuses (3-4 fetuses per dam) 4 h after the last feeding on ED20. Compared to controls, dams exposed to kynurenine showed a ~3-4-fold elevation in KYNA levels in the brain, and quantitatively similar increases were seen in fetal brains and livers. NAC treatment did not attenuate the kynurenine-induced KYNA formation in fetal brain and liver. This could be due to the very low KAT II activity in the fetus (Ceresoli-Borroni and Schwarcz, 2000, and unpublished data). Unexpectedly, NAC also failed to inhibit the kynurenine-induced ~3-fold increase in the brain of dams, and NAC treatment alone did not influence the endogenous levels of KYNA in tissues assessed in either embryos or dams. Our results demonstrate that treatment of pregnant rats with NAC during the last week of gestation is not an effective strategy to reduce KYNA levels in the fetal brain.

Disclosures: K.V. Sathyasaikumar: None. **M.A.R. Thomas:** None. **R. Schwarcz:** None.

Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.28/CC30

Topic: H.03. Schizophrenia

Title: Mitigating role of antioxidant supplementation in N-methyl-D-aspartate receptor hypofunction in a Wistar rat model of schizophrenia

Authors: *O. O. AFOLAYAN[1], A. OLAIBI[1], I. O. ISHOLA[2], A. O. OKANLAWON[1]; [1]Anat., [2]Pharmacol., Univ. of Lagos, Lagos, Nigeria

Abstract: Introduction: The *N*-methyl-D-aspartate (NMDA) receptor hypofunction is one of the postulated hypothesis of schizophrenia that describes its cognitive, positive and negative

symptoms. Many antipsychotics are used in the treatment of schizophrenia but most have been observed to have significant side effects. Bioflavonoids and certain vitamins have been postulated to have individual/synergistic neuroprotective and antioxidant properties. Thus, this study sought to investigate ameliorative effects of rutin, ascorbic acid and α-tocopherol in ketamine-induced NMDA receptor hypofunction in Wistar rats. **Methodology**: Forty male Wistar rats (12 weeks old) were randomly divided into eight groups: control (10 ml/kg distilled water p.o), ketamine (25 mg/kg, i.p), ketamine (25 mg/kg, i.p) + haloperidol (0.25mg/kg, i.p), ascorbic acid (10 mg/kg, p.o.) + ketamine (25 mg/kg, i.p.), ketamine + haloperidol + α-tocopherol (100 mg/kg, p.o), ketamine + haloperidol + rutin (25mg/kg, p.o), ketamine + haloperidol + combination of rutin, ascorbic acid and α-tocopherol, ketamine + combination of rutin, ascorbic acid and α-tocopherol. Administration lasted 14 days, within which the following behavioural tests were performed: Y-Maze test, Beam balance test and Light-dark box test on days 0, 1, 7 and 14. Thereafter, oxidative stress markers were analysed in the prefrontal cortices on day 14. **Results:** Haloperidol induced increased rearing and grooming behaviour, which was ameliorated by rutin, ascorbic acid and α-tocopherol treatments. Ketamine-induced deficits in spatial working memory and exploratory activity were prevented by the treatment of rats with rutin, ascorbic acid and α-tocopherol combination. In addition, ketamine reduced the levels of superoxide dismutase, catalase, and glutathione, while increasing malonaldehyde levels. However, these effects were reversed by the treatment of rats with ascorbic acid, α-tocopherol and rutin. **Conclusion**: Findings from this study showed that the combined use of rutin, ascorbic acid and α-tocopherol as adjuvants alleviate ketamine-induced schizophrenic-like behaviour and extrapyramidal side-effects caused by treatment with haloperidol by enhancing the antioxidant defence system. **ETHICAL APPROVAL DETAILS**: This research was approved by the Health Research Ethics Committee of the College of Medicine, University of Lagos with protocol number CMUL/HREC/10/18/448.

Disclosures: O.O. Afolayan: None. **A. Olaibi:** None. **I.O. Ishola:** None. **A.O. Okanlawon:** None.

Poster

610. Schizophrenia Models and Drug Development

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Program #/Poster #: 610.29/CC31

Topic: H.03. Schizophrenia

Support: NIH Grant MH071533
NIH Grant MH103204

Title: MAP2 pathology in schizophrenia: Postmortem patterns and functional consequences

Authors: *R. A. DEGIOSIO[1], R. KELLY[2], M. GRUBISHA[1], A. M. DEDIONISIO[1], J. T. NEWMAN[1], K. N. FISH[1], A. R. SAMPSON[2], D. A. LEWIS[1], R. A. SWEET[1,4,3];
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Abstract: As a predominant regulator of dendritic cytoskeletal organization, microtubule-associated protein 2 (MAP2) is known to influence dendritic arbor and spine morphology, which are altered in schizophrenia (SZ). Several groups have demonstrated that the immunoreactivity (IR) of MAP2 is significantly lower in several cortical regions of individuals with SZ relative to non-psychiatric comparison subjects (NPCs), despite no observed change in expression levels of the protein. Further, we have previously demonstrated that MAP2-IR is correlated with dendritic spine density in one cortical region in SZ, indicating that IR changes may reflect a structural change in MAP2 which bears functional consequence. We set out to determine whether: 1) MAP2-IR deficit occurs throughout cortex within an individual subject with SZ; 2) whether MAP2 phosphorylation state- a common post-translational modification which can alter protein structure- may be altered in SZ; and, if so, 3) whether SZ-associated MAP2 (de)phosphorylation events are capable of altering MAP2 function and/or dendritic morphology. We characterized patterns of MAP2-IR across three cortical regions at different levels of the rostral-caudal axis in subjects with SZ and NPCs. MAP2-IR levels were measured by quantitative fluorescence microscopy in deep layer 3 of dorsolateral prefrontal cortex (DLPFC), lateral intraparietal cortex (LIP) and primary visual cortex (V1). We observed significantly lower levels of MAP2-IR in SZ subjects relative to NPCs, without a significant region by diagnosis interaction. Logs of within-pair ratios (SZ:NPC) of MAP2-IR were significantly correlated across the regions. These findings demonstrate that MAP2-IR deficits in SZ are consistent across three neocortical regions within individual subjects. We also present evidence that the phosphorylation state of MAP2- which is known to regulate its biological functions- is altered in SZ, and that mimicry of a SZ-associated MAP2 phosphorylation event (S1782E) can alter protein function *in vitro* as well as dendritic morphology *in vivo*. Together, these data prompt further investigation of MAP2 dysregulation via phosphorylation as a potential mediator of dendritic pathology in SZ in multiple cortical regions.

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Poster

610. Schizophrenia Models and Drug Development

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 610.30/CC32

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: CONACYT Grant 575264
CONACYT Grant 252808
CONACYT Grant 926349
CONACYT Grant 55569

Title: Olanzapine administration improvement social interaction and reduced neuronal abnormalities in prefrontal cortex and basolateral amygdala induced by animal model of schizophrenia in the rat

Authors: *R. A. VAZQUEZ-ROQUE, Sr[1], D. J. APAM-CASTILLEJOS[2], H. TENDILLA[3], A. J. VÁZQUEZ HERNÁNDEZ[4], G. FLORES[5];
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Abstract: Nowadays atypical antipsychotics are widely used in the treatment of Schizophrenia (SCHZ), Olanzapine (OLZ) is a drug used to reduce positive and negative symptoms, however its mechanism of action has not been fully described yet. Besides the neonatal ventral hippocampal lesion (nVHL) has emerged as a model of schizophrenia-related behavior in the rat. These rats exhibit behavioral changes that manifest mainly after puberty. This animal model induces behavioral alterations like social interaction and deficits in memory and learning. We recently demonstrated that nVHL animals exhibit dendritic atrophy and spine loss in the Prefrontal Cortex (PFC) and Basolateral Amygdala (BLA). This study aimed to determine whether OLZ treatment (0.25 mg/kg/day for 21 days) was capable of reducing PFC layer V and BLA neuronal alterations in morphology and density spines observed in nVHL rats. We evaluated social interaction in these animals. The morphological evaluation included examination of dendrites and spines density using the Golgi-Cox procedure.
Golgi-Cox staining revealed that nVHL induced dendritic retraction and spine loss in PFC pyramidal neurons of layer V and glutamatergic neurons in BLA. Interestingly, repeated OLZ treatment ameliorated dendritic pathology and neuronal loss in the PFC layer V and BLA of the nVHL rats. Our data show that OLZ may foster recovery of PFC layer V and BLA damage in post-pubertal nVHL rats and suggests that the use of neuroleptic agents for the management of some schizophrenia-related symptoms may help to understand the PFC and Nacc alterations pathways in these disorders (Supported by: CONACyT grants to Vazquez-Roque (No. 55569) (No. 926349) to Apam-Castillejos (No. 575264) to Tendilla-Beltrán and (No. 252808) to G Flores.

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Poster

611. Spatial Transcriptomics Techniques

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 611.01/CC33

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Title: Spatial gene expression: Resolving the mammalian brain by combining anatomical and sequencing data

Authors: *C. R. UYTINGCO[1], Y. YIN[1], J. CHEW[1], M. FREY[1], S. ZIRALDO[1], F. MESCHI[1], A. HARTNETT[1], E. R. IYER[1], S. GIACOMELLO[1], A. JUREK[1], J. CHELL[1], S. CHATTERJEE[1], A. PULEO[1], J. ABOUSOUD[1], S. WILLIAMS[2], E. BORGSTROM[2], A. HE[2], N. DSHKHUNYAN[2], N. WEISENFELD[2], N. DELANEY[2], Z. BENT[1], J. HERSCHLEB[1], T. S. MIKKELSEN[1];
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Abstract: Identifying individual cells and their genetic makeup are critical for understanding their roles in how the central nervous system (CNS) physiologically functions, develops, and organizes; as well as how these modalities are altered in diseased states. Traditional analytical methods lack either the cellular resolution and/or throughput necessary to fully compare the different cell types that exists within the mammalian CNS. Single cell RNA sequencing (scRNA-seq) has become a viable strategy for generating vast cellular expression datasets, while simultaneously highlighting previously obscured or unknown subpopulations of cell types within the mammalian brain. However, dissociation of neurons and glial cells from native tissues results in the loss of the spatial localization of the cells. In recent years, spatial transcriptomics technology addressed these limitations by integrating both histological and sequencing data. This was achieved by capturing polyadenylated RNA transcripts from brain tissue sections placed onto a spotted oligo array containing unique spatially encoded barcodes. The generated sequencing libraries were then combined with the histological images from the same brain tissue section to provide a detailed spatial reference. Here we demonstrated a significantly improved version of the spotted oligo array technology that increases tissue coverage and spatial resolution by reducing the spot size, and increasing spot number and packing density. Through advancements in the biochemistry, we exhibited substantially increased sensitivity while simultaneously reducing experiment duration. To better illustrate the capabilities of our approach, we applied our technology on the APPSWE [Tg2576] mouse model of familial Alzheimer's Disease, outlining the added benefits from standard scRNA-seq data alone. Together, this confluence of imaging and sequencing will serve as a valuable tool for understanding the relationships between CNS cell types and functions by providing researchers with an unbiased anatomical and gene expression-driven method of analysis.

Disclosures: **C.R. Uytingco:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **Y. Yin:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **J. Chew:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **M. Frey:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **S. Ziraldo:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **F. Meschi:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **A. Hartnett:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **E.R. Iyer:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **S. Giacomello:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **A. Jurek:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **J. Chell:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **S. Chatterjee:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **A. Puleo:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **J. Abousoud:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **S. Williams:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **E. Borgstrom:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **A. He:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 10X Genomics. **N. Dshkhunyan:** A. Employment/Salary (full or part-time):; 10X Genomics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual

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Poster

611. Spatial Transcriptomics Techniques

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 611.02/CC34

Topic: I.02. Systems Biology and Bioinformatics

Title: Pairing gene expression and spatial location to learn whole brain patterns of transcription

Authors: *S. LU, D. FÜRTH, A. ZADOR, J. GILLIS;
Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: To fully appreciate the brain as a complex system, its component parts should be studied across multiple modalities of data. One such source of information from the brain is spatial gene expression. We generated a whole-brain, adult mouse spatial gene expression dataset using Spatial Transcriptomics (ST), an array-based transcriptome-wide mRNA assay that maintains the spatial origin of transcripts. After benchmarking a variety of analytical approaches, we found that most well-represented brain areas, as annotated by mapping the ST spots to the Allen Reference Atlas, are learnable using LASSO regression with respect to all other brain areas using only gene expression. We further extend these analyses through meta-analysis of the Allen Institute's transcriptome-wide adult mouse in situ hybridization data (ABA ISH). Specific brain areas that were learnable in the ST data are similarly learnable in the ABA ISH data. Encouragingly, preliminarily LASSO models trained in the ST dataset have performed similarly in learning brain areas on held out ST data and on the ABA ISH data, and vice versa. Through this meta-analysis, I will determine the replicability of learning canonical anatomically-derived brain area assignments using gene expression from various types of spatial transcriptomic data and ultimately propose new transcriptionally-defined groupings.

Disclosures: **S. Lu:** None. **D. Fürth:** None. **A. Zador:** None. **J. Gillis:** None.

Poster

611. Spatial Transcriptomics Techniques

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 611.03/CC35

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Title: Spatial cell type analysis in tissue sections by next generation *in situ* sequencing

Authors: *M. KÜHNEMUND[1], X. QIAN[2,1];
[1]CARTANA, Stockholm, Sweden; [2]Sci. for Life Laboratory, Stockholm Univ., Solna, Sweden

Abstract: Single cell RNA sequencing (scRNAseq) has enabled the classification of cell types from nearly all tissue types based on their unique gene expression patterns. scRNAseq methods, however, require the isolation of cells from its natural morphological context inside the tissue losing the information of the spatial organization of cell types. A range of spatial transcriptomics techniques have been devised over the past few years, all with their unique advantages and drawbacks. *In Situ* Sequencing (ISS) takes place in intact morphologically preserved tissue sections and can be used to sequence short stretches of cDNA or barcodes inside ligated probes. A key advantage of ISS over other multiplexed *in situ* hybridization or sequencing methods is its high specificity, enabling mutation and splice variant analysis, and high throughput (10cm^2 of tissue/week). At CARTANA, we have developed an improved protocol for targeted *in situ* sequencing using barcode padlock probes and a new sequencing chemistry that requires less manual steps, generates higher signal/noise ratios and better preserves the tissue, making it possible to combine the ISS assay with protein staining in the same tissue section. We now apply our new ISS technology to map scRNAseq-defined cell types- and states by targeted probe panels for cell type marker genes in rodent and human brain and spinal cord samples generating cell type tissue maps.

Disclosures: **M. Kühnemund:** None. **X. Qian:** None.

Poster

611. Spatial Transcriptomics Techniques

Location: Hall A

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Program #/Poster #: 611.04/CC36

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: CZI Pilot Projects for the Human Cell Atlas

Title: Using *in situ* sequencing to map spatial distribution of brain cell types

Authors: *X. QIAN, D. GYLLBORG, M. NILSSON;
Stockholm Univ., Stockholm, Sweden

Abstract: Single-cell RNA-sequencing (scRNA-seq) has revealed hundreds of transcriptomically defined cell types in the brain. Categorizing all cell types is an important step towards understanding the building blocks of the brain, but this is far from answering the functional and structural interactions between cells that underlie the complex functions of an organ. Studying cells *in situ* and spatially mapping scRNA-seq defined cell types is an indispensable step towards this goal (1).
Multiple methods are currently available for spatially resolved transcriptomics. SpaceTx project, part of Human Cell Atlas initiative (2), is an effort towards standardization and controlled comparison of different methods for their suitability in spatial cell type mapping. Our group previously developed *in situ* sequencing (ISS) technology (3). The technology, combined with a probabilistic cell calling algorithm and termed pciSeq, has been used to create a spatial atlas of fine interneuron cell types in mouse hippocampus CA1 (4).
ISS is based on padlock probes and rolling circle amplification. The amplification generates bright signals and thus does not require high-power imaging, which makes ISS a high-throughput method. In the current study, we developed ISS v2.0 to resolve more signals and generates even brighter and cleaner signals, which is advantageous when working with human samples, where lipofuscin poses a serious challenge for many imaging-based methods.
We generated ISS benchmarking dataset for human and mouse brain samples, targeting 120 and 119 genes respectively, which were a result of automatic gene selection and manual curation of SpaceTx consortium. The generated dataset is a great resource for the whole neuroscience community to develop computational methods. And the preliminary results of pciSeq on the data also validates the known biology of laminar structure of cortex.
References: 1. E. Lein, L. E. Borm, S. Linnarsson, Science. 358, 64-69 (2017).2. A. Regev et al., eLife. 6, e27041 (2017).3. R. Ke et al., Nat. Methods. 10, 857-860 (2013).4. X. Qian et al., bioRxiv, 431957 (2018).

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Poster

611. Spatial Transcriptomics Techniques

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 611.05/CC37

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH 1R21HG009749-01
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Title: Genome-wide *in situ* sequencing

Authors: *A. PAYNE[1], Z. CHIANG[2], P. REGINATO[1], E. MURRAY[3], S. MANGELIMELI[3], C.-C. YAO[1], G. CHURCH[4], J. BUENROSTRO[2], F. CHEN[3], E. S. BOYDEN[1];
[1]MIT, Cambridge, MA; [2]Harvard Univ., Cambridge, MA; [3]Broad Inst., Cambridge, MA; [4]Harvard Med. Sch., Boston, MA

Abstract: The spatial organization of the genome plays an important role in cell fate and function through control of nuclear processes such as gene regulation. In principle, the nucleus is amenable to study in its native context via high resolution imaging, which can capture many spatial and structural features simultaneously. However, in practice, no tools exist for genome-wide imaging.

We have developed an *in situ* sequencing method to directly resolve the 3D structure of the genome in its native context within single cells. Here we describe the methodological developments underpinning this new imaging/sequencing approach. In brief, we construct a whole-genome sequencing library *in situ* in fixed cells via enzymatic fragmentation, adaptor ligation, and amplification of genomic DNA. We then sequence the amplicons *in situ*, with each cycle read out using fluorescence microscopy. This sequencing process is automated using a fluorescence microscope with integrated computer-controlled fluidics.

As a proof of principle, we use this approach to spatially resolve hundreds of genome-wide reads per cell from ~200 individual cells. We expect this platform technology will expand the scope of possible measurements of genome organization, including high-throughput genome-wide architectural mapping of higher order chromatin folding and chromosome domains. We anticipate these novel imaging-based genomic measurements will yield new insights about the processes that underlie genome structure and regulation.

Disclosures: **A. Payne:** None. **Z. Chiang:** None. **P. Reginato:** None. **E. Murray:** None. **S. Mangelimeli:** None. **C. Yao:** None. **G. Church:** None. **J. Buenrostro:** None. **F. Chen:** None. **E.S. Boyden:** None.

Poster

611. Spatial Transcriptomics Techniques

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 611.06/CC38

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: MIT Media Lab
Chan Zuckerberg Initiative
NIH U01MH114819
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Ludwig Foundation

Title: Targeted and untargeted *in situ* sequencing in thick, physically magnified brain tissue

Authors: *A. SINHA[1], D. GOODWIN[1], S. ALON[2], A. WASSIE[1], F. CHEN[1], Y. CUI[1], Y. BANDO[3], A. KAJITA[4], A. PAYNE[1], C.-C. YAO[1], A. H. MARBLESTONE[5], G. M. CHURCH[6], E. S. BOYDEN[1];
[2]Media Lab., [1]MIT, Cambridge, MA; [3]Toshiba Memory America, Inc., San Jose, CA; [4]Fixstars Solutions Inc., Cambridge, MA; [5]MIT Media Lab., Cambridge, MA; [6]Harvard Med. Sch., Boston, MA

Abstract: Mapping the precise sequences and locations of RNAs within cells in intact tissues is important for understanding diverse biological processes. In the brain, the transcriptome defines cell types and states, and prescribes the available mechanisms for high speed neural computations, long-term synaptic changes, and disease progression. To date, methods for multiplexed single-molecule RNA imaging in tissue have been limited to thin sections and lack high resolution subcellular landmarks, limiting the ability to assign transcripts to cells, and to probe the subcellular organization of transcripts into nanoscale compartments.
We here report the ability to perform both untargeted and targeted *in situ* sequencing in intact thick tissue sections, alongside antibody-based morphological analysis. Our strategy, expansion sequencing (ExSeq), builds upon expansion microscopy (ExM) [1, 2], which physically expands biological specimens to enable super-resolution imaging. RNA molecules are anchored to a swellable hydrogel synthesized throughout the specimen, and isotropically separated from one another, creating space for subsequent chemical and enzymatic steps to be performed to prepare the DNA library for readout by *in situ* sequencing [3, 4].

Using untargeted *in situ* sequencing, we were able to observe tens of thousands of reads from hundreds of neurons in mouse brain, with an average read length of 76 bases, allowing for subcellular mapping of the locations of expressed genes, analysis of splice variation, detection of novel expressed sequences, and other details previously difficult to study. We utilized targeted *in situ* sequencing, in which oligonucleotide barcodes target specific transcripts, to perform highly multiplexed gene expression mapping, revealing cell types, and nanoscale organization of transcripts, within dendritic processes in mouse brain hippocampus.

References:
[1] Science. 2015 Jan 30;347(6221):543-8.
[2] Nat Methods. 2016 Aug;13(8):679-84.
[3] Science. 2014 Mar 21;343(6177):1360-3.
[4] Nat Methods. 2013 Sep;10(9):857-60.

Disclosures: **A. Sinha:** None. **D. Goodwin:** None. **S. Alon:** None. **A. Wassie:** None. **F. Chen:** None. **Y. Cui:** None. **Y. Bando:** None. **A. Kajita:** None. **A. Payne:** None. **C. Yao:** None. **A.H. Marblestone:** None. **G.M. Church:** None. **E.S. Boyden:** None.

Poster

611. Spatial Transcriptomics Techniques

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 611.07/CC39

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH Grant DP2 AG058488-01
NIH Grant 1DP5OD024583
Schmidt Fellows Program at the Broad Institute
Hertz Foundation Graduate Fellowship
NSF GRFP Award #1122374

Title: Slide-seq: A scalable technology for measuring genome-wide expression at high spatial resolution

Authors: *S. G. RODRIQUES[1], R. R. STICKELS[2], A. GOEVA[3], C. A. MARTIN[4], E. MURRAY[3], C. R. VANDERBURG[4], J. WELCH[4], L. CHEN[4], F. CHEN[4], E. MACOSKO[5]; [1]MIT, Cambridge, MA; [2]Neurosci., Harvard University/ Broad Inst., Cambridge, MA; [3]Broad Inst. of Harvard and MIT, Cambridge, MA; [4]The Broad Inst. of Harvard and MIT, Cambridge, MA; [5]Harvard Med. Sch., Brookline, MA

Abstract: Spatial positions of cells in tissues strongly influence function, yet a high-throughput, genome-wide readout of gene expression with cellular resolution is lacking. We developed Slide-seq, a method for transferring RNA from tissue sections onto a surface covered in DNA-

barcoded beads with known positions, allowing the locations of the RNA to be inferred by sequencing. Using Slide-seq, we localized cell types identified by scRNA-seq datasets within the cerebellum and hippocampus, characterized spatial gene expression patterns in the Purkinje layer of mouse cerebellum, and defined the temporal evolution of cell-type-specific responses in a mouse model of traumatic brain injury. These studies highlight how Slide-seq provides a scalable method for obtaining spatially resolved gene expression data at resolutions comparable to the sizes of individual cells.

Disclosures: **S.G. Rodriques:** None. **R.R. Stickels:** None. **A. Goeva:** None. **C.A. Martin:** None. **E. Murray:** None. **C.R. Vanderburg:** None. **J. Welch:** None. **L. Chen:** None. **F. Chen:** None. **E. Macosko:** None.

Poster

611. Spatial Transcriptomics Techniques

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 611.08/CC40

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH Grant U19MH114821
Simons Foundation 350789

Title: Mixed long-range projections of transcriptomic subtypes of intratelencephalic neurons revealed by *in situ* barcode sequencing

Authors: ***X. CHEN**[1], Y.-C. SUN[1], A. M. ZADOR[2];
[1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Zador Lab., Cold Spring Harbor Lab., Cold Spg Hbr, NY

Abstract: The vertebrate brain consists of myriad neurons with diverse characteristics, such as anatomy, gene expression, and activity. How neurons are organized by these different characteristics into functional circuits is largely unknown. Previously, we have reported highly diverse but organized long-range projections in the cortex using BARseq, a high-throughput single-cell projection mapping technique based on *in situ* barcode sequencing. However, it remains unclear how projection patterns are organized by neuronal subtypes defined by gene expression. Here we combine BARseq with multiplexed *in situ* hybridization to interrogate the transcriptomic subtypes and long-range projections of thousands of intratelencephalic (IT) neurons in the auditory cortex at cellular resolution. We identify distinct distribution of projections across transcriptomic IT subtypes and further identify projection correlates of gene expression within a subtype. These differences across subtypes, however, do not explain the majority of variance in projection patterns: projection patterns remain largely overlapping across transcriptomic subtypes and highly diverse within a subtype. Our results indicate that adult

neuronal subtype defined by transcriptomics is not a major determinant of long-range projections across neuronal types.

Disclosures: X. Chen: None. **Y. Sun:** None. **A.M. Zador:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); owner and founder of MapNeuro.

Poster

611. Spatial Transcriptomics Techniques

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 611.09/CC41

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH Grant U19

Title: Correlation between combinatorial cadherin expressions and neuronal projections revealed by targeted *in situ* sequencing

Authors: *Y.-C. SUN[1], X. CHEN[1], A. M. ZADOR[2];
[1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Zador Lab., Cold Spring Harbor Lab., Cold Spg Hbr, NY

Abstract: In vertebrate brains, the combinatorial expression of genes, such as cell adhesion molecules, are required to establish the highly diverse neuronal projections in the vertebrate brain. Understanding the organization of neuronal circuits thus requires characterizing, among various neuronal properties, how combinatorial gene expressions directs neuronal connectivity. This requires high-throughput gene detection and projection mapping in the same neurons while retaining spatial information at cellular resolution. Here, we combine targeted *in situ* sequencing and BARseq, a high-throughput technique for mapping long-range axonal projections based on *in situ* sequencing of RNA barcodes, to correlate gene expression and projections at cellular resolution. We use this approach to test the hypothesis that combinatorial cadherin expressions specify neuronal connectivity in the mouse auditory cortex. Our method uncovers the degree to which combinatorial cadherin expressions can predict neuronal projection patterns and thus potentially illuminate the gene expression logic underlying neuronal connectivity.

Disclosures: Y. Sun: None. **X. Chen:** None. **A.M. Zador:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MapNeuro owner/founder.

Poster

611. Spatial Transcriptomics Techniques

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 611.10/CC42

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: CIHR Grant
Alfred P. Sloan Foundation

Title: A spatial-temporal map of the protocadherin expression code in the CNS

Authors: *W. X. WANG, J. L. LEFEBVRE;
Neurosciences and Mental Hlth., Hosp. for Sick Children Res. Inst., Toronto, ON, Canada

Abstract: The assembly of neuronal circuits is dependent on complex and selective cell-cell interactions, mediated by cell-surface receptors. Studies to date have focused on receptor interactions at the level of cell-types, despite evidence that individual neurons within the same cell-type are also shaped by distinct cues. A promising candidate for generating single neuron identities is the clustered Protocadherins (Pcdhs), a family of 58 cell-surface recognition molecules. Profiling studies suggest that stochastic and combinatorial expression of Pcdh isoforms in single neurons further amplifies Pcdh expression diversity to an astounding 10 billion combinations. However, it remains unknown if combinatorial Pcdh expression is a general feature in the nervous system, and whether Pcdh signatures change during development. To tackle these questions, we devised a novel strategy using multiplexed, single-molecule fluorescence *in situ* hybridization (multiplex smFISH) techniques to map the spatial-temporal expression profiles of all 58 highly-related Pcdh isoforms across neuron types in the cerebellum, cortex, and retina. To increase the number of targets that can be imaged simultaneously, we are employing sequential barcoding techniques to combinatorially label each isoform with a colored (fluorophore) barcode, which is decoded through sequential rounds of single molecule RNA imaging. This work aims to gain insight into the logic behind molecular diversity and complexity, and their roles during neuronal wiring.

Disclosures: W.X. Wang: None. **J.L. Lefebvre:** None.

Poster

611. Spatial Transcriptomics Techniques

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 611.11/CC43

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH U01MH105982
CZI Human Cell Atlas Pilot

Title: A spatial census of transcriptomically defined cortical cells

Authors: Z. M. MALTZER[1], T. NGUYEN[4], E. J. GARREN[4], R. D. HODGE[5], J. A. MILLER[1], T. BAKKEN[4], *J. L. CLOSE[6], B. R. LONG[4], R. NICOVICH[4], B. TASIC[7], H. ZENG[2], E. LEIN[3];
[2]Structured Sci., [3]Human Cell Types, [1]Allen Inst. for Brain Sci., Seattle, WA; [5]Cell Types Program, [6]Imaging, [7]Cell and Circuit Genet., [4]Allen Inst. For Brain Sci., Seattle, WA

Abstract: Single cell transcriptomics datasets provide unprecedented detail regarding the variety of molecularly defined cell types in the cortex. Recent work in mouse and human cortex has identified hundreds of discrete, transcriptomically defined cell types which may have unique spatial distributions, connectivity, intrinsic membrane properties and function. However, due to the nature of single cell transcriptomics, the number, proportion and spatial location of these cell types are not precisely understood. To provide an accurate census of these cell types and describe their spatial relationship to one another, we generated combinatorial gene panels designed to identify molecularly defined cell types with a minimum number of genes. Using these gene panels as a starting point, we identified and mapped these cell types in brain tissue to create a spatial census of brain cell types. These data describe the spatial distribution of each discrete type investigated, its proportion in a given area of tissue relative to other types, and provide insight into the probable function of transcriptomically defined types within brain tissue.

Disclosures: J.L. Close: None. **T. Nguyen:** None. **E.J. Garren:** None. **R.D. Hodge:** None. **J.A. Miller:** None. **T. Bakken:** None. **B.R. Long:** None. **R. Nicovich:** None. **B. Tasic:** None. **E. Lein:** None. **H. Zeng:** None. **Z.M. Maltzer:** None.

Poster

611. Spatial Transcriptomics Techniques

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 611.12/CC44

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Title: A high-throughput pipeline for addressing the correspondence problem through spatial transcriptomics in intact tissue

Authors: *R. NICOVICH[1], M. TAORMINA[4], M. GORHAM[4], K. BERRY[4], T. NGUYEN[4], E. GARREN[4], B. R. LONG[1], E. THOMSEN[1], B. P. LEVI[1], C. A. BAKER[1], B. TASIC[2], J. L. CLOSE[3], E. LEIN[5], H. ZENG[6];
[2]Cell and Circuit Genet., [3]Human Cell Types, [1]Allen Inst. For Brain Sci., Seattle, WA; [5]Human Cell Types, [6]Structured Sci., [4]Allen Inst. for Brain Sci., Seattle, WA

Abstract: Defining a complete set of cell types within the cortex requires reconciling disparate results achieved through diverging methodologies. To address this correspondence problem, multiple methodologies must be applied to the same cells across multiple single-cell experiments. We present an approach applying spatial transcriptomics using multiplexed fluorescence *in situ* hybridization, (mFISH) to brain tissue previously interrogated through two photon optogenetic mapping of synaptic connectivity or whole-brain serial two photon tomography. This approach can resolve the anatomical, transcriptomic, connectomic, electrophysiological, and morphological characteristics of single cells within the mouse cortex. A systematic interrogation of the correspondence between single-modality-defined types and the diversity within these types requires a large-scale effort to capture these details at sufficient resolution. To this end we describe a data generation pipeline capable of completing dozens of experiments per week. Key components include cross-team specimen hand-off, data, reagent, and probe tracking infrastructure, and workflow optimizations. We will describe several of these advances and how they support the goal of a robust, auditable, and reliable pipeline for multimodal correspondence data generation. With this pipeline infrastructure, we can disambiguate cell types within cells expressing a sub-class-level transgenic reporter. We focus on putative somatostatin-expressing interneurons. Within this sub-class the mFISH pipeline can distinguish unique cell types by probing a modest set of 15 or fewer transcript targets. Aligning results from the mFISH analysis with those from an upstream synaptic connectivity experiment provides cell-type resolution of connectivity rates and strength while maintaining the high-throughput capabilities of both light sheet imaging and two-photon optogenetic probing.

Disclosures: **R. Nicovich:** None. **M. Taormina:** None. **M. Gorham:** None. **K. Berry:** None. **T. Nguyen:** None. **E. Garren:** None. **B.R. Long:** None. **E. Thomsen:** None. **B.P. Levi:** None. **C.A. Baker:** None. **B. Tasic:** None. **J.L. Close:** None. **E. Lein:** None. **H. Zeng:** None.

Poster

611. Spatial Transcriptomics Techniques

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 611.13/CC45

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Title: Confirmation and spatial mapping of diverse striatal cells identified by single cell RNA sequencing in the mouse brain at single-cell resolution with a multiplex *in situ* hybridization technology

Authors: J. PHATAK, H. LU, *L. WANG, H. ZONG, M. ROUAULT, C. MAY, C. ANDERSON, B. ZHANG, X.-J. MA;
Advanced Cell Diagnostics, Newark, CA

Abstract: Complex, highly heterogeneous tissues such as the brain are comprised of multiple cell types and states with exquisite spatial organization. Single cell RNA sequencing (scRNA-seq) has become a universal tool for classifying and characterizing known and novel cell populations of complex heterogenous tissues, leading to a new age of single cell biology. However, scRNA-seq is limited to dissociated cells and results in the loss of spatial organization of these cell populations, thus requiring a multiplexed spatial approach that can interrogate gene expression with single cell resolution in the tissue context. In this study, we used the RNAscope Multiplex Fluorescent and HiPlex RNA *in situ* hybridization (ISH) assays to confirm and spatially resolve the diverse striatal neurons identified by scRNA-seq in the mouse brain (Gokce *et al*, *Cell Rep*, 16(4):1126-1137, 2016). We confirmed the gene-signatures of two discrete D1 and D2 subtypes of medium spiny neurons (MSN): *Drd1a/Foxp1, Drd1a/Pcdh8, Drd2/Htr7*, and *Drd2/Synpr*. Further cellular heterogeneity within the MSN sub-populations was marked by a transcriptional gradient, which we could spatially resolve with RNA ISH. scRNA-seq also revealed that the mouse striatum was comprised of numerous non-neuronal cell populations, including vascular cells, immune cells, and oligodendrocytes, which the presence and co-expression of these cell markers was confirmed with the multiplex ISH assay. Lastly, to simultaneously visualize the spatial organization of the D1 and D2 MSN subtypes identified by Gokce et al. we utilized the RNAscope HiPlex assay, which allows for visualization of up to 12 targets simultaneously in intact tissues. In conclusion, we have demonstrated the capabilities of two multiplexed RNAscope assays for the confirmation and spatial mapping of scRNA-seq results in the highly complex and heterogenous mouse striatum at the single cell level. Single-cell transcriptomics combined with spatial mapping by the RNAscope technology is well suited for resolving heterogeneous tissues at cellular resolution and providing insights into cellular organization and function of diverse cell types in healthy and disease states.

Disclosures: **J. Phatak:** None. **H. Lu:** None. **L. Wang:** None. **H. Zong:** None. **M. Rouault:** None. **C. May:** None. **C. Anderson:** None. **X. Ma:** None.

Poster

611. Spatial Transcriptomics Techniques

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 611.14/CC46

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: Ni5T32DA007268
R01 DA044960
K08 DA037912
T32 DA007268

Title: Cellular compartment analysis of temporal activity by fluorescent *in situ* hybridization (catFISH) in the rat transcardially perfused brain

Authors: *A. GHEIDI[1], V. KUMAR[1], C. J. FITZPATRICK[2], R. ATKINSON[1], J. D. MORROW[2];
[2]Psychiatry, [1]Univ. of Michigan, Ann Arbor, MI

Abstract: *Background:* Cellular compartment analysis of temporal activity by fluorescent in *situ* hybridization catFISH allows high spatiotemporal resolution mapping of immediate early genes in the brain in response to internal/external stimuli. One caveat of this technique and indeed other methods of *in situ* hybridization is the necessity of flash-freezing the brain prior to staining. Often however, the mammalian brain is transcardially perfused to use the brain tissue for immunohistochemistry, the most widely-used technique to study gene expression. *New Method:* We have developed a technique, modified from that of Guzowsky and Worley, 2001, that allows the catFISH method to be used in adult rats that have been transcardially perfused with 4% paraformaldehyde. *Results* c-Fos activity induced by either an auditory tone or status epilepticus was visualized using the catFISH procedure. We see clear distinction of the compartmental distribution of c-Fos mRNA in the nuclei and cytoplasmic regions of the rat prefrontal cortex, hippocampus and amygdala. Furthermore, the qualitative proportion of c-Fos compartmentalization is similar to previous reports of c-Fos expression pattern in rodents navigating novel environments. *Conclusion:* c-Fos catFISH on perfused rodent brains is an attractive addition to the traditional histological methods using fluorescently labeled riboprobes, and opens several avenues for future investigations.

Disclosures: **A. Gheidi:** None. **V. Kumar:** None. **C.J. Fitzpatrick:** None. **R. Atkinson:** None. **J.D. Morrow:** None.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.01/CC47

Topic: I.04. Physiological Methods

Support: W.M. Keck Foundation (GR529005)
The National Institutes of Health (R21MH101525; R21EY026427; U01NS099709)
National Science Foundation (CBET-1464686; NeuroNex-1707352)
Swedish Research Council (2016-06760)

Title: Selective behavioral and circuit deficits in adulthood following widespread postnatal excitation of neocortical pyramidal cells

Authors: *A. BJOREFELDT[1], W. E. MEDENDORP[3], A. PAL[4], M. L. WADDELL[4], C. I. MOORE[2], U. HOCHGESCHWENDER[5];
[1]Dept. of Neurosci., [2]Neurosci., Brown Univ., Providence, RI; [3]Neurosci., Central Michigan Univ., Mount Pleasant, MI; [5]Neurosci., [4]Central Michigan Univ., Mt Pleasant, MI

Abstract: The amount and pattern of neuronal activity present during the early developmental period is believed to guide structural and functional properties of neural circuit assembly that persist into adulthood. Thus, alterations in neuronal activity during this time period may lead to aberrant circuit formation, a mechanism that has been implicated in certain psychiatric disorders such as autism. Here we took advantage of a bimodal experimental approach, bioluminescence-driven optogenetics, to assess the impact of cortical pyramidal cell hyperexcitation during this critical time period. To enable manipulation of cortical pyramidal cell activity during development, mice expressing the excitatory luciferase-opsin fusion LMO3 (sbGluc fused to VChR1) under a Lox-Stop-Lox sequence were crossed with Emx1-Cre mice. In presence of the luciferase substrate coelenterazine (CTZ), light emission from sbGluc drives activation of VChR1 to depolarize the cell and evoke action potential firing. CTZ was delivered intraperitoneally once a day during post-natal days 4-14 in developing mouse pups. Starting at postnatal day 50 (P50), mice that received either CTZ or vehicle treatment during development were tested in a number of behavioral paradigms and effects on morphological and electrophysiological properties were examined. Behavioral testing revealed that CTZ-treated Emx1-Cre/LSL-LMO3 mice display adult behavioral phenotypes similar to those observed in existing animal models of autism. Taking advantage of the option to interrogate the same LMO3-expressing neurons using optogenetics in *in vivo* and *ex vivo* electrophysiological recordings from cortex, these animals showed evidence of neurophysiological alterations in the form of altered neuronal network oscillations, excitation-inhibition balance and intrinsic excitability. In

conclusion, we leveraged the advantage of a dual chemo- and optogenetic approach to study the impact of neuronal activity during early development on adult neurophysiology and behavior that could aid investigation of pathophysiological mechanisms underlying psychiatric disorders such as autism.

Disclosures: A. Bjorefeldt: None. **W.E. Medendorp:** None. **A. Pal:** None. **M.L. Waddell:** None. **C.I. Moore:** None. **U. Hochgeschwender:** None.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.02/CC48

Topic: I.04. Physiological Methods

Support: Howard Hughes Medical Institute
Royal Society
BBSRC (BB/G018723/1)

Title: A new approach to anatomical and functional imaging: Recording and labelling of insect auditory neurons through the intact neurolem

Authors: *B. HEDWIG[1], M. D. ISAACSON[2], K. KOSTARAKOS[3];
[1]Zoology, Univ. of Cambridge, Cambridge, United Kingdom; [2]Janelia Farm Res. Campus, Howard Hughes Med. Institute,, Ashburn, VA, VA; [3]Zoology, Univ. of Graz, Graz, Austria

Abstract: The delivery of tracers into populations of neurons is essential to visualize their anatomy and to analyze their function. Some model systems allow a genetically-targeted expression of fluorescent proteins; however, these genetic tools are not available for most organisms and alternative labeling methods are very limited. We developed a new method for neuronal labeling by electrophoretic dye delivery from a suction electrode, filled with a polar tracer, directly through the neurolem of nerves and ganglia in insects. Application of current delivered the dye into the neuronal tissue and labeled the neurons at the opening of the electrode. In the peripheral nervous system polar tracer molecules were injected into the locust auditory nerve without destroying its function, simultaneously staining peripheral sensory structures in the hearing organ and central axonal projections. Upon the delivery of calcium indicators, we recorded sound evoked fluorescent signals in the central metathoracic auditory neuropils. In cricket brains, single auditory neurons and local populations could be labelled directly through the neurolem. The specificity and selectivity of the electrophysiological recordings were determined by the electrode location. The same electrodes were used to deliver fluorescent tracers into the brain by means of electrophoresis. This allowed us to retrograde label recorded ascending auditory neurons, and to reveal their cell body and dendritic structure in the first

thoracic ganglion. By adjusting the amount of dye injected, we specifically stained the ring-like auditory neuropil in the brain, demonstrating the clusters of cell bodies contributing to it. Furthermore in-vivo optical imaging of sound-evoked activity in brain neurons was achieved through the delivery of calcium indicators. Our method provides a new tool for studying how sensory stimuli are processed in peripheral and central sensory pathways and is a significant advance for the study of nervous systems in "non-model" invertebrates.

Disclosures: B. Hedwig: None. **M.D. Isaacson:** None. **K. Kostarakos:** None.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.03/CC49

Topic: I.04. Physiological Methods

Support: W.M. Keck Foundation (GR529005)
National Institutes of Health (R21MH101525; R21EY026427; U01NS099709)
National Science Foundation (CBET-1464686; NeuroNex-1707352)

Title: Bioluminescence driven control of photosensory proteins

Authors: *E. L. CRESPO[1], G. LAMBERT[3], N. C. SHANER[3], U. HOCHGESCHWENDER[2]; [1]Central Michigan Univ., Mount Pleasant, MI; [2]Neurosci., Central Michigan Univ., Mt Pleasant, MI; [3]UCSD, San Diego, CA

Abstract: Bioluminescence is light emitted by a luciferase oxidizing its substrate. We previously demonstrated that such "biological" light can activate optogenetic elements, such as channelrhodopsins and pumps, effecting membrane potential changes and resulting in activation or silencing of neurons in vitro and in vivo. We explored whether bioluminescent light production can be utilized beyond activating ion-moving photoreceptors to the larger array of photosensory proteins employed as optical switches in cellular processes such as protein translocation and transcription. In initial proof-of-concept experiments we co-transfected HEK293 cells with a blue light emitting luciferase and a blue light sensing photoreceptor. Light emitters were sbGLuc, a copepod luciferase variant, NanoLuc, a luciferase derived from shrimp, as well as two novel engineered synthetic luciferases. Photoreceptors were CRY/CIB, a light-gated dimerization system, and LOV, based on light dependent protein unhinging. Bioluminescence driven activation of these photoreceptors was measured as increased transcription of luminescent and fluorescent reporter proteins in direct comparison to LED driven activation. Quantification of bioluminescence driven photoreceptor activation revealed that both light-gated switches, cryptochrome protein dimerization and light-oxygen-voltage J-alpha helix unfolding can be efficiently activated by biological light sources. Furthermore, the higher light

emission of our synthetic luciferases resulted in better activation of transcription. There are many ways to improve further on these basic results. Collectively, bioluminescence driven activation of the larger families of photoreceptors will expand their use for in vivo applications that benefit from non-invasive light sources and engagement of spatially distributed cells.

Disclosures: E.L. Crespo: None. **G. Lambert:** None. **N.C. Shaner:** None. **U. Hochgeschwender:** None.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.04/CC50

Topic: I.04. Physiological Methods

Support: NSF Grant DBI-1707352

Title: Modular family of readily interchangeable head-post attachments for drug delivery, imaging, electrophysiology and brain maintenance in awake, behaving mice

Authors: *J. W. MURPHY[1], N. G. FRIEDMAN[1], D. CELINSKIS[2], D. LIPSCOMBE[1], N. C. SHANER[3], U. HOCHGESCHWENDER[4], M. GOMEZ-RAMIREZ[1], C. I. MOORE[1]; [1]Neurosci., [2]Sch. of Engin., Brown Univ., Providence, RI; [3]Neurosciences, Univ. of California at San Diego, San Diego, CA; [4]Neurosci., Central Michigan Univ., Mt Pleasant, MI

Abstract: Cranial windows for optical imaging in rodents are widespread and useful. They allow for long-term imaging of neural activity as well as optical access for the stimulation of optogenetic elements. As genetically targeted imaging and manipulation of neural activity *in vivo* becomes increasingly widespread, certain experimental questions necessitate direct access to the brain otherwise typically sealed beneath glass. Specifically, the delivery of drugs directly to the restricted brain area beneath the optical window in an even and controlled manner while maintaining suitable optical access for imaging is a central challenge to many experimental preparations. A second challenge is the frequent need for simultaneous acquisition of imaging and electrophysiological data, which requires access of the recording probe to the tissue of interest. Previous approaches to these challenges have either allowed for access to only a small sub-region of the entire cranial window via a re-sealable hole in a glass or silicone window, or are sealed microfluidic devices that do not allow for direct access to the tissue. We sought to design an inexpensive, modifiable and scalable device for simultaneous optical imaging, drug delivery and electrophysiological recording. The device we present is 3D printed and affixes to our pre-existing titanium headposts through the use of thin (<1mm) neodymium disc magnets. The device was designed using open source software (OpenSCAD) and printed on a low cost 3D printer (Creality Ender 3). Central to the design of the device is that the swappable magnetic

approach allows for interchangeable attachments geared toward the specific task. For instance, a microfluidic chamber enclosed by a glass window allows for drug infusion with simultaneous optical access for imaging while an optically opaque cover with a silicone disk allows for compression and protection of the craniotomy while the animal is in its home cage. We present data showing the successful activation of a bioluminescent enzyme expressed in cortical neurons by infusion of the corresponding bioluminescent substrate through our magnetic perfusion chamber. Additionally, we show that optical access remains clear over multiple experimental sessions.

Disclosures: **J.W. Murphy:** None. **N.G. Friedman:** None. **D. Celinskis:** None. **D. Lipscombe:** None. **N.C. Shaner:** None. **U. Hochgeschwender:** None. **M. Gomez-Ramirez:** None. **C.I. Moore:** None.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.05/CC51

Topic: I.04. Physiological Methods

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NIH Grant R21MH101525
NIH Grant R21EY026427
NIH Grant Uo1NS099709
NSF Grant CBET-146486
NSF NeuroNex-1707352

Title: Transsynaptic neuronal activation via bioluminescent optogenetics

Authors: *R. SCHUMAKER, M. PRAKASH, A. PAL, E. CRESPO, U. HOCHGESCHWENDER;
Central Michigan Univ., Mount Pleasant, MI

Abstract: Biological light activation of optogenetic sensors across synaptic partners offers the potential to optogenetically dissect synaptic communication non-invasively. The genetically encoded light source, a luciferase, is expressed pre-synaptically, and the light-sensing opsin is expressed post-synaptically. In the presence of the luciferase substrate, coelenterazine (CTZ), the pre- and post-synaptic partners will be in close proximity to allow activation of the opsin by luciferase-produced light. In order to improve the specificity of trans-synaptic signaling, we are exploring several designs of trans-synaptic reconstitution of split molecules. First, Gaussia luciferase (GLuc) is split into inactive N- and C-terminal portions, each of which are then tethered to the pre-synaptic membrane or post-synaptic opsin, respectively. Second, in a

luciferase - fluorescent protein fusion construct the fluorescent protein is split such that resonance energy transfer from the luciferase and subsequent light emission for opsin activation only occurs in the presence of CTZ in synapses allowing reconstitution of the fluorescent protein. Experiments are carried out in HEK cells and cultured primary neurons.

Disclosures: R. Schumaker: None. **M. Prakash:** None. **A. Pal:** None. **E. Crespo:** None. **U. Hochgeschwender:** None.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.06/CC52

Topic: I.04. Physiological Methods

Support: NIH NS088413, NS091585 and NS085568
VA Merit Award RX000666, RX001473
AHA Award CDA34110317

Title: Behavioral outcomes after cerebral ischemic stroke of young adult and aged mice receiving transplantation of iPSC-derived neural progenitor cells and optochemogenetics treatment

Authors: Z. Z. WEI, M. J. H. LEE, W. W. ZHONG, A. WU, S. P. YU, *L. WEI;
Anesthesiol./Neurol., Emory Univ. Sch. Med., Atlanta, GA

Abstract: Stroke is a major cause of death and paralysis; stroke survivors often develop long-term sensorimotor and cognitive deficits, as well as emotional disturbances. Aging and aged populations are the most vulnerable groups to strokes. Our previous investigations developed a focal cerebral ischemic stroke rodent model with low mortality rates. This cortical stroke model is suitable for long-term studies of the target specific neuronal repair and functional/behavioral alterations in aging and aged mice. In the present investigation, we tested the effects of transplantation of iPSC-derived neural progenitor cells (iPSC-NPC) in aged (18-month-old) male and female mice and compared with that in young (2-month-old) adults. Mouse iPSC-NPC were transduced with a novel optochemogenetics fusion protein, enhanced luminopsin 3 (eLMO3), which consists of a bioluminescent luciferase, *Gaussia* luciferase (GLuc), and an opsin, *Volvox* Channelrhodopsin 1 (VChR1). These eLMO3-iPSC-NPC can be activated by either photostimulation using light or by the luciferase substrate coelenterazine (CTZ). Stroke mice received vehicle or cell transplantation 7 days after stroke and daily intranasal delivery of CTZ (2 mg/kg). At 21 days after stroke, mice received eLMO3-iPSC-NPC and CTZ treatment showed significantly higher levels of SDF-1, synapsin-1, and PSD-95 in the peri-infarct region. The home-cage monitoring system was used to assess animal behaviors at different time points (7-21

days after stroke) in a native environment without human intervention. Compared to non-eLMO3-cell-transplanted animals, significant improvements in general home-cage activities were observed in mice receiving eLMO3-iPSC-NPC and CTZ treatment. All eLMO3-iPSC-NPC-treated animals were able to show less depressive like behavior in the sucrose splash test and the sucrose preference test 28 days following the ischemic insult in all transplantation groups. Pain and other abnormal behaviors were also monitored and measured. Our data provide information and evidence to explain the distinctive neurological consequences of our recently developed iPSC-NPC and optochemogenetics therapy after ischemic stroke at young and old ages. The sensitive and significant functional improvement with lower mortality rates of this ischemic stroke suggests that it is an appropriate stroke model for aged rodents and suitable for evaluation of potential cell therapies for ischemic stroke under clinically relevant conditions.

Disclosures: Z.Z. Wei: None. **M.J.H. Lee:** None. **W.W. Zhong:** None. **A. Wu:** None. **S.P. Yu:** None. **L. Wei:** None.

Poster

612. Optic Methods: Development and Applications

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Program #/Poster #: 612.07/CC53

Topic: I.04. Physiological Methods

Title: Use of bioluminescent optogenetics (BL-OG) to enhance motor axon regeneration after peripheral nerve transection and repair

Authors: O. C. MISTRETTA[1], A. J. LOPEZ[2], C. WYNANS[1], K. BERGLUND[3], ***A. W. ENGLISH**[1];
[1]Cell BIology, Emory Univ. Sch. of Med., Atlanta, GA; [2]Rehabil. Med., [3]Neurosurg., Emory Univ., Atlanta, GA

Abstract: Activity-dependent experimental therapies, including optogenetic stimulation, have been most effective in enhancing the regeneration of motor axons following peripheral nerve injury in laboratory rodents. Bioluminescent optogenetics (BL-OG) uses luminopsins, light-sensing ion channels fused with light-emitting luciferase. When exposed to a cognate substrate (i.e. coelenterazine, CTZ), bioluminescence is generated by the luciferase moiety and the attached opsin is activated. We propose that BL-OG using an excitatory opsin, such as channelrhodopsin, could be used as a pharmacologic version of an activity-dependent therapy to treat nerve injuries. Mice expressing cre recombinase under control of the promoter for choline acetyl transferase (ChAt-cre) were induced to express an excitatory luminopsin (eLMO3) either by breeding with mice expressing a cre-dependent eLMO3 or by sciatic nerve injection of an adeno-associated viral (AAV) vector expressing cre-dependent eLMO3. Application of CTZ in these mice produced intense bioluminescence in the sciatic nerve that was detectable *in vivo* for

at least 45 min. Functioning eLMO3 expression in both model systems was confirmed by increases in motoneuron excitability following CTZ application (10 mg/Kg, i.p.). No increase in resting EMG activity was found after CTZ injections but stimulus thresholds for producing fast spinal evoked motor potentials decreased by 15% within 5 minutes of CTZ application and returned to baseline after four hours. In both groups of eLMO3-expressing mice treated once with CTZ at the time of sciatic nerve transection and repair, amplitudes of direct muscle EMG responses (M waves) were four-fold larger than found in untreated eLMO3-expressing mice or CTZ-treated wild type mice four weeks later. More spinal motoneurons could be retrogradely labeled in treated eLMO3-expressing mice than controls and more muscle fibers had been reinnervated in mice exposed to the BL-OG-based treatment. Treatment of injured peripheral nerves using BL-OG is an effective means of applying an activity-dependent therapy to promote regeneration of motor axons after peripheral nerve injury.

Disclosures: O.C. Mistretta: None. **A.J. Lopez:** None. **C. Wynans:** None. **K. Berglund:** None. **A.W. English:** None.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

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Program #/Poster #: 612.08/CC54

Topic: I.04. Physiological Methods

Support: Mirowski Family Foundation

Title: Chemogenetic activation of GABAergic neurons in dorsal and ventral hippocampus reduces epileptiform discharges in a mouse pentylenetetrazole seizure model

Authors: *A. M. FERNANDEZ[1], S.-E. PARK[3], K. BERGLUND[4], C.-A. N. GUTEKUNST[2], R. E. GROSS[5];
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Abstract: One third of patients with epilepsy are resistant to drug therapy. Thus, there is a need for alternative modes of treatments for seizures. Optogenetics has proven to be a useful tool to understand network dynamics, but it has translational challenges. We have developed a chemogenetic tool, called luminopsins (LMOs), that consists of a light-sensitive channel fused with a luciferase enzyme that bioluminesces in the presence of its substrate coelenterazine (CTZ), eliminating the need for external hardware. Previous studies in our laboratory have shown that simultaneous inhibition of glutamatergic neurons in the dentate gyrus and anterior nucleus of thalamus with an inhibitory luminopsin reduces seizure severity and duration in a pentylenetetrazole (PTZ) seizure model (Tung et al., 2018). The present study aimed at exploring

the effect of specifically activating GABAergic neurons in dorsal and ventral hippocampus with the goal of achieving greater seizure control. We hypothesized that activation of GABAergic neurons suppresses electrographic spike-and-wave discharges (SWDs) at a low dose (40 mg/kg) of PTZ, as well as behavioral events (i.e. jerks and tonic-clonic seizures) at a higher dose (50 mg/kg) of PTZ. To test this, adult VGAT-Cre mice received intracranial bilateral injections of a recombinant adeno-associated viral vector carrying the floxed excitatory luminopsin gene into dorsal and ventral hippocampi. Mice were implanted with EEG screws over frontal and parietal cortex and subjected to a PTZ test two weeks after virus injection. Mice were pre-treated with either vehicle or CTZ (intraperitoneally or intranasally) 20 minutes before PTZ injection and monitored for 45 minutes. One week later, this procedure was repeated in the same mice, with the opposite treatment. For the following two weeks, the dose of PTZ was increased. The rate of SWDs and behavioral events were quantified. Mice pretreated with CTZ showed a reduction in the rate of SWDs and behavioral events. Postmortem histology confirmed adequate targeting of the dorsal and ventral hippocampus with luminopsin. These results support our hypothesis of seizure suppression in the PTZ model due to inhibition of the entire hippocampal formation, underscoring the importance of inhibitory circuits in a seizure-prone state.

Disclosures: **A.M. Fernandez:** None. **S. Park:** None. **K. Berglund:** None. **C.N. Gutekunst:** None. **R.E. Gross:** None.

Poster

612. Optic Methods: Development and Applications

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Topic: I.04. Physiological Methods

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NIH Grant NS085568
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NIH Grant NS079268
NIH Grant NS079757
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NSF Grant CBET1512826

Title: Improved membrane trafficking of luminopsins for more efficient optogenetic and chemogenetic control of neuronal activity

Authors: *K. BERGLUND, J. Y. ZHANG, J. K. TUNG, Z. WANG, S. YU, R. E. GROSS, L. WEI;
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Abstract: Luminopsins (LMOs) are fusion proteins consisting of a luciferase and an opsin. They provide control for neuronal activity via chemogenetic and optogenetic activation. We have shown that both an external light source and the luciferase substrate, coelenterazine (CTZ), could modulate neuronal activity *in vitro* and *in vivo*, although luminopsin's efficacy can be further improved. In this study, we aimed at improving membrane expression of the third version of LMO (LMO3) by inserting a Golgi trafficking signal (TS) sequence. In cortical neurons in culture, expression of enhanced LMO3 (eLMO3) resulted in significant reductions in the formation of protein aggregates, as well as in a significant increase in total photocurrents. Furthermore, we corroborated the findings *in vivo* by injecting adeno-associated viral vectors into the barrel cortex of male mice. We observed significantly reduced fluorescent puncta in eLMO3-expressing cortical neurons compared to the original LMO3. Finally, we quantified CTZ-driven behavior, namely whisker touching behavior. After CTZ administration, mice with eLMO3 displayed significantly longer whisker responses than mice with LMO3. We did not observe any noticeable behavioral change when vehicle was injected instead of CTZ as control. In conclusion, we have engineered the superior LMO by improving membrane trafficking and demonstrated improved efficacy of LMOs through multiple readouts.

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Poster

612. Optic Methods: Development and Applications

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PECASE
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Chen Institute at Caltech
NSF NeuroNex Technology Hub1707316

Title: AAV engineering by multiplexed-create selection and rational peptide insertion yields variants with enriched targeting of CNS astrocytes upon systemic delivery

Authors: *X. CHEN, S. RAVINDRA KUMAR, X. DING, V. GRADINARU;
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Abstract: Astrocytes are key CNS contributors at around 30% of the total cells (Liddelow, et al, Immunity, 2017) and are involved in synapse development, neuronal activity, and maintenance of immune homeostasis. Astrocytes could therefore be an important gene therapy target for a variety of neurological and psychiatric diseases. However, the commonly-used intra-cranial injection required to bypass the blood-brain barrier (BBB) and access CNS cells can cause local inflammation and drive astrocyte reactivity (Liddelow, et al, Immunity, 2017) therefore confounding research results and causing side effects. Systemic AAV delivery provides a noninvasive alternative for broad gene delivery to the CNS. We previously identified a few highly efficient CNS transducing variants including AAV-PHP.A (Deverman BE, et al, Nat. Biotech., 2016) and AAV-PHP.eB (Chan K, et al, Nat. Neuro., 2017) using the Cre recombination-based AAV targeted evolution (CREATE) method. PHP.eB can transduce astrocytes but is also very efficient at transducing neurons brain-wide, creating concerns with off-target effects when targeting astrocytes under strong ubiquitous promoters. PHP.A, on the other hand, target astrocytes with better specificity but is a subpar virus producer, limiting its application. To identify AAV variants that can more specifically target astrocytes, we utilized the newly-developed Multiplexed-CREATE method (Kumar, et al, under review, 2019): M-CREATE is a high-confidence positive and negative AAV selection platform that uses next generation sequencing (NGS) to obtain a comprehensive recovery of viral capsid libraries. For the lead variants, we then performed site-targeted rational peptide insertion to fine-tune their specific tropism. This combined approach of directed evolution of AAV capsids and rational peptide insertion allowed us to identify several novel variants showing more specific transduction of astrocytes in mice upon systemic delivery. This systemic AAV toolbox tailored for gene delivery across the BBB for astrocytes could be enabling for research focused on neuron-immune interactions and gene therapy for disease models.

Disclosures: X. Chen: None. **S. Ravindra Kumar:** None. **X. Ding:** None. **V. Gradinaru:** None.

Poster

612. Optic Methods: Development and Applications

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Support: NIH Director's New Innovator IDP20D017782-01
PECASE
Heritage Medical Research Institute
Chen Institute at Caltech
CZI Neurodegeneration Challenge Network

Title: Approaches towards engineering the neuronal Arc capsid for efficient and targeted RNA delivery

Authors: *T. DOBREVA[1], A. TAIBI[2], M. FLYNN[1], X. DING[1], M. ELOWITZ[1], J. SHEPHERD[2], V. GRADINARU[1];
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Abstract: Efficient and targeted RNA delivery could have numerous applications, from trafficking undesired RNA to degradation sites and studying intracellular trafficking, to perturbation studies of intercellular communication. The neuronal immediate early gene, Arc, has been found to contribute to virus-like particles and transfer RNA intercellularly [1]. Inspired by this finding, we are engineering Arc to target specific RNA for delivery to sites of interest. Deactivated Cas13 (dCas13) enzymes, such as dPspCas13b and dLwaCas13a, have been shown to bind RNA without cleaving the target [2]. Cox, et. al have also demonstrated that dCas13 enzymes fused to ADAR2, an RNA-binding and editing protein, edit RNAs specifically. As such, in order to target Arc to a specific RNA, we have generated and tested fusions of Arc and deactivated Cas13 enzymes. We observed dCas13-Arc monomer fusions between 75 kDa and 100 kDa using fluorescent western blot against Arc antibody, an increase from the native 50 kDa size of Arc. Using transmission electron microscopy (TEM), we have also observed capsid formation of these dCas13-Arc fusions from capsids and extracellular vesicles purified by ultracentrifugation from HEK cells. Performing the donor-recipient assay [1], we observed transfer, albeit at low efficiency, of RNA with dCas13-Arc fusions into untransfected naïve HEK cells. Due to modest release of Arc capsids from HEK cells, it was necessary to increase Arc capsid release for downstream detection assays. In HIV and EIAV, p6 and p9 gag motifs, respectively, bind ESCRT proteins and assist with viral budding [3]. Given Arc's primary sequence structural similarity to HIV capsid domain, we hypothesized that integrating these domains into Arc could potentially enhance capsid release [4]. To this end, we have investigated two approaches: (1) fusion, insertion, and substitution of p9 and p6 gag motifs with Arc from EIAV and HIV viruses, respectively; and (2) co-transfection with tetraspanin proteins such as ALIX, CD9, CD81, and TSG101. We then characterized RNA transfer and capsid formation. Overall, we demonstrate that it is possible for Arc to maintain its capsid-forming ability and to traffick RNA when fused with a dCas13 enzyme, as well as other motifs intended for increased capsid release. These preliminary results support the possibility of engineering Arc as a scientific tool for RNA delivery.
[1] Pastuzyn, E. D. et al. (2018). Cell, 172(1–2), 275–288.
[2] Cox, D. B. T. et al. (2017). Science, 358(6366), 1019–1027.
[3] Strack, B. et al. (2003). Cell, 114(6), 689–699.
[4] Shepherd, J. D. (2018). Seminars in Cell & Developmental Biology, 77, 73–78.

Disclosures: T. Dobreva: None. **A. Taibi:** None. **M. Flynn:** None. **X. Ding:** None. **M. Elowitz:** None. **J. Shepherd:** None. **V. Gradinaru:** None.

Poster

612. Optic Methods: Development and Applications

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Program #/Poster #: 612.12/CC58

Topic: I.04. Physiological Methods

Support: NIH Director's New Innovator IDP20D017782-01
PECASE
NIH BRAIN RF1MH117069
Heritage Medical Research Institute
Chen Institute at Caltech
Beckman Institute

Title: Deep brain optical imaging uncovers motivational salience and prediction error encoding by dorsal raphe dopamine neurons

Authors: *J. CHO[1], X. CHEN[1], A. KAHAN[2], D. A. WAGENAAR[1], V. GRADINARU[3]; [1]Caltech, Pasadena, CA; [2]Biol. and Biol. Engin., Caltech, San Marino, CA; [3]Biol. and Biol. Engin., Caltech, Pasadena, CA

Abstract: Increasing evidence shows that DA neurons are functionally heterogeneous from encoding reward or reward prediction error to signaling aversion or salience [1]. DRN DA neurons are anatomically distinct from ventral midbrain DA neurons and respond to salient stimuli regardless of valence, suggesting that they may encode motivational salience [2]. To address this hypothesis, we first performed fiber photometry recordings [3] of DRN DA neurons during appetitive and aversive conditioning tasks where mice learn the association between neutral cues and positive or negative outcomes. Across learning, initially unresponsive DRN DA neurons developed positive response to cues paired with both reward and punishment ($n = 5$ mice, $p < 0.0001$ in two-way ANOVA, $p < 0.01$ in post-hoc Bonferroni tests), suggesting that DRN DA neurons at the population level track motivational salience rather than value [1]. In addition, DRN DA neurons signaled salience prediction error, showing enhanced neural activity in response to unexpected outcomes over expected ones ($n = 5$ mice, $p < 0.05$). However, these neurons did not show activity suppression in response to unexpected omission. The degree of DRN DA salience response was modulated by animal's internal motivational state, as response to reward-predicting cues was diminished after satiety ($n = 5$ mice, $p < 0.05$ in two-way ANOVA, $p < 0.001$ in post-hoc Bonferroni tests). In ongoing work, we are evaluating the VTA DA dynamics in the aforementioned tasks to compare with the DRN DA findings. Finally, we are performing deep brain optical imaging with two-photon microscopy via implanted gradient index lenses during conditioning tasks to investigate the DRN DA neuronal dynamics at the single-cell resolution. Altogether, these data deepen our understanding of the functional

properties of DRN DA neurons and expand on the functional heterogeneity of DA signaling.

Reference:

[1] Bromberg-Martin ES, Matsumoto M, Hikosaka O. (2010) Dopamine in motivational control: rewarding, aversive, and alerting. Neuron *68*, 815-834.
[2] Cho JR, Treweek JB, Robinson JE, Xiao C, Bremner LR, Greenbaum A, Gradinaru V. (2017) Dorsal raphe dopamine neurons modulate arousal and promote wakefulness by salient stimuli. Neuron *94*, 1205-1219.e8.
[3] Lerner TN, Shilyansky C, Davidson TJ, Evans KE, Beier KT, Zalocusky KA, Crow AK, Malenka RC, Luo L, Tomer R, Deisseroth K. (2015) Intact-brain analyses reveal distinct information carried by SNc dopamine subcircuits. Cell *162*, 635-647.

Disclosures: J. Cho: None. **X. Chen:** None. **A. Kahan:** None. **D.A. Wagenaar:** None. **V. Gradinaru:** None.

Poster

612. Optic Methods: Development and Applications

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Program #/Poster #: 612.13/CC59

Topic: I.04. Physiological Methods

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A.K. is supported by The Hebrew University postdoctoral fellowship for women abroad, IL and by Caltech fellowship for postdoctoral scholar, US

Title: VIP neurons in the suprachiasmatic nucleus of female mice underline the bidirectional influence between estrus cycle and circadian rhythm

Authors: *A. KAHAN, G. M. COUGHLIN, V. GRADINARU;
Caltech, Pasadena, CA

Abstract: Female mice ovulate every 4-5 days at the beginning of the dark phase. The temporal specificity of this process points to a role for the circadian clock, and thereby the suprachiasmatic nucleus (SCN), the circadian rhythm pacemaker, in ovulation. One key neuronal population in the SCN expresses vasoactive intestinal peptide (VIP); this signaling peptide has both direct and indirect effects on gonadotropin releasing hormone (GnRH) neurons, the neuronal population

that controls the release of reproductive hormones, such as luteinizing hormone (LH). Although signaling from SCN^{VIP} to GnRH neurons has been hypothesized to control estrous cycle timing, it is not known whether the activity of SCN^{VIP} neurons depends on estrous state. In addition, it is not clear that SCN^{VIP} neurons are the source for VIP peptide release and the exact relevance of SCN^{VIP} neuronal activity for the circadian timing of ovulation is uncertain. To address the first, we recorded calcium dependent fluorescence signal (via fiber-photometry, FP) from SCN^{VIP} neurons in-vivo in both male and female mice. These bulk neuronal activity recordings were supported by single cell resolution imaging using Inscopix miniscopes. We recorded SCN^{VIP} neuronal activity at the transitions from light to dark (ZT12), and two hours before dark (ZT10), which corresponds to the LH surge onset. FP data showed that SCN^{VIP} activity around ZT12 is estrous cycle dependent; at ZT10 these neurons tend to be active at a rate of 0.1 ± 0.02 events/min when recording from females in estrus; lower by factor of 3 to 4 compared to the event rate in other estrous stages. On the other hand, in the first hour of the dark phase (ZT12-13), females in estrus tend to have higher rate (0.38 ± 0.01 events/min), whereas those in other estrous stages and males exhibit a rate of ~0.3 events/min. These results suggest that SCN^{VIP} neurons are under hormonal control, likely involving estrogen and progesterone. To investigate the importance of SCN^{VIP} neurons on the regulation of estrous cycles, we experimentally manipulated the circadian rhythm by: (1) a 'Jet-lag' experiment, by exposing animals to six hours phase advance every 4-5 days (n=7); and (2) ablating SCN^{VIP} neurons through viral-mediated expression of Caspase-3, which triggers cell-autonomous apoptosis (n=5 control, n=6 experimental). In both experiments we observed a significant decrease in estrous cycle regularity and a significant reduction in proestrus events ($P < 0.001$). These experiments provide a direct evidence for the role of SCN^{VIP} neurons as the source of VIP peptide in the circadian regulation of ovulation, and suggest that SCN^{VIP} neuronal activity is affected by the estrous cycle.

Disclosures: A. Kahan: None. **G.M. Coughlin:** None. **V. Gradinaru:** None.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

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Topic: I.04. Physiological Methods

Support: NIH Grant MH111499

Title: Development of a two-channel head mounted miniscope for imaging two colors simultaneously in freely moving mice

Authors: *D. M. KIRCHER[1], Z. DONG[1], T. SHUMAN[2], D. KLEINFELD[4], D. B. AHARONI[5], D. J. CAI[3], P. A. SLESINGER[6];
[1]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Neurosci., [2]Mount Sinai, New

York, NY; [4]Dept. of Physics, Univ. of California at San Diego, La Jolla, CA; [5]Dept. of Neurol., UCLA, Agoura Hills, CA; [6]Professor, Dept. of Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Head-mounted miniature microscopes (Miniscopes) provide a powerful tool for real-time imaging of neuronal activity in freely moving animals that express genetically-encoded calcium indicators (GECIs) (e.g., GCaMP). While current Miniscopes only record a single wavelength of light, a Miniscope capable of recording two separate wavelengths of light would greatly add functional flexibility to allow for imaging different calcium indicators, cell-type specific labeling while imaging and FRET (Fluorescence Resonance Energy Transfer)-based imaging in freely behaving animals. Here, we used our two-channel Miniscope to measure FRET responses *in vivo* from cell-based neurotransmitter fluorescent engineered reporters (CNiFERs) implanted subcortically. CNiFERs are biosensors capable of measuring the release of neurotransmitters or neuropeptides in real-time, and utilize a genetically-encoded FRET-based calcium sensor in conjunction with a specific G-protein coupled receptor. We created a two-channel Miniscope prototype, based on the opensource UCLA Miniscope design, by adding a second optical path and corresponding CMOS sensor. Emission light from the brain passes through an additional dichroic that splits the image into separate wavelengths of light each detected by its own CMOS sensor. The two-channel Miniscope prototype was first validated *in vitr*o by injecting M1 CNiFERs that respond to acetylcholine into agar and measuring changes in the FRET ratio during infusion of acetylcholine. The Miniscope was validated *in vivo* by injecting dopamine sensing D2 CNiFERs directly into the premotor cortex, mounting the scope with GRIN lens, and measuring changes in FRET ratio during electrical stimulation of the substantia nigra. We plan to use the two-channel scope to measure FRET changes in response to endogenous transmitter release in freely behaving mice. Injection of acetylcholine and somatostatin sensing CNiFERs into the CA1 of the hippocampus will allow for the detection of endogenously released acetylcholine and/or somatostatin during free exploration of an open field. In summary, our two-channel Miniscope prototype is capable of measuring changes in FRET. Future refinements and adaptations of this two-channel Miniscope will allow for FRET or any multiplexed recordings of multiple sensors or fluorophores with reduced weight, minimal bleaching, and improved optics.

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Poster

612. Optic Methods: Development and Applications

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Klingenstein-Simons Fellowship
Brain Research Foundation Award
NARSAD Young Investigator Award
Botanical Center Pilot Award
CURE Award
American Epilepsy Society Award

Title: Minian: An open-source miniscope analysis pipeline with interactive visualization tools

Authors: *Z. DONG[1], Y. FENG[1], W. MAU[2], L. CHEN[1], Z. T. PENNINGTON[1], Y. ZAKI[1], K. RAJAN[1], T. SHUMAN[1], D. AHARONI[3], D. J. CAI[1];
[1]Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Boston Univ., Boston, MA; [3]Dept. of Neurol., UCLA, Los Angeles, CA

Abstract: Miniature microscopes have gained a lot of traction for *in vivo* calcium imaging in freely behaving animals. However, extracting calcium signals from raw videos is a computationally complex problem and remains a bottleneck for many researchers utilizing single photon *in vivo* calcium imaging. Recently, a few analysis pipelines have been developed and work well on extracting calcium events. However, most analysis packages that are available either have key parameters that are hard-coded or lack detailed documentation on how to set parameters properly. Furthermore, there is a need for a user-friendly tool that offers informative visualization of how altering parameters affect the output of the data. Our open-source analysis pipeline, Minian, facilitates transparency and accessibility of the underlying algorithm of the pipeline. Minian contains interactive visualization tools for every analysis step, as well as detailed documentation and tips on parameter tuning. The visualization tool guides users to explore and select the appropriate parameters which is especially helpful in analyzing different cell-types and brain regions. Minian has been validated to reliably and robustly extract calcium events across different cell types and brain regions. In practice, Minian provides an open-source calcium imaging analysis pipeline with user-friendly interactive visualization to explore parameters and validate results.

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Poster

612. Optic Methods: Development and Applications

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.16/CC62

Topic: I.04. Physiological Methods

Support: NSF Grant DBI-1707408

Title: FPGA-based real-time processing for integrated electrophysiology and calcium imaging with the UCLA miniscope

Authors: *Z. CHEN[1], G. BLAIR[2], D. AHARONI[3], P. GOLSHANI[3], J. CONG[1], H. T. BLAIR[2]; [1]Computer Sci. Dept., [2]Dept. of Psychology, [3]Dept. of Neurol., UCLA, Los Angeles, CA

Abstract: The UCLA miniscope is an open-source head mounted device that is capable of monitoring the activity of a large population of neurons in freely behaving mice or rats *in vivo*. Here we introduce an accessory real-time processing module (RTPM) for the UCLA miniscope, which processes a standard miniscope video stream at 30 fps with an image resolution of 480x752 and 8-bit pixel intensity. The RTPM is designed on the field programmable gate array (FPGA) of an SoC device to perform the rigid/non-rigid motion correction, image enhancement and calcium trace extraction in real time, and is controlled by a user interface terminal that connects to the RTPM via ethernet from a host computer. The motion correction is accomplished with ~80 μs latency, by using folding to accelerate the contrast filtering, and utilizing unrolling to accelerate FFT operations that are necessary in computing the cross correlation in the frequency domain. The image enhancement is accomplished with <1 ms latency by accelerating morphological operations (erosion and dilation) with dedicated streaming array processing architecture.The modules for calcium trace extraction and cell identification/registration using convolutional neural network inference are under development. In addition to the calcium image processing, the RTPU can also process electrophysiology data in real time by using the compact LSTM inference kernel (CLINK) for filtering and closed-loop feedback (Chen, Blair & Cong, ISLPED 2018). The ultimate goal for the RTPM is to provide flexible hardware for real-time processing and decoding of *in vivo* calcium image and electrophysiology data and to be incorporated it into systems for neurofeedback and closed-loop control of neural activity.

Disclosures: Z. Chen: None. **G. Blair:** None. **D. Aharoni:** None. **P. Golshani:** None. **J. Cong:** None. **H.T. Blair:** None.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.17/CC63

Topic: I.04. Physiological Methods

Support: NIMH (R01 MH113071)
NIA (R01 AG013622)
NINDS (RO1 NS106969)

Title: Ccr5 closes the window for contextual memory linking by regulating neuronal ensemble overlap

Authors: *Y. SHEN[1], M. ZHOU[1,2], D. CAI[1,3], Y. CAI[1], A. LAVI[1], D. NECULA[1], A. LIU[1], X. KANG[1], S. HUANG[1], T. SILVA[1], A. J. SILVA[1];
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Abstract: Although the mechanisms involved in the encoding, consolidation and retrieval of memory have been widely studied, little is known about the mechanisms that link multiple memories across time. Previous studies in our laboratory showed that when there is substantial overlap between the neuronal ensembles of two memories encoded close in time, recall of one memory increases the likelihood of recalling the other memory, thus linking the two memories across time. Understanding the mechanisms that regulate the temporal window of memory linking is critical for understanding how different memories are either linked or separated across time. Here, we show that that C-C chemokine receptor type 5 (CCR5) plays a key role in closing the temporal window for memory linking. Following contextual conditioning there was a delayed increase in the levels of Ccr5 mRNA in the mouse dorsal hippocampal CA1. When CCR5 activity was measured with the iTANGO-CCR5 system, after learning there was also a delayed increase in neuronal CCR5 activation in a temporal pattern consistent with the hypothesis that these increases in CCR5 expression or activation have an impact on memory linking. Indeed, Ccr5 null mutation resulted in an extension of the window for contextual memory linking, and calcium imaging results with head-mounted fluorescent miniscopes showed that this mutation also extended the temporal window for the overlap between CA1 neural ensembles encoding two separate contextual memories. Aging increases the levels of both Ccr5 and its endogenous ligand Ccl5 in dorsal hippocampus, and importantly, both Ccr5 mutation and CCR5 antagonist reversed the decline in contextual memory linking in aged mice, suggesting that the increase in CCL5/CCR5 signaling in the aged hippocampus contributes to age-related deficits in memory linking. Our results demonstrate that a delayed increase in CCR5 following learning decreases the overlap between the neuronal ensembles encoding two contextual memories acquired distal in time, and therefore close the window for the linking of these memories.

Disclosures: **Y. Shen:** None. **M. Zhou:** None. **D. Cai:** None. **Y. Cai:** None. **A. Lavi:** None. **D. Necula:** None. **A. Liu:** None. **X. Kang:** None. **S. Huang:** None. **T. Silva:** None. **A.J. Silva:** None.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.18/CC64

Topic: I.04. Physiological Methods

Support: 1700408 Neurotech Hub

Title: Miniscope neuronex hub: Miniaturized open source devices for calcium imaging, electrophysiology, and real-time control of neural activity

Authors: *D. AHARONI[1], P. ZHAO[1], M. SEHGAL[8], L. YANG[2], Z. CHEN[9], G. BLAIR[3], R. RESHEF[1], S. W. HUR[1], Y. CAI[4], F. SANGIULIANO JIMKA[1], R. CHANG[1], T. NOEBAUER[10], A. J. SILVA[11], A. VAZIRI[10], H. T. BLAIR, IV[5], J. CONG[6], S. C. MASMANIDIS[7], P. GOLSHANI[12];
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Abstract: Over the past decade, advancements in genetically encoded calcium indicators (GECIs) and head-mounted lightweight imaging devices have enabled researchers to study network dynamics with single cell precision in freely behaving animals. These miniature microscopes (miniscopes) have already provided significant insight into a broad range of neuroscience topics and are likely to continue to be a key technology for investigating neural activity in the context of behavior. When done in parallel with miniscope imaging, electrophysiology recordings can provide complementary information about the brain including high-temporal resolution extracellular spikes and local field potential (LFP) oscillations.
A central goal of our NeuroNex Hub is to design, develop, and implement an electrophyiology integrated miniscope (e-scope) capable of both imaging GECIs as well as recording electrophysiology signals simultaneously in unrestrained animals. We have built a 32 channel e-scope and have successfully tested it in both freely behaving mice and rats. While this system is natively supported by our newest generation of Miniscopes, it also can be easily retrofitted on all previously disseminated Miniscope designs. The ephys electronics interface with the Miniscope imaging electronics requiring no additional cabling between the animal and a data acquisition (DAQ) system. Using a custom flex printed circuit and high density Molex slimstack connectors, the head-mounted ephys electronics can interface with a range of electrodes including single electrodes, tetrodes, and silicon probes. We are now developing 64 and 128 channel e-scopes along with a new generation of DAQ systems.

Here we will present the current status of this project and lay out a roadmap for the coming years.

Disclosures: D. Aharoni: None. **P. Zhao:** None. **M. Sehgal:** None. **L. Yang:** None. **Z. Chen:** None. **G. Blair:** None. **R. Reshef:** None. **S.W. Hur:** None. **Y. Cai:** None. **F. Sangiuliano Jimka:** None. **R. Chang:** None. **T. Noebauer:** None. **A.J. Silva:** None. **A. Vaziri:** None. **H.T. Blair:** None. **J. Cong:** None. **S.C. Masmanidis:** None. **P. Golshani:** None.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.19/CC65

Topic: I.04. Physiological Methods

Support: McKnight Memory and Cognitive Disorders Award
Klingenstein-Simons Fellowship
Brain Research Foundation Award
NARSAD Young Investigator Award
Botanical Center Pilot Award
CURE Award
American Epilepsy Society Award

Title: Eztrack, an open-source video analysis pipeline for the investigation of animal behavior

Authors: *Z. T. PENNINGTON, Z. DONG, R. BOWLER, Y. FENG, L. M. VETERE, T. SHUMAN, D. J. CAI;
Mount Sinai Sch. of Med., New York, NY

Abstract: Tracking small animal behavior by video is one of the most common tasks in the fields of neuroscience and psychology. Although commercial software exists for the execution of this task, this software often presents enormous cost to the researcher, and can also entail purchasing specific hardware setups that are not only expensive but lack adaptability. Moreover, the inaccessibility of the code underlying this software renders them inflexible. Alternatively, available open source options frequently require extensive model training and can be challenging for those inexperienced with programming. Here we present an open source and platform independent set of behavior analysis pipelines using interactive Python (iPython/Jupyter Notebook) that researchers with no prior programming experience can use. Two modules are described. One module can be used for the positional analysis of an individual animal across a session, amenable to a wide range of behavioral tasks including conditioned place preference, water maze, light-dark box, open field, and elevated plus maze, to name but a few. A second module is described for the analysis of conditioned freezing behavior. In addition to a range of

interactive plots and visualizations to confirm that chosen parameters produce results that conform to the user's approval, batch processing tools for the fast analysis of multiple videos is provided, and frame-by-frame output makes aligning the data with neural recording data simple. Lastly, options for cropping video frames to mitigate the influence of fiberoptic/electrophysiology cables, analyzing specified portions of time in a video, and defining regions of interest, can be implemented with ease.

Disclosures: **Z.T. Pennington:** None. **Z. Dong:** None. **R. Bowler:** None. **Y. Feng:** None. **L.M. Vetere:** None. **T. Shuman:** None. **D.J. Cai:** None.

Poster

612. Optic Methods: Development and Applications

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Program #/Poster #: 612.20/CC66

Topic: I.04. Physiological Methods

Support: NSF Career award (CBET-1351692)
HFSP Young Investigators award (RGY0088)

Title: MiniFAST (miniscope with a fast and sensitive image sensor and fast locking baseplate)

Authors: *J. JUNEAU[1], G. DURET[1], A. V. RODRIGUEZ[1], S. MOROZOV[1], D. AHARONI[2], J. T. ROBINSON[1], F. ST-PIERRE[3,1], C. KEMERE[1];
[1]Electrical and Computer Engin., Rice Univ., Houston, TX; [2]Dept. of Neurol., UCLA, Los Angeles, CA; [3]Neurosci., Baylor Col. of Med., Houston, TX

Abstract: In recent years, miniaturized fluorescence head-mounted microscopes have enabled experiments aimed at long-term imaging of cell networks in freely behaving animals. The success of this technology relies on fluorescent neural activity sensors such as calcium indicators (e.g. GCaMP). All fluorescence based neural activity sensors suffer from cell brightness degradation due to photobleaching and thus limit the time of the experimental imaging session (~20-45 minutes for currently available head-mounted microscopes). Photobleaching is caused by microscope excitation light intensity and is directly correlated with image sensor sensitivity and gain levels. Furthermore, new neural activity sensors, such as genetically-encoded voltage indicators (GEVIs), are emerging providing kinetics that can closely match the temporal resolution of action potentials. Presently, GEVIs are significantly dimmer than calcium indicators and require faster frames rates that can match the GEVI's on/off fluorescence kinetics. Due to these technological limitations, imaging of GEVIs with head-mounted microscopes have not been reported. In order to meet emerging neural activity sensor advancements and reduce photobleaching effects, we aim to bridge the gap by improving the technology of head-mounted microscopes.

Here we present the design and *in vivo* results of open-source MiniFAST, a miniaturized fluorescence head-mounted microscope capable of ultra-fast frame rates (> 500 frames per second) and super low-light sensing ability (analog gain up to 30 dB). The design is built upon the open-source Miniscope platform and is compatible with the Miniscope Data Acquisition Board, optical lenses and the single cable serializer/deserializer system. MiniFAST's printed circuit board, with a size of 13 mm by 22 mm, integrates a Sony CMOS image sensor with a total of 2.13 megapixels, 2.9 um pixel size and featuring 1080p video at 30 frames per second. Increased frame rates are achieved by reducing the frame height. The new features of MiniFAST are incorporated into the Miniscope Windows GUI. Additionally, the 3-D printed optics housing is updated for the larger sensor size and provides a fast new easy locking baseplate that maintains stability with animal movement. Without the requirement of tightening set screws, the MiniFAST baseplate design decreases animal handling time from ~2-3 weeks to ~2 days. We demonstrate the camera with *in vivo* imaging of the CA1 region of the hippocampus in freely behaving mice injected with GCaMP6f. Furthermore, we show results from *in vitro* cell patch-clamping and *in vivo* imaging of a genetically-encoded voltage indicator.

Disclosures: **J. Juneau:** None. **G. Duret:** None. **A.V. Rodriguez:** None. **S. Morozov:** None. **D. Aharoni:** None. **J.T. Robinson:** None. **F. St-Pierre:** None. **C. Kemere:** None.

Poster

612. Optic Methods: Development and Applications

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Program #/Poster #: 612.21/CC67

Topic: I.04. Physiological Methods

Support: NIH RO1 MH084315
R01 RO1 MH113071
NIH RO1 AG013622

Title: Temporal dynamics of spatial information encoding within retrosplenial cortex

Authors: *M. SEHGAL[1], S. MARTIN[1], A. PEKCAN[1], D. AHARONI[2], S. HUANG[3], A. LAVI[4], D. J. CAI[5], A. J. SILVA[6];
[1]Univ. of California Los Angeles, Los Angeles, CA; [2]Dept. of Neurol., UCLA, Agoura Hills, CA; [3]Neurobio., UCLA, Los Angeles, CA; [4]Dept. of Neurobiology, Psychiatry, Psychology and the Brain Res. Instit, Univ. of California, Los Angeles (UCLA), Los Angeles, CA; [5]Neurosci., Mount Sinai, New York, NY; [6]Dept Neurobiol, UCLA Med. Ctr., Los Angeles, CA

Abstract: Memories are dynamic in nature and a cohesive representation of the world requires memories to be altered over time, linked with other memories and eventually integrated into a larger framework of sematic knowledge. Our laboratory has recently demonstrated that

overlapping ensemble of hippocampal neurons mediate linking of two contextual memories encoded close in time whereby the recall of one can lead to the recall of linked memory (*Cai et al. 2016*). Retrosplenial cortex or RSC is another brain structure that is critical for contextual learning and memory. It is unclear whether memory linking is due to overlap in neuronal ensembles in certain key brain regions, such as hippocampus for contextual memories, or the entire neural circuit involved in contextual memory formation displays this neuronal overlap. We addressed this question by investigating the overlap in neuronal ensembles encoding contextual memories at varying time intervals within the RSC. Using head-mounted miniature microscopes, we imaged GCaMP6f-meadiated calcium dynamics in retrosplenial cortical neurons while the mice explored distinct contexts. We found greater overlap in the neuronal ensemble activated in response to two distinct contexts when the contexts were explored 5h vs. 7d apart. These data indicate that the RSC can mediate temporal memory linking by recruiting a shared neuronal ensemble for memories encoded within a day. We are currently investigating whether manipulating this neuronal overlap in RSC would allow us to manipulate linking of contextual memories. Furthermore, to understand whether such ensemble overlap was driven by neurons encoding spatial information, we performed linear track experiments where RSC calcium transients were imaged using miniaturized microscopes. We found that a subset of RSC cells displayed place cell like dynamics. Furthermore, the same cells could be tracked over repeated linear track sessions and displayed stable firing patterns indicating retention of spatial information over days. We are currently investigating whether reactivation of RSC neurons is influenced by spatial information encoded by these cells. Our data indicate that co-allocation of neuronal ensembles encoding temporally proximate contextual memories may be a general mechanism of memory linking across the brain regions that process spatial and contextual information.

Disclosures: **M. Sehgal:** None. **S. Martin:** None. **A. Pekcan:** None. **D. Aharoni:** None. **S. Huang:** None. **A. Lavi:** None. **D.J. Cai:** None. **A.J. Silva:** None.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.22/CC68

Topic: I.04. Physiological Methods

Title: Registration across *in vivo* neuronal imaging modalities: Miniature microscopes to high resolution microscopy

Authors: P. S. XU, S. GULATI, *A. M. STAMATAKIS;
Inscopix, Palo Alto, CA

Abstract: The ability to register data from freely moving imaging experiments to data from high resolution confocal or multi-photon imaging will begin to provide crucial links between activity dynamics and anatomical, molecular, and/or connectivity profiles of distinct neuronal populations. Here, we have developed methodology to register the exact same neurons imaged with the Inscopix nVista miniature microscope to neurons imaged with a Zeiss Airyscan confocal microscope. To ensure we are recording from the same focal plane, we designed a hardware component that allows the experimenter to make the nVista and Airyscan parfocal. Freely-behaving Ca2+ imaging is first performed with the nVista, followed by head-fixed recordings with the Airyscan microscope. After acquiring data from the two imaging modalities, we extract functional cell maps from each Ca2+ imaging data set using Inscopix Data Processing Software. To align the cell maps from both microscopes, we combine cell maps with structural images containing blood vessel patterns and a few shared landmarks. The different scale, rotation, and elastic deformations between the images are then corrected using the bUnwarpJ algorithm in ImageJ. After alignment, the same cells are recognized from the different imaging modalities. Using this hardware and analytical solution, we have demonstrated the feasibility of identifying the same GCaMP neurons imaged in the mPFC with the nVista and Airyscan microscopes. The deformation matrix obtained here can subsequently be applied to other images collected from the corresponding imaging modalities. For example, a static red indicator can be imaged using the confocal microscope, enabling the ability to identify projection-specific, genetically-defined, or activity-dependent subtypes of GCaMP neurons. Importantly, the registration method described here can be expanded to other high-resolution imaging modalities such as two photon or light sheet microscopy.

Disclosures: **P.S. Xu:** A. Employment/Salary (full or part-time):; Inscopix. **S. Gulati:** A. Employment/Salary (full or part-time):; Inscopix. **A.M. Stamatakis:** A. Employment/Salary (full or part-time):; Inscopix.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.23/CC69

Topic: I.04. Physiological Methods

Support: NIH BRAIN UF1NS107668 (MAB and PG)

Title: An open source, wireless, miniature microscope for monitoring neuronal activity in macaque monkeys

Authors: D. AHARONI[1], A. FABRO[2], C. GUO[1], J. CHOI[4], D. A. LEOPOLD[5], R. C. SAUNDERS[5], B. PESARAN[4], P. GOLSHANI[3], *M. A. BASSO[2];
[1]Dept. of Neurol., [2]Psychiatry and Biobehavioral Sci. and Neurobio., [3]Departments of Neurol.

and Psychiatry and Biobehavioral Sci., UCLA, Los Angeles, CA; [4]Ctr. for Neural Sci., New York Univ., New York, NY; [5]Lab. of Neuropsychology, NIMH, Bethesda, MD

Abstract: Understanding how populations of neurons and the circuits they create give rise to complex behavior and higher mental function remains a key endeavor of systems neuroscience. Novel imaging tools combined with the development of new Ca^{++} indicators have advanced neuroscience by introducing the ability to (1) monitor large populations of neurons simultaneously, (2) track identified neurons for extended periods of time, and (3) introduce causal manipulations of individual or small groups of molecularly characterized neurons together with recording of population activity. The goal of our work supported by a BRAIN award, is to fill a critical gap in neuroscientific technology by extending microendoscopy imaging approaches, currently used in mice, to macaque monkeys, allowing for the first time imaging experiments for extended periods of time in alert, freely moving monkeys. As a first step toward this aim, we have implemented a novel chamber, grid and manipulator system for implantation in macaque monkeys that allows for targeting of viral injections and precise placement of GRIN lenses for later imaging. Once placed, the manipulator system allows for vertical movement of the GRIN lens with ~25µm resolution, to identify the optimal imaging plane and subsequent permanent placement of the GRIN lens. Our first design allows for the placement of a single GRIN lens and is designed to scale up to hold multiple GRIN lenses for future array recordings. We have also designed a miniaturized microscope optimized for use in macaque monkeys. There are two embodiments of this design which differ in physical size, FOV and working distance. These systems can image a 2mm or 3mm FOV, have adjustable working distances of between 1.5mm and 3mm, and have footprints on the skull of one to two square cm. All tools and devices will be shared through Miniscope.org.

Disclosures: D. Aharoni: None. **A. Fabro:** None. **C. Guo:** None. **J. Choi:** None. **D.A. Leopold:** None. **R.C. Saunders:** None. **B. Pesaran:** None. **P. Golshani:** None. **M.A. Basso:** None.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.24/CC70

Topic: I.04. Physiological Methods

Support: NSF NeuroNex Technology Hub 1707408

Title: Projection specific medial prefrontal cortex and nucleus accumbens neural dynamics underlying social interactions

Authors: *P. ZHAO[1], X. CHEN[1], W. HONG[2], D. AHARONI[1], A. ARAC[1], P. GOLSHANI[1]; [1]Dept. of Neurol., [2]Dept. of Biol. Chem., UCLA, Los Angeles, CA

Abstract: Deficits in social interactions are the main clinical manifestations of autism spectrum disorder (ASD), yet the neural mechanisms driving social interactions are still poorly understood. While the nucleus accumbens (NAc) is well known for its role in motivation, reward, and drug addiction, it is still unclear whether and how NAc and its connected brain regions like medial prefrontal cortex (mPFC) encode and drive social interaction. Using the UCLA miniature fluorescence microscope (UCLA Miniscope), we recorded neural activity in NAc neurons expressing the calcium indicator GCaMP6f as animals interacted with conspecifics or with an object in a chamber. We extracted neuronal ensemble signal by CNMF-E and performed Receiver Operating Characteristic (ROC) analysis to identify cells that were either significantly excited or inhibited during social interactions or cells that were significantly excited or inhibited by interactions with the object. Overall, 16.8±6.1% of neurons were activated during social interactions while 3.9±3.1% of neurons were inhibited. Conversely, 7.8±4.3% of neurons were excited by interactions with the object while 6.0±2.0% of neurons were inhibited. A Partial Least Squares Regression (PLSR) decoder showed higher performance in predicting episodes of interaction with social target compared to object target. In contrast, far lower proportion of mPFC neurons were activated by social interaction (6.1±1.1%) and the decoder showed lower performance in predicting episodes of interaction with social target when provided mPFC ensemble activity patterns. Using retroAAV-Cre and FLEXed GCaMP6f in mPFC, we are performing recordings of neural activity in mPFC neurons specifically projecting to NAc, mediodorsal thalamus, basolateral amygdala or the ventral tegmental area. Preliminary results show that among these subgroups of PFC neurons, PFC-BLA neurons contain the highest percentage of neurons significantly activated by social interaction. Therefore, social interactions are encoded by a coordinated activation of neurons in multiple brain regions that are differentially activated by interactions with conspecifics. Future work will determine whether these networks are aberrantly activated in models of autism with impaired social interactions.

Disclosures: P. Zhao: None. **X. Chen:** None. **W. Hong:** None. **D. Aharoni:** None. **A. Arac:** None. **P. Golshani:** None.

Poster

612. Optic Methods: Development and Applications

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Program #/Poster #: 612.25/CC71

Topic: I.04. Physiological Methods

Support: Brain Research Foundation Award
Klingstein-Simons Fellowship

NARSAD Young Investigator Award
McKnight Memory and Cognitive Disorder Award

Title: The aging hippocampus- Loss of learning-induced excitability in CA1

Authors: *L. CHEN[1], S. RAMIREZ[2], R. L. CLEM[1], D. J. CAI[1];
[1]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Psychological and Brain Sci., Boston Univ., Boston, MA

Abstract: With a gradually aging population, the prevalence of age-related neurodegenerative diseases is on the rise; therefore it is essential to identify the mechanisms that underlie the normal age-related cognitive deficits. A remarkable feature of the brain is its ability to "file" and "cross-reference" memories so that they can later be retrieved. We previously showed that two contextual memories become linked when they are learned within a day and they also share a common neural representation in the hippocampus; and this temporal memory-linking process is disrupted in older mice. We further showed that hippocampal CA1 neuronal excitability mediated memory-linking processes, and prior studies suggest that excitability may be altered with aging. In this study, we test the hypothesis that temporal memory-linking deficits observed in older mice are caused by age-related alterations with neuronal excitability in CA1. We used an activity-dependent tagging strategy (cFos tTA + TRE-eYFP virus) to selectively label CA1 neurons that were active during contextual learning with YFP in young adult (3-6 m) and aged (22-24 m) mice, then performed whole-cell current-clamp recording of evoked action potentials in both YFP+ and YFP- neurons. In young adult mice, we found an increase in learning-induced excitability specifically in the ensemble neurons (increased evoked action potentials and reduced inter-spike interval (ISI) of YFP+ neurons compared to YFP- neurons) 5 hours after contextual learning. This increase in learning-induced excitability in YFP+ neurons returned to baseline within 7 days. In aged mice, there was a deficit in specifically the learning-induced excitability, however, baseline excitability of CA1 neurons were no different than in young adult mice. These results suggest that CA1 may be susceptible to learning-induced changes in excitability with normal aging, despite other forms of intrinsic excitability remaining normal. Furthermore, we used *in vivo* calcium imaging with Miniscopes during behavioral linking tasks to test the hypothesis that decreased learning-induced excitability in older mice would disrupt temporal memory-linking. We found aged mice with deficits in learning-induced excitability in CA1 had deficits in temporal memory-linking (both at the circuit and behavioral levels). Aberrations in CA1 neuronal excitability may serve as a cellular mechanism that leads to reduced ensemble overlap in the memory-linking process and to other cognitive deficits during normal aging. Our research also underscores the importance of using ensemble-specific tagging strategies to selectively detect learning-induced changes in the brain.

Disclosures: **L. Chen:** None. **S. Ramirez:** None. **R.L. Clem:** None. **D.J. Cai:** None.

Poster

612. Optic Methods: Development and Applications

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.26/CC72

Topic: I.04. Physiological Methods

Title: Large-scale cellular-resolution calcium imaging in 4D during free behavior

Authors: *K. ZITELLI, M. MILLER, S. XU, S. GULATI, A. STAMATAKIS;
Inscopix, Inc., Palo Alto, CA

Abstract: We have developed nVista, a head-mounted miniaturized microscope-based system that enables neuroscientists to record and monitor large-scale Ca2+ dynamics at single-cell resolution in freely behaving rodents over months. To expand upon this system, we have utilized an electronically tunable lens, synchronized to a global shutter image sensor, to enable multi-plane imaging. The fast step-response of the lens (<10 ms) allows for the ability to rapidly move the object plane through a pre-defined volume of brain tissue. We created a video stream containing images of three user-selected focal planes in an interleaved format. With a 60 fps sensor rate, the effective sampling interval per plane is 50 ms with a 16 ms exposure (20 fps) per video frame. To validate this multi-plane imaging approach in a freely behaving animal model, we injected AAV9-CAG-GCaMP6s into the medial prefrontal cortex of mice. During a live imaging session, we selected three focal planes 60 microns apart and recorded Ca2+ activity using this interleaved method. Using a conservative analytical registration approach, we first determined the percentage of cell overlap between imaging planes. After disregarding identical cells that were visibly co-localized in multiple planes, we found that we are able to record from an additional ~50% cells that were unique to their plane. This increase in the number of cells recorded during a single session has several scientific applications, such as improving a behavioral decoder. Other exciting potential applications of this technique remain to be explored, such as imaging multiple sub-nuclei pseudo-simultaneously, or imaging multiple cortical columns through a prism GRIN lens.

Disclosures: **K. Zitelli:** A. Employment/Salary (full or part-time):; Inscopix, Inc. **M. Miller:** A. Employment/Salary (full or part-time):; Inscopix, Inc. **S. Xu:** A. Employment/Salary (full or part-time):; Inscopix, Inc. **S. Gulati:** A. Employment/Salary (full or part-time):; Inscopix, Inc. **A. Stamatakis:** A. Employment/Salary (full or part-time):; Inscopix, Inc..

Poster

612. Optic Methods: Development and Applications

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 612.27/CC73

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: DFG, SPP 1665/P1
DFG, SPP1926/P11
DFG, SFB 936/B7
DFG, SFB 1328/A07
DFG, FOR 2419
ERC-2016-stG 714762
NIH GM13132

Title: SynTagMA: A new tool for mapping active synapses

Authors: *B. C. FEAREY[1], A. PEREZ-ALVAREZ[1], C. SCHULZE[1], R. J. O'TOOLE[3], W. YANG[2], I. ARGANDA-CARRERAS[4], P. J. LAMOTHE-MOLINA[1], B. MOEYAERT[5], E. R. SCHREITER[5], J. S. WIEGERT[2], C. E. GEE[1], M. B. HOPPA[3], T. G. OERTNER[1];
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Abstract: Calcium imaging has given major insights into the function of individual synapses and the mechanisms underlying synaptic strengthening and weakening. Simultaneously measuring functional responses from thousands of synapses across a dendritic tree is possible in two-dimensional culture systems, but not in intact brain tissue: Laser-scanning microscopy is inherently slow when high spatial resolution in 3D is required. To tackle the challenge of functional imaging from thousands of synapses, we employed the photoconvertible calcium integrator, CaMPARI2, by targeting it to either the pre-synapse, preSynTagMA, or to the post-synapse, postSynTagMA (**Syn**aptic **Tag** for **M**apping **A**ctivity). SynTagMA marks synapses according to their internal calcium levels $[Ca^{2+}]_i$ by irreversible photoconversion from green-to-red fluorescence triggered by a brief violet light pulse. Using back-propagating action potentials (bAPs) to activate voltage-gated Ca^{2+} channels in dendrites and spines, we could visualize the attenuation of bAPs along the dendrite. Interestingly, we observed spine-to-spine and branch-to-branch differences in photoconversion, pointing to a heterogeneous distribution of voltage-gated channels. By pairing subthreshold synaptic stimulation and violet light, we labeled a sparse subset of synapses, presumably activated by direct synaptic input. The relatively fast turnover of postSynTagMA affords the opportunity to relabel post-synapses after about two hours, making it

possible to capture multiple activity maps. To find and track thousands of individual synapses over multiple time points, we developed SynapseLocator, a MATLAB-based software package. In summary, SynTagMA is a new tool that allows the user to simultaneously study thousands of synapses in living tissue and to generate exhaustive maps of active excitatory inputs to individual neurons.

Disclosures: **B.C. Fearey:** None. **A. Perez-Alvarez:** None. **C. Schulze:** None. **R.J. O'Toole:** None. **W. Yang:** None. **I. Arganda-Carreras:** None. **P.J. Lamothe-Molina:** None. **B. Moeyaert:** None. **E.R. Schreiter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); E.R.S. is an inventor on US patent number 9,518,996 and US patent application 15/335,707. **J.S. Wiegert:** None. **C.E. Gee:** None. **M.B. Hoppa:** None. **T.G. Oertner:** None.

Poster

613. Physiological Methods: Novel Assays

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 613.01/CC74

Topic: I.04. Physiological Methods

Title: Phenotyping mouse sociability using fully-automatic scoring of social interactions

Authors: *C. K. E. JUNG[1], N. SCHWAERZLER[2], A. SCHATZ[2], A. I. ISTUDOR[2], M. RIVALAN[3], Y. WINTER[2];
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Abstract: Scoring the social interactions between mice is a necessity for quantifying an individual's social behaviour phenotype. At the same time it is labor intensive and has been difficult to automate. We succeeded by first observing visually identical mice using video and ID chip sensors, and then combining this with the computer-automated algorithmic scoring of social interactions. This gave us an index of sociability for each mouse. We fused sensor information from a video tracker positioned above and an ID sensor grid placed underneath the cage. This allowed us to track individual position and body orientation within pairs of mice, over time durations between hours to days. Using a thermal camera provided independence from mouse fur color and changes in bedding material or illumination. We scored social interactions algorithmically following the approach pioneered by deChaumont et al. (2012). Mice were presented as vectors and the dynamic orientation of one vector towards the other was used to classify contact events, relative position events, and dynamic events. We collected data for mice in different pairings and positively validated the system. Deficits in social interaction in a mouse model of autism were clearly detected. This system is a ready-to-use setup for obtaining an index

of mouse sociability with automation and high time efficiency. We consider it to have great potential as a high-throughput phenotyping technology.

Disclosures: **C.K.E. Jung:** A. Employment/Salary (full or part-time):; Employee of PhenoSys GmbH. **N. Schwaerzler:** None. **A. Schatz:** None. **A.I. Istudor:** None. **M. Rivalan:** None. **Y. Winter:** A. Employment/Salary (full or part-time):; CEO of PhenoSys GmbH.

Poster

613. Physiological Methods: Novel Assays

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 613.02/DP13/CC75

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: I.04. Physiological Methods

Support: NIH
HBI

Title: Continuous recordings of whole-body kinematics across the rodent behavioral repertoire

Authors: ***J. D. MARSHALL**[1], D. E. ALDARONDO[1], T. W. DUNN[2], W. WANG[1], G. BERMAN[3], B. OLVECZKY[1];
[1]Harvard Univ., Cambridge, MA; [2]Duke Univ., Durham, NC; [3]Biol., Emory Univ., Atlanta, GA

Abstract: A longstanding goal of neuroscience has been to understand how different brain areas contribute to the acquisition and control of movement. While techniques for large-scale neural recordings are bringing us closer to this goal, complementary techniques for characterizing motor output have been slower to emerge. As a result, experiments probing the relationship between neural activity and movement often do so across a limited set of task-oriented behaviors, preventing a more general understanding of the relationship between movement and brain activity. To extend the range of behaviors and contexts that can be studied, we developed a new behavioral monitoring system, CAPTURE, that combines motion capture and deep learning to track the 3D movement of twenty points on a freely behaving rat's trunk and appendages, continuously over week-long timescales. We validated CAPTURE's ability to identify over 1000 distinct movement elements and describe the known kinematics, sequential organization, and circadian modulation of grooming and locomotor behaviors. Our measurements and analysis revealed unanticipated variability in the kinematics and sequencing of behaviors such as grooming and detected previously undescribed perturbations in movements and behavioral organization following pharmacological challenges and in a rat model of Fragile X syndrome. We then combined CAPTURE with continuous neural recordings in the dorsolateral striatum, a brain region with a known, if debated, role in controlling diverse aspects of movement

kinematics, action selection, and behavioral sequencing. Preliminary analyses of striatal recordings revealed that neurons are active across multiple behaviors, involving disparate poses and appendage movements. However, analyses at longer timescales revealed that striatal neurons are preferentially tuned to individual long-timescale behavioral states, suggesting that behavioral context strongly influences movement encoding in the brain. Overall, CAPTURE should enable new efforts in behavioral phenotyping, studies of behavioral organization, and significantly advance our understanding of how the brain underlies motor behavior.

Disclosures: J.D. Marshall: None. **D.E. Aldarondo:** None. **T.W. Dunn:** None. **W. Wang:** None. **G. Berman:** None. **B. Olveczky:** None.

Poster

613. Physiological Methods: Novel Assays

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ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: I.04. Physiological Methods

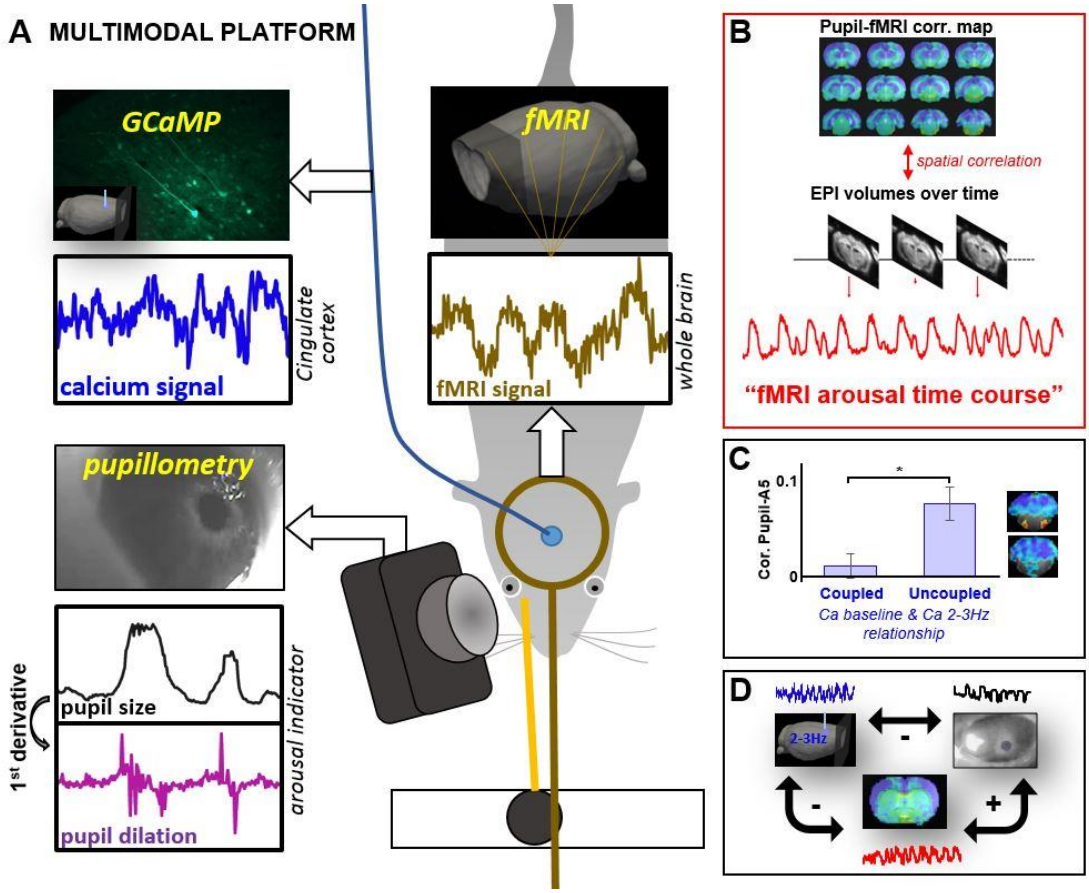
Support: DFG; Germany Research Foundation YU 215/3-1
NIH: 1R01AT009829-01
BMBF: 01GQ1702

Title: Simultaneous pupillometry, calcium recording and fMRI to track brain state changes in the rat

Authors: *P. PAIS-ROLDÁN, K. TAKAHASHI, Y. CHEN, H. ZENG, Y. JIANG, X. YU; Max Planck Inst. For Biol. Cybernetics, Tübingen, Germany

Abstract: *Introduction.* The pupil size can inform about arousal or attention. Animal studies have combined pupillometry with electrophysiology and behavior to infer arousal linked to neuronal firing patterns from specific locations. Whole-brain functional magnetic resonance imaging (fMRI) allows tracking the connectivity patterns that emerge upon distinct neurological states. However, fMRI is not compatible with behavior tests. In this work, we merge fMRI with pupillometry and cingulate cortex (Cg) calcium recordings (**Fig. 1A**) to investigate the missing link between the brain state and the whole-brain neural activity. *Methods.* GCaMP was expressed in Cg on 4-week old SD rats. After 3-4 weeks, an optical fiber was implanted on Cg and the anesthetized animals (alpha-chloralose) were transferred to a 14T MRI scanner. An MRI-compatible camera was used to track pupil size changes. fMRI (n=71 trials, 10 animals) was acquired using GE-EPI (TR=1s, TE=12.5ms, resolution=0.4x0.4x0.6mm). Biopac was used to record neuronal activity from Cg. The pupil size was extracted from each video frame using

Matlab. A pupil-fMRI correlation map was obtained from the voxel-wise correlation between pupil dilations and the fMRI signal. *Results.* fMRI revealed negative correlations between the pupil dynamics and most of the brain. The momentary spatial correlation between the pupil-fMRI map and each fMRI volume allowed creating an fMRI arousal time course (fAtc), indicative of the varying arousal level during fMRI (**Fig. 1B**). A region in the brainstem (A5) was positively correlated with dilations, but only under a particular electrophysiological state (during uncoupling of the calcium oscillations) (**Fig. 1C**). The pupil dynamics and the fAtc were negatively correlated with the neuronal activity in the 2-3Hz band (i.e. dilations were associated to less synchronized states) (**Fig. 1D**). *Conclusion.* This new platform (concurrent fMRI + pupillometry + GCaMP) constitutes a powerful tool to track brain state changes from fMRI, which is critical in whole-brain studies investigating consciousness from animal models.



Disclosures: **P. Pais-Roldán:** None. **K. Takahashi:** None. **Y. Chen:** None. **H. Zeng:** None. **Y. Jiang:** None. **X. Yu:** None.

Poster

613. Physiological Methods: Novel Assays

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Program #/Poster #: 613.04/CC77

Topic: I.04. Physiological Methods

Support: NSF GRFP 1058262 to VJE
NINDS F99NS108537 to VJE
NIMH R01MH108729 to RDB

Title: A fully automated location bi-conditional spatial memory task using floor projection

Authors: *V. J. ESTELA, R. D. BURWELL;
Brown Univ., Providence, RI

Abstract: Bi-conditional behavioral assays often require manual manipulation of the subject as well as cues and the apparatus, limiting the number of trials that can be completed in a given session. This is especially problematic when analyzing behavioral correlates of electrophysiology data, as the power of an observed effect can depend on the number of trials. In the field of spatial memory, there is a growing need to maximize both the number of cells recorded and the number of trials per session in a given behavioral paradigm, especially when the task is complex or cells in the target region are sparsely distributed. Here, we present a fully automated location bi-conditional spatial memory task that can be used in conjunction with freely moving *in vivo* electrophysiology, optogenetic or pharmacological neuronal manipulation, and intracranial stimulation as a reward. During training on our 2D floor-projected task, the rat is tracked by LEDs mounted on the electrophysiological implant, facilitating automation of the task and providing precise spatial tracking information including head direction (Figure 1A). We use a bow-tie shaped maze in which the east side is distinguished from the west side by visual and olfactory intramaze cues and visual extramaze cues. Animals learn that one of a pair of 2D objects back-projected to the floor of the maze is correct on the West side of the maze and the other is correct on the East (Figure 1B). Importantly, the presentation of 2D objects on the floor capitalizes on rodents' bias toward using the lower visual hemifield to discriminate objects, while allowing for unlimited options for 2D images to be used as objects. The task is designed such that real-time manipulation of variables allows for animal-specific behavioral shaping, such as correction of side biases, object preferences, and pacing of trials. This paradigm provides the complexity necessary to identify higher-order neuronal representations along with the automation necessary to achieve sufficient power to analyze the resulting complex behavioral correlates.

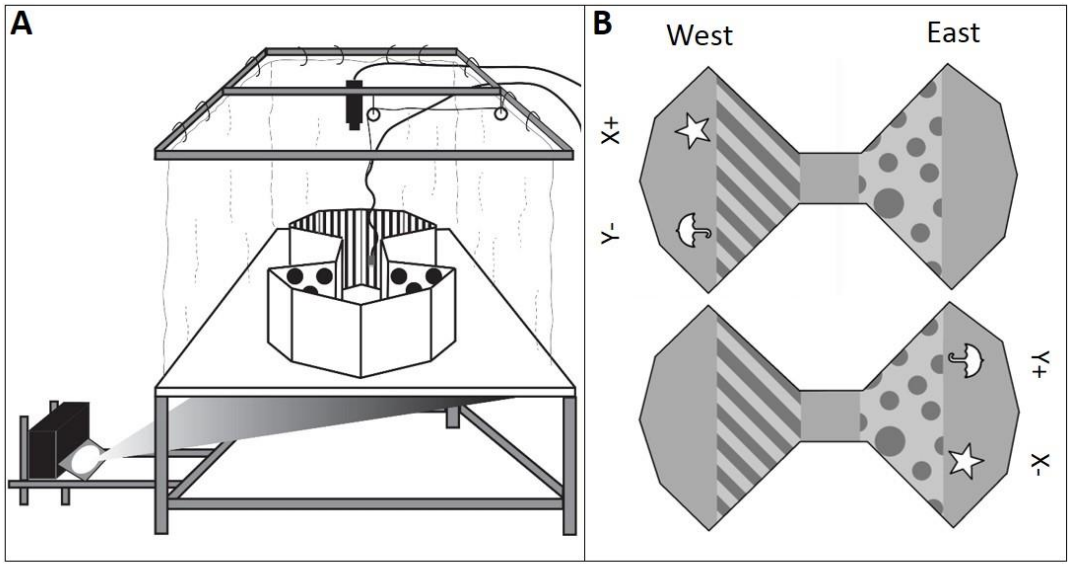

Figure 1. A. Schematic of Floor Projection Maze; B. Location Biconditional (locBCD) Task paradigm.

Disclosures: V.J. Estela: None. **R.D. Burwell:** None.

Poster

613. Physiological Methods: Novel Assays

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Topic: I.04. Physiological Methods

Support: NIGMS Grant P20GM103430

Title: A novel approach to evaluating social distance processing in rats: Implications for understanding the posterior parietal cortex

Authors: *T. B. WISE[1], R. D. BURWELL[1], V. L. TEMPLER[2];
[1]Brown Univ., Providence, RI; [2]Providence Col., Providence, RI

Abstract: Recent literature points to a potential link between the evolution of complex social behavior and the posterior parietal cortex (PPC) in human and non-human primates. Parkinson and Wheatley (2013) hypothesized that the PPC, an area responsible for evaluating egocentric physical distance, is also implicated in understanding the strength of social relationships, termed "social distance". Thus far, this theory has been overlooked in other highly social animals, such as rats, which may have evolved in a similar way due to social selective pressures. Using experimental lesion approaches and the 3-Chamber Sociability and Social Novelty task, we found evidence implicating rats' PPC in social function (unpublished data). This task, however,

does not directly address the underlying mechanisms of social cognition. To better investigate the potential overlap between physical and social distance evaluations, we developed a novel experimental apparatus designed to permit testing both spatial and social cognition. Using a multi-level apparatus (Figure 1), subjects are trained to discriminate equally familiar conspecifics that are located at near and far physical distances. Once at performance criteria, subjects are then probed for physical to social distance transfer. Subjects are presented with conspecifics that are equally far away but differ in terms of social distance. Our prediction is that rats will complete a physical to social distance transfer. In future experiments, we plan to use this task to examine the role of the rodent PPC in spatial and social distance. This task can also be used to investigate rodent models of human social deficits.

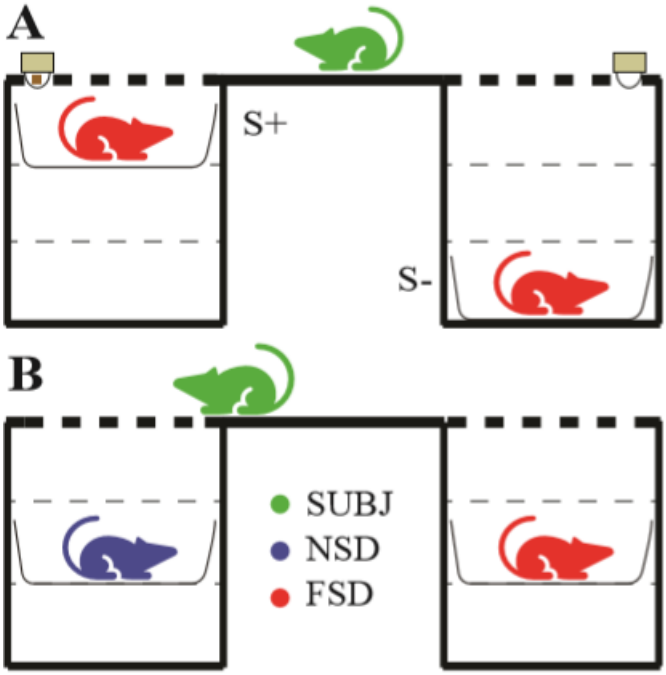

Figure 1. Spatial to social distance task. A) Training: nearest Far Social Distance (FSD) rat is correct (near vs. far correct, counterbalanced across subjects). B) Probe: Subject rats are presented with one Near Social Distance (NSD) rat and one FSD rat, equidistant from subject. We predict subjects will transfer spatial distance to social distance, choosing the NSD rat.

Disclosures: **T.B. Wise:** None. **R.D. Burwell:** None. **V.L. Templer:** None.

Poster

613. Physiological Methods: Novel Assays

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Program #/Poster #: 613.06/DD1

Topic: I.04. Physiological Methods

Support: IT202417
DGAPA Apoyo beca estancia post-doctoral

Title: Characterization of marine gelatin films for potential application in dermal wound healing

Authors: *D. L. MEDINA BUENO[1], A. ESPADAS ALVAREZ[2], G. VALVERDE AGUILAR[3], M. ALVAREZ PEREZ[2], C. QUIROZ REYES[3], E. GARCIA RAMIREZ[2], P. VERGARA ARAGON[2], E. RODRIGUEZ PEREZ[2];
[1]IPN. CICATA LEGARIA., México City, Mexico; [2]UNAM, México City, Mexico; [3]IPN, CICATA LEGARIA, México City, Mexico

Abstract: The extraction and purification of collagen are of great interest due to its biological function and medicinal applications. Although marine invertebrates are abundants in the animal kingdom our knowledge of their extracellular matrix, which mainly contains collagen, is lacking. The functions of collagen isolated from marine invertebrates remain an untouched source of the proteinaceous component in the development of groundbreaking pharmaceuticals. The composite of marine collagen based biomaterials displays a promising biocompatibility through the dermal wound healing process as well as an evidence of biodegradability. Results suggested that the curcumin incorporated collagen film and chitosan incorporated exhibited excellent wound healing activity (75%) in both full thickness excision and linear incision in rats.

Disclosures: D.L. Medina Bueno: None. **A. Espadas Alvarez:** None. **G. Valverde Aguilar:** None. **M. Alvarez Perez:** None. **C. Quiroz Reyes:** None. **E. Garcia Ramirez:** None. **P. Vergara Aragon:** None. **E. Rodriguez Perez:** None.

Poster

613. Physiological Methods: Novel Assays

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Program #/Poster #: 613.07/DD2

Topic: I.04. Physiological Methods

Support: Volkswagen Stiftung Grant A112582
Neuratect Challenge, NC3Rs

Title: An *in vitro* 3D platform for functional and structural interrogation of neuronal circuits

Authors: *B. MOLINA MARTINEZ[1], P. D. JONES[2], L. JENTSCH[1], P. CESARE[1];
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Nanotechnology Engineer, NMI, Reutlingen, Germany

Abstract: In the quest for developing new therapies for neurological disorders, researchers are still largely dependent on 2D in vitro experiments and animal models. Poorly representing the multifaceted nature of neurodegenerative processes in the human brain, these approaches have shown low predictive value in clinical studies.
To fill this gap, several public and private initiatives are focusing on the development of so called organs-on-chips. By combining advanced microfabrication and 3D cell culture technologies, these are expected to better recapitulate the physiology of the brain and capture its complexity at both structural and functional level, which may eventually lead to more relevant in vitro models of human neuronal disorders and consequently to a more efficacious drug discovery process.
However, despite the recent progresses in this field, none of the currently available technologies has the capability to directly measure electrical excitability of individual neurons synaptically connected in 3D neuronal circuits.
To address this need, our group is developing a novel phenotypic platform based on the integration of microfabrication methods, electrode arrays and microfluidics to reconstruct, record and image 3D brain circuits non-invasively in a high-throughput format.
For this purpose, mouse primary hippocampal neurons are grown embedded within hydrogel scaffolds to recreate 3D multicellular architectures inside microfabricated, pumpfree bioreactors. Microelectrode arrays are then integrated into the microfluidic design and used to monitor the electrical activity of enclosed neuronal cells at different time points and in response to a range of neuroactive compounds. In parallel, morphological and 3D structural information of neurons can be collected at high-resolution by confocal microscopy following transduction with AAV particles encoding for fluorescent proteins. To meet the throughput requirements associated to pre-clinical research, up to twelve independent experiments can be carried out simultaneously on a single device having a footprint of only 49 x 49 mm. Future developments may include integration of such technology into a format compatible with multi-well plates.
Collectively, such technology has the potential to introduce a new paradigm in basic and applied neuroscience by providing a novel ground-breaking platform for investigating 3D neuronal circuits in vitro. By enabling a more physiologically relevant disease modelling, this will lead to: i) better understanding of basic neuronal mechanisms; ii) refinement of pre-clinical research methods; iii) reduction in the number of animal studies.

Disclosures: B. Molina Martinez: None. **P.D. Jones:** None. **L. Jentsch:** None. **P. Cesare:** None.

Poster

613. Physiological Methods: Novel Assays

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 613.08/DD3

Topic: I.04. Physiological Methods

Title: Gauging relevance and reproducibility of human iPSC-derived 3D neuralspheroids for high throughput neuroscience drug discovery and toxicology testing

Authors: A. WHITE, C. CARROMEU, ***B. D. ANSON**, C. CHAPMAN, C. TOMARO-DUCHESNEAU, M. JOHNSON, J. SEELKE, N. PAIDIMUKKALA, F. ZANELLA, M. PERIS; Stemonix, Maple Grove, MN

Abstract: The human cerebral cortex is a highly sophisticated three-dimensional structure which comprises multiple different neural cell types intricately interconnected to form a functional organ. Recent work has focused on the development of *in vitro* models capable of recapitulating brain composition and function. We have developed a three-dimensional human-induced Pluripotent Stem Cell (hiPSC)-derived model amenable to high-throughput drug discovery and toxicology studies. This platform is comprised by neurospheroids measuring approximately 600 µm, populated by cortical neurons and astrocytes. Transcriptional analysis confirms a neuronal expression pattern, immunocytochemistry analysis demonstrates the complex interconnection of cortical neurons and astrocytes and the expression of maturity markers and glutamate transporters typically present in human cortical tissue, and functional analysis demonstrates appropriate neuronal behavior. The functional assays highlight the utility of the platform where it can be used as a phenotypic readout for drug efficacy and toxicity. Specifically, kinetic calcium flux analysis, assayed using a Fluorometric Imaging Plate Reader (FLIPR), provides a measurement of the underlying neuronal activity and highlights the high-throughput capabilities of this platform for the detection and quantification of calcium oscillations both at unstimulated baseline and when exposed to known reference compounds, pathway modulator, and/or toxicants. Variability studies investigating spheroid size, calcium flux and immunocytochemistry, demonstrate the robustness of the platform for high-throughput screening. We also demonstrate that this platform is a highly stable model with a broad assay window of use once differentiated. Taken together, the model described herein provides a highly reliable and stable *in vitro* platform for high-throughput drug discovery and toxicology investigations.

Disclosures: **A. White:** A. Employment/Salary (full or part-time):; StemoniX. **C. Carromeu:** A. Employment/Salary (full or part-time):; StemoniX. **B.D. Anson:** A. Employment/Salary (full or part-time):; StemoniX. **C. Chapman:** A. Employment/Salary (full or part-time):; StemoniX. **C. Tomaro-Duchesneau:** A. Employment/Salary (full or part-time):; StemoniX. **M. Johnson:**

A. Employment/Salary (full or part-time):; StemoniX. **J. Seelke:** A. Employment/Salary (full or part-time):; StemoniX. **N. Paidimukkala:** A. Employment/Salary (full or part-time):; StemoniX. **F. Zanella:** A. Employment/Salary (full or part-time):; StemoniX. **M. Peris:** A. Employment/Salary (full or part-time):; StemoniX.

Poster

613. Physiological Methods: Novel Assays

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 613.09/DD4

Topic: I.04. Physiological Methods

Support: NRF 2017M3C7A1028866

Title: Analyzing individual neuronal connectomes of cultured network using micropattern

Authors: *J. KIM[1], J. RYU[1], W. SUN[2];
[1]Anat., [2]Anat. and Brain Korea 21 Plus Biomed. Sci., Korea University, Col. of Med., Seoul, Korea, Republic of

Abstract: The understanding of connection profile of neural circuits at the cellular level is essential to understand neural function. Nevertheless, the monitoring system for neuronal network has not yet been established due to the complexity of the neuronal circuits. Micro-contact printing is a practical tool to simplify the neuronal circuit architecture in 2D. Recently we developed Semaphorin 3F (Sema3F) dot-surroundings patterning system to guide the axonal growth and confine the area for synaptic formation [Ryu et al., 2016]. In this study, various patterns were investigated to optimize the condition for analyzing circuit structure of cultured neural networks. During the maturation of the cultured network of neurons, axons tend to escape from permissive (poly-l-lysine) to repulsive (Sem3F) zone at the angular point, while dendrites appeared to remain within the permissive area due to relatively short growth. Through a series of such the growth processes on defined patterns, a simplified neuronal circuit was achieved, where most of dendrites and cell bodies were trapped in the permissive region to form receptive field, and axon grew to reach synaptic partners. The extent of axonal growth affected by the size of the pattern and spacing between the patterns was able to adjust the complexity of the network. To separate individual cell morphology, the stochastic multicolor labeling via viral transfection was recruited [Chan et al., 2017]. Combining the synaptic compartmentalization and individual cell labeling allowed to read a whole network structure at cellular level. This new model system is the first experimental model enabling to study neural computation at cellular level in a closed circuit of neurons, allowing to investigate basic characteristics and functional roles of specific types of neurons in neural circuits as well as an *in vitro* testbed to study brain disorder.

Disclosures: **J. Kim:** None. **J. Ryu:** None. **W. Sun:** None.

Poster

613. Physiological Methods: Novel Assays

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 613.10/DD5

Topic: I.04. Physiological Methods

Support: COI, MEXT

Title: Conductive polymer based fiber-eledtrode for bioactivity measurement

Authors: *K. TORIMITSU, K. MIURA;
Tohoku Univ., Sendai, Japan

Abstract: Development of a flexible electrode for bio-activity measurement is important for understanding our physiological conditions. Usage of conductive polymer, a poly(3,4-ethylenedioxythiophene) based compound improved the electrode characteristic and biocompatibility in MEA and/or fiber electrode. We reported previously continuous measurement of chick brain activity using this type of electrode. Here we report the flexible fiber electrodes based on silk and Japanese paper for bioactivity measurement. As the conductive polymer modified fibers allowed us for a higher biocompatibility, we could use this electrode not only for an implantable electrode, but for behavior analysis. Stable signal detection and wireless recordings has been achieved. Application of this electrode for a fabric and furniture as a primary evaluation of behavior analysis is one of our interest.

Disclosures: K. Torimitsu: None. **K. Miura:** None.

Poster

613. Physiological Methods: Novel Assays

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 613.11/DD6

Topic: I.04. Physiological Methods

Support: R21AG053740 (to A.L.)

Title: Synaptic E/I receptor ratio preservation during extremely long post-mortem interval

Authors: *P. SCADUTO[1], D. PANDYA[1], A. LIMON[2];
[1]Neurol., [2]Neurol. and Mitchell Ctr. for Neurodegenerative Dis., UTMB, Galveston, TX

Abstract: The excitation to inhibition balance can be defined as the average amount of depolarizing to hyperpolarizing neuronal synaptic currents (global synaptic E/I ratio or just E/I ratio) in a particular region (Vogels, et al., 2011; PMID: 22075724) and is critical for coherent neural coding (Zhou and Yu PMID: 30334221). Alterations of the E/I ratio have been proposed to underlie neuropsychiatric and neurodegenerative disorders such as schizophrenia and Alzheimer's disease. However, the E/I ratio in humans is poorly understood due to the difficulty to perform electrophysiological studies in postmortem tissue. A critical factor in these studies is the potential degradation, and variability, due to the *post-mortem* interval (PMI), which is the time elapsed from death to the preservation of brain specimens by freezing. Here, we used Microtransplantation of Synaptic Membranes (MSM), a technique that allow us to perform functional studies of synaptic receptors from *post-mortem* brains, and western blotting (WB) to determine the global E/I ratio and the effects of the PMI upon this ratio. By simulating morgue conditions using euthanized rats kept at different temperatures (4° and 21°C) and across different PMIs (0, 6, 16, 24, 48, 120 h) we tested the effect of PMI and temperature on the function of synaptic receptors (glutamate and GABA receptors) and anchor protein levels (PSD-95 and Gephyrin) that determine the E/I ratio. We found that temperature played a larger role than PMI in preserving levels and functions of receptors. Brains kept at 4°C preserved synaptic electrophysiological currents and the E/I ratio up to 120h after death showing no statistical difference from control (One-way ANOVA test for differences in excitatory currents, $p= 0.08$; inhibitory currents, $p=0.5$; and E/I ratio, $p=0.4$). WB analysis showed uniform degradation of PSD95 and gephyrin over time ($p<0.001$ ANOVA for both), maintaining the E/I ratio constant compared to control ($p=0.06$ ANOVA). In contrast, brains kept at 21°C had severe loss of excitatory and inhibitory receptors functionality, which was mirrored by levels of anchoring proteins. Surprisingly, brains kept at 21°C maintained the E/I ratio of currents up to 24h and protein levels after 16h ($p=0.93$ and $p=0.85$, ANOVA Dunnett's test, respectively). Our results indicate that E/I ratio measured by protein quantification or functional assay is preserved at low temperatures and reduced the variability among experiments and within each group. This metric might be useful to investigate the human global E/I ratio while reducing the interindividual variability that characterizes human studies of receptors.

Disclosures: P. Scaduto: None. **D. Pandya:** None. **A. Limon:** None.

Poster

613. Physiological Methods: Novel Assays

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Program #/Poster #: 613.12/DD7

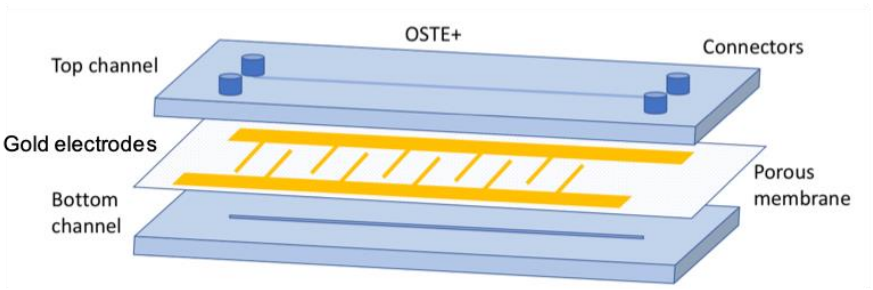
Topic: I.04. Physiological Methods

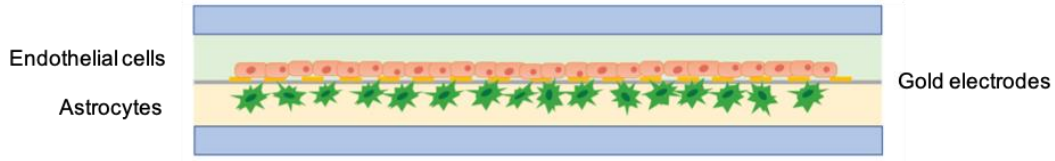
Support: Knut and Alice Wallenberg foundation

Title: Real time monitoring of the human blood-brain barrier modeled on a microfluidic chip

Authors: *I. MATTHIESEN[1], T. E. WINKLER[1], D. VOULGARIS[1], P. NIKOLAKOPOULOU[2], A. HERLAND[1,2];
[1]KTH Royal Inst. of Technol., Stockholm, Sweden; [2]Karolinska Inst., Stockholm, Sweden

Abstract: The blood-brain barrier (BBB), known to protect the brain from foreign compounds and pathogens, likewise prevents passage of drugs and therapeutics. A better understanding of the BBB is thus needed for design of new brain-targeting drugs (Kesselheim, Nature Rev. Drug Disc., 2015). Currently, BBB studies are mainly performed in animal models with low human translation or *in vitro* in cell cultures which fail to recapitulate physiological BBB function and fluid flow. Moreover, dynamic BBB cellular mechanisms and interactions remain challenging to investigate, since most characterizations and assays are end-point-based. The blood flow that provides sheer force, is important for the characteristics of the endothelial cells of the BBB and studies with microfluidic chips have been shown to give higher BBB like functionality compared to static cultures. Problems such as chip material choices, sensor integration, and continuous monitoring still remain. The most commonly used chip material, polydimethylsiloxane (PDMS), is not suitable for drug studies since it is known to absorb small molecules (Toepke, Lab on a Chip., 2006). We aim to recreate the human BBB on a microfluidic chip, with integrated real time sensors for cell substrate impedance sensing (CSIS) during dynamic flow to monitor the barrier strength. To prevent drug absorption, we use the novel polymer off-stoichiometry thiol-ene-epoxy (OSTE+) (Carlborg, J. Polym. Sci., 2014). The chip, shown below, consists of two layers with channels, separated by a porous polycarbonate membrane, with integrated gold electrodes for the CSIS. The top channel in the device, representing the apical side of the BBB, is seeded with human induced pluripotent stem cell (hiPSC) derived microvascular brain endothelial cells (Stebbins, Methods 2016). Growing on top of the gold electrodes, the cells can be monitored for barrier alternations induced by cellular stress or drug exposure. The bottom channel of the device is seeded with NES-astrocytes (Lundin, Stem Cell Rep., 2018) to recapitulate astrocyte-endothelial interaction of the BBB.





Disclosures: I. Matthiesen: None. **T.E. Winkler:** None. **D. Voulgaris:** None. **P. Nikolakopoulou:** None. **A. Herland:** None.

Poster

613. Physiological Methods: Novel Assays

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 613.13/DD8

Topic: I.04. Physiological Methods

Title: 3D bioprinting of human motor neurons in CELLINK LAMININK

Authors: I. REDWAN[1], J. BLELL[1], N. DUONG[1], E. GATENHOLM[1], K. LAHA[2], ***B. DUNGAR**[3];
[1]CELLINK, Gothenburg, Sweden; [2]Brainxell, Inc., Madison, WI; [3]Brainxell, Madison, WI

Abstract: *In vitro* systems that more closely model the human nervous system are needed for physiological cell models, human disease models, and drug library screening. The use of iPSC-derived human neurons in a three-dimensional (3D) culture can provide a physiologically relevant system that reflects the microenvironment, cell-to-cell interactions, and biological processes that occur *in vivo*. Here we demonstrate 3D bioprinting of BrainXell's human motor neurons using a CELLINK BIO X printer. An appropriate bioink, CELLINK LAMININK, was identified that supported healthy cell growth of motor neurons when printed in small droplets of 15 µl with a cell concentration of 30 million cells/ml bioink. LDH assays over the first two weeks in culture show that cell health is stable. Live/dead staining and visualization by multiphoton microscopy confirmed strong viability and cell morphology similar to that of native motor neurons. Furthermore, motor neurons were co-cultured with astrocytes, demonstrating the potential to print multiple cell-types of relevant interest for modelling the nervous system.

Disclosures: I. Redwan: A. Employment/Salary (full or part-time):; CELLINK. **J. Blell:** A. Employment/Salary (full or part-time):; CELLINK. **N. Duong:** A. Employment/Salary (full or part-time):; CELLINK. **E. Gatenholm:** A. Employment/Salary (full or part-time):; CELLINK. **K. Laha:** A. Employment/Salary (full or part-time):; BrainXell. **B. Dungar:** A. Employment/Salary (full or part-time):; BrainXell.

Poster

613. Physiological Methods: Novel Assays

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 613.14/DD9

Topic: I.04. Physiological Methods

Support: Swedish Research Council, grant 2016-06195
NanoLund
Lund University

Title: A novel tubular neural electrode with a dissolvable core for adaptable flexibility - biocompatibility aspects

Authors: *J. AGORELIUS[1,2], L. GÄLLENTOFT[1], L. M. PETTERSSON[1,2], C. J. ERIKSSON LINSMEIER[1], P. THORBERGSSON[1], J. SCHOUENBORG[1,2];
[1]Section for Neurophysiology, Neuronano Res. Center, Medicon Village, Dept of Exp Med. Sci., [2]NanoLund, Lund Univ., Lund, Sweden

Abstract: A big challenge within the field of Brain-Machine-Interface (BMI) is to overcome the tissue reactions to the implanted electrodes. These tissue reactions include glial reactions and loss of neurons nearby which result in an unstable and deteriorating signal quality over time. Our previous studies have shown that microforces between the implanted electrodes and nearby tissue caused by micromotions play a key role in triggering these reactions. In this study, we characterize the tissue reactions to a new type of implantable electrode that is stiff enough to be implanted without support and which transforms into a highly flexible tubular construction after implantation. Methods and materials: Tube electrodes (60-80 um in outer diameter) comprised of a central gold lead (12 um in diameter) covered by dry glucose and insulated with a 4 um thick Parylene C coating, were manufactured using a combination of electrospinning and Parylene C vapor deposition. The distal end of the tubes was cut obliquely with a sharp knife. The entire tube was either coated with a thin layer of dry gelatin (n=8 rats) using dip coating or non-coated (n=8 rats). Control electrodes made of tungsten coated with Parylene C and gelatin with same dimensions as the tube electrodes were also implanted (n=8 rats). The electrodes were implanted in motor cortex in Sprague Dawley rats. The animals were sacrificed after 6 weeks, perfused with PFA and the relevant part of the brain was cut in 16 um thick sections with the tube electrodes resident inside the tissue using a cryostate. The control electrodes had to be explanted before tissue sections. The sections were stained with GFAP, CD68, NeuN and DAPI using immunocytochemistry. Results: The astrocytic and microglial reactions were significantly reduced in both the gelatin coated and non-gelatin coated electrodes as compared to the tungsten control electrodes. There were also significantly more neurons in the inner zone (0-20 um) surrounding the tube electrode as compared to the control electrodes. For all three groups,

neurons were present within 20 um from the tube electrodes and there was no void between tube and tissue.Conclusion: a novel tube electrode with promising biocompatibility has been developed.

Disclosures: **J. Agorelius:** None. **L. Gällentoft:** None. **L.M. Pettersson:** None. **C.J. Eriksson Linsmeier:** None. **J. Schouenborg:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); share holder in Neuronano Inc. that holds a patent on the electrode design.. **P. Thorbergsson:** None.

Poster

613. Physiological Methods: Novel Assays

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 613.15/DD10

Topic: I.04. Physiological Methods

Support: JSPS KAKENHI Grant 24590268

Title: Multi dry electrode plate sensor for noninvasive assessment of the role of central nervous system in cardiac autonomic control in response to emotional and physical stressors

Authors: *S. SATO;
Akita Univ. Grad. Sch. of Med., Akita, Japan

Abstract: A novel multi-dry-electrode plate (MDEP) sensor system has been developed to monitor electrocardiogram (ECG) and heart rate (HR) noninvasively in freely behaving mice without the need for device/electrode implantation surgery and a recovery period of 1-3 weeks, which are prerequisite in case of telemetry studies. A mouse can walk around freely on the MDEP sensor, which is a rectangular plate with 15 gold-plated stripe pattern electrodes and detects ECG basically whenever ≥2 paws (footpads) come in contact with the electrodes. The MDEP sensor detected distinct QRS complexes although ECG was fragmented due to locomotion and insufficient perspiration on the footpads. Thereby, HR time courses at every 10 minutes for 1 h were successfully obtained after intraperitoneal injection of drugs. Indeed, isoproterenol and metoprolol injections caused typical responses as a significant increase (+151 ± 15 bpm) and decrease (−77 ± 6 bpm) in HR, respectively, compared to vehicle (saline injection) at 20-60 min postdose. In addition, signal averaging was effective to observe P waves, which were mostly invisible due to the large baseline noise, and to detect ECG intervals such as PR and QT. Meanwhile, no-drug and saline treated mice showed similar HR time courses after being lifted by the tail and released on the MDEP sensor; the HR decreased approximately 200 bpm during the first 30min, which was followed by a resting HR (~500 bpm) with a small variation. Interestingly, the HR at the start of measurement was higher in no-drug group (746 bpm) than that in drug-treated groups (710 bpm; $p < 0.038$), despite the mice were exposed to the stronger

handling stress by holding the scruff of the neck for drug injection. It seems that the stronger stress facilitated both sympathetic and parasympathetic nervous system activities and caused the HR suppression as seen in animals playing death feigning to cope with stressful situations. These results were obtained owing to the complete noninvasiveness of the MDEP-sensor and the simplicity of the measurement protocol, which provides an easy-to-use, high-throughput measurement of ECG/HR, and saves tremendous cost and time. Thus, although the ECG quality still needs to be improved, the MDEP-sensor system would provide an efficient tool to evaluate acute and chronic ECG/HR changes following pharmacological challenges, emotional/physical stressors, and genetic/pathological abnormalities, and also to understanding better the role of the central nervous system that governs the cardiac autonomic control in response to a variety of stressors including pharmacological intervention.

Disclosures: S. Sato: None.

Poster

613. Physiological Methods: Novel Assays

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 613.16/DD11

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH-NIMH Contract
NASA-DC Space Grant - American University
American University Faculty Research Support Grant

Title: Polymer modified carbon-fiber microelectrodes for the simultaneous detection of neurotransmitters

Authors: *A. G. ZESTOS, D. RAJU, P. WONNENBERG;
Chem. and Ctr. for Behavioral Neurosci., American Univ., Washington, DC

Abstract: Our laboratory has developed novel methods to detect neurotransmitters and their metabolites. Traditionally, carbon-fiber microelectrodes (CFMEs) have been utilized to detect dopamine, serotonin, and other important neurotransmitters. However, this method is limited due to a poor limit of detection of these sensors to detect physiologically relevant concentrations of these neurotransmitters. Carbon nanotube and polymer modified microelectrodes will be utilized to detect physiologically low levels of neurotransmitters that also resist surface fouling and have high temporal resolution to detect fast changes of neurotransmitters. Furthermore, novel electrode coatings and waveforms will also be utilized to detect several neurotransmitter metabolites such as 3,4-dihydroxy-benzeneacetaldehyde (DOPAL), 3-methoxytyramine (3-MT), homovanillic acid (HVA), and 3,4 dihydroxyphenylacetic acid (DOPAC). Currently, dopamine is thought to be an important neurotransmitter concerning several disease states such Parkinson’s

disease, drug abuse (amphetamine, cocaine, etc.), and even for gambling and sex-disorders. However, dopamine is metabolized on a subsecond timescale, and studies have pointed to the importance of neurotransmitter metabolites in these disease states apart from dopamine. Presently, there is no method to selectively measure these neurotransmitter metabolites of dopamine utilizing voltammetry. Through several waveform modifications and polymer electrode coatings, we develop a novel method for dopamine metabolite detection utilizing fast scan cyclic voltammetry, which will help differentiate the cyclic voltammograms of dopamine and dopamine metabolites through the shapes and positions of their respective cyclic voltammograms. This will help develop a method for detecting and differentiating several dopamine metabolites.

Disclosures: A.G. Zestos: None. **D. Raju:** None. **P. Wonnenberg:** None.

Poster

613. Physiological Methods: Novel Assays

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 613.17/DD12

Topic: G.02. Motivation

Support: NSF Grant 81430010
NSF Grant 31627802
China Ministry SciTech2015AA020515
R56 MH115681

Title: Amygdalo-cortical networks revealed by high-field fmri during infrared neural stimulation of amygdalar subnuclei in the macaque monkey

Authors: *Y. RUI[1], A. XU[1,2], J. WANG[1,2], S. SHI[1], A. EDATHODATHIL[1], K. M. GOTHARD[3], A. W. ROE[1];
[1]Interdisciplinary Inst. of Neurosci. and Technology, Zhejiang Univ. Sch. of Med., Hangzhou, China; [2]Key Lab. of Biomed. Engin. of Ministry of Education, Col. of Biomed. Engin. and Instrument Science, Zhejiang Univ., Hangzhou, China; [3]Univ. Arizona, Col. Med., Tucson, AZ

Abstract: In nonhuman primates, the amygdala is central to different processing loops important for cognitive behavior: (1) Sensory loops that connect the amygdala to uni- or multisensory sensory cortical areas, (2) Evaluation loops that connect the amygdala to areas that process the intrinsic and learned value (or salience) of sensory stimuli, and (3) Action observation and action planning loops, important coordinatingthe actions of others with actions of self. Currently, we lack sufficient anatomical knowledge about these networks at whole brain scale, especially as they relate to the mm-scale subnuclei within the amygdala.
Here, we used a novel network mapping technique (INS-fMRI, Xu et al 2019 Science Advances,

DOI: 10.1126/sciadv.aau7046), which maps locations of hemodynamic response induced by infrared neural stimulation (INS) delivered via a fine 200 μm fiber optic to selected locations in the brain. By systematically stimulating different amygdalar targets and mapping in a Siemens 7T MRI, we were able to map associated networks with high precision and at whole brain scale. We established that the laser stimulation was reliable, consistent, and intensity dependent. Significant voxels at connected sites in multiple brain areas were detected using a general linear model.
Confirming activation of sensory loops, we found that stimulating some nuclear targets in the amygdala revealed activations in visual, tactile, auditory, gustatory, and olfactory cortical areas. Consistent with evaluative loops, other stimulation sites activated areas in the orbital, medial, and lateral prefrontal cortex, areas of subgenual and anterior cingulate, and areas of the anterior insula. Finally, amygdala stimulation also activated multiple components of the action observation network, including frontal premotor, motor, and parietal areas.
These patterns of activation were congruent with and further extended previous track-tracing studies. The power of this laser-fMRI method is evident, as whole brain networks associated with submillimeter stimulation sites are revealed at high spatial resolution *in vivo*. We are currently evaluating the degree of segregation and overlap between these multiple amygdalar networks.

Disclosures: **Y. Rui:** None. **A. Xu:** None. **J. Wang:** None. **S. Shi:** None. **A. Edathodathil:** None. **K.M. Gothard:** None. **A.W. Roe:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.01/DD13

Topic: I.05. Biomarker and Drug Discovery

Title: Human iPSC-derived neural 3D cultures provide a novel high-throughput screening platform for drug discovery

Authors: *C. B. ANDERSEN, A. FENTON, T. CHU, R. GORDON, F. ZANELLA, O. GUICHERIT, C. CARROMEU;
Stemonix, San Diego, CA

Abstract: Spheroid-based cellular platforms are considered to enable more complex, biologically relevant, and predictive assays for compound screening, safety evaluation and toxicity studies. Thus, here we deployed a high throughput spheroid co-culture of cortical glutamatergic and GABA-ergic neurons as well as astrocytes, more closely resembling the tissue constitution of native human brain tissue. Whole genome RNAseq profiling demonstrated neural tissue expression patterns with high content imaging validating neuronal and astrocytic cell

populations while showing highly reproducible spheroid size across 96 and 384-well plates. Functional neuronal circuitry was confirmed with MEA recordings and visualized under high-throughput conditions as robust spontaneous, synchronized calcium oscillations with reproducible baseline activity patterns across wells and plates.
In order to validate the capabilities of the platform for compound profiling and discovery, a library of 1622 FDA approved compounds was screened in single point at 10μM final concentration using Ca^{2+} oscillations as a functional phenotypic readout. The library included drugs covering a wide spectrum of targets such as oncology, cardiology, anti-inflammatory, immunology, neuropsychiatry and analgesia. DMSO was used as control and showed a standard deviation of 9% across all plates and a Z'of 0.73 was observed for the whole screen. Hits were identified as responses that were at least 3 standard deviations from DMSO control responses. As expected, the highest number of hits arrived from targets associated with neuronal signaling (serotonin, dopamine, GABA and adrenergic receptors). Interestingly, several compounds leading to higher cAMP accumulation lead to increase in peak count similar to what is noted using 4-AP, a known pro convulsant. Hit confirmation in 7 point dose response and exploration of pathways is currently ongoing. In conclusion, high throughput functional assays using the human iPSC-derived 3D neuronal spheroids platform deployed in this study demonstrated the ability to identify a wide range of hits spanning multiple target areas. Thus this model may serve as phenotypic and target-based platform for identifying new starting points for novel CNS discovery.

Disclosures: C.B. Andersen: None. **A. Fenton:** None. **T. Chu:** None. **R. Gordon:** None. **F. Zanella:** None. **O. Guicherit:** None. **C. Carromeu:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.02/DD14

Topic: I.05. Biomarker and Drug Discovery

Support: Hopstem biotechnology

Title: Human 2D neural cells and 3D brain organoids resembling neuronal networks for high throughput assays

Authors: *J. FAN, A. WANG, T. ZOU, Q. LIU, F. REN, Y. YAN, Z. LU, J. XU;
Hopstem Biotech. Co. Ltd., Houston, TX

Abstract: Using RONA method reported in Xu et al., 2016, large amount of high purity and multipotent human neural stem cells and progenitor cells can be stably derived from human pluripotent stem cells including patient induced Pluripotent Stem Cells (iPSCs). Due to the lack

of structure/size consistency, stability and mature function of 3D brain organoids produced by most methods, it is hard to compare developmental and structure differences between organoids, not to mention carrying out high throughput screens. Based on the needs, we have developed a robust, stable and low-cost method to produce functional 3D brain organoids that resemble the prefrontal cortex. These cerebral organoids contain excitatory (70-80%) and inhibitory (20-30%), including subtypes of inhibitory neurons that are critical in the neural development, maturation and balanced functions, such as PV, nNOS, SST interneurons. These organoids have 6 layers of cortical markers, astrocyte (~50%) and oligodendrocytes at about 80 days *in vitro*. They have synchronized spontaneous firings starting 20 days *in vitro* and can be maintained for years and up to 6mm diameters. Smaller organoids can also be generated with small variations between organoids for high throughput assays including viability, MEA, high content imaging with clearing and immunohistochemistry etc. Microglia invaded 3D brain organoids are also generated for studies involving neuroinflammation. This novel method will provide great aid to the mechanism study and drug discovery using *in vitro* hiPSC models for neurological disorders, including autism, schizophrenia, epilepsy, and even AD or PD.

Disclosures: **J. Fan:** None. **A. Wang:** None. **T. Zou:** None. **Q. Liu:** None. **F. Ren:** None. **Y. Yan:** None. **Z. Lu:** None. **J. Xu:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.03/DD15

Topic: I.05. Biomarker and Drug Discovery

Support: NIH Grant R01AG050626-01A1
SFI Grants 12/TIDA/I2308 and 15/IA/3176

Title: *In vivo* monitoring of cholinergic neurotransmission with a microelectrochemical choline biosensor

Authors: S. DOYLE[1], M. M. DORAN[1], K. L. BAKER[1], C. CUNNINGHAM[2], *J. P. LOWRY[1]; [1]Chem., Maynooth Univ., Maynooth, Ireland; [2]Sch. of Biochem. and Immunol., Trinity Col. Dublin, Dublin, Ireland

Abstract: Acetylcholine acts as a key neuromodulator within the central nervous system, capable of altering neuronal excitability and coordinating neuronal firing patterns. Conversely, cholinergic neurotransmission plays a crucial role in a variety of cognitive functions, including the encoding of new memories. Cholinergic neuronal loss, and the resulting drop in cholinergic neurotransmission (collectively referred to as hypocholinergia), is closely associated with cognitive dysfunction in a number of chronic neurodegenerative disorders including Alzheimer's

disease. However, conventional analytical techniques for monitoring *in vivo* cholinergic neurotransmission lack the spatiotemporal resolution required to accurately detect endogenous cholinergic dynamics. Here we validate in mice a Pt-based electrochemical biosensor for selective monitoring of choline, a verified marker of cholinergic transmission. Enzymatic choline biosensors (modified with choline oxidase) were sterotaxically implanted in the medial prefrontal cortex (mPFC) and contralateral dorsal hippocampus (dHPC) of female C57Bl6J mice. Real-time choline current recordings over a period of several days revealed circadian fluctuations in both regions, with extracellular choline levels highest during light phases. Administration of pharmacological compounds known to induce central acetylcholine release, scopolamine (1mg/kg) and amphetamine (4mg/kg), evoked a robust increase in choline current. In contrast, peripheral injection of the reversible acetylcholinesterase inhibitor, donepezil (3mg/kg), produced a marked decrease in recorded choline current. The induction of systemic inflammation with bacterial lipopolysaccharide (LPS; 500µg/kg) produced characteristic 'sickness behaviour' in mice and evoked a tonic rise in central choline levels in both the mPFC and dHPC. Furthermore, the induction of hypocholinergia in selected mice was preformed via intracerebroventricular injections of murine-p75-saporin immunotoxin (1.2µg). Evoked cholinergic neurotransmission was dramatically attenuated in lesioned (hypocholinergic) mice. Collectively, the data suggests that microelectrochemical choline biosensors may serve as a powerful tool for monitoring cholinergic neurotransmission across a number of behavioural and disease states.

Disclosures: S. Doyle: None. **M.M. Doran:** None. **K.L. Baker:** None. **C. Cunningham:** None. **J.P. Lowry:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.04/DD16

Topic: I.05. Biomarker and Drug Discovery

Support: This research study was supported by the grant P/PROFOCIE- 2014-24MSU0011E-12 from the University of San Luis Potosi, by CONACYT fellowship (417216 to LA) and the kind donation of E. Myers in honor of R. Myers.

Title: Skin-brain biomarkers

Authors: *R. A. NORMAN[1], M. JIMENEZ-CAPDEVILLE[2], I. RODRÍGUEZ-LEYVA[3]; [1]Neuro-Dermatology, Robert A. Norman, D.O., P.A., Ft. Lauderdale, FL; [2]Ctr. de Investigación en Ciencias de la Salud y Biomedicina, Univ. Autónoma de San Luis Potosí, San Luis Potosí, Mexico; [3]Dept. de Neurología, Hosp. "Ignacio Morones Prieto", San Luis Potosí, Mexico

Abstract: Skin-Brain Biomarkers have been underutilized when identifying neurological diseases. Skin and oral mucosa have been used as biomarkers to screen for proteinopathies in cognitively impaired patients. Our study using p-Tau quantification by flow cytometry supports using skin-brain biomarkers as excellent neurologic disease detection tools. (Frontiers in Neurology 2017)
The purpose of our study was to determine whether there is a differential Tau expression in oral mucosa cells according to cognitive impairment. Eighty-one subjects were enrolled in the study and classified per Mini-Mental State Examination test score into control, mild cognitive impairment (MCI), and severe cognitive impairment (SCI) groups. More positivity was present in subjects with cognitive impairment than in control subjects, both in the nucleus and cytoplasm, in a speckle pattern. These findings demonstrate the higher presence of p-Tau and Tau transcript in the oral mucosa of cognitively impaired subjects when compared with healthy subjects. The feasibility of p-Tau quantification by flow cytometry supports the prospective analysis of oral mucosa as a support tool for screening of proteinopathies in cognitively impaired patients.
Although proteinopathies have previously been assumed to be exclusive to the central nervous system (CNS), several recent studies demonstrate their presence in peripheral tissue. These findings strongly suggest that proteinopathies are systemic diseases whose fingerprints could be tracked in an accessible peripheral tissue.
Pertinent References
Salgado Bustamante M, Enriquez-Macias L, Eng W, Norman RA and Jimenez-Capdeville ME (2017) Tau Protein in Oral Mucosa and Cognitive State: A Cross-sectional Study. Front. Neurol. 8:554.
Rodríguez-Leyva I, Calderón-Garcidueñas AL, Jiménez-Capdeville ME, Rentería-Palomo AA, Hernandez-Rodriguez HG, Valdés-Rodríguez R, et al. (2014). α-Synuclein inclusions in the skin of Parkinson's disease and parkinsonism. Ann. Clin. Transl. Neurol. 1:471–8.
Rodríguez-Leyva I, Chi-Ahumada E, Calderón–Garcidueñas A, Medina-Mier V, Santoyo M, Martel-Gallegos G, et al. (2015). Presence of Phosphorylated Tau Protein in the Skin of Alzheimer´s Disease Patients. J. Mol. Biomark. Diagn. s6.

Disclosures: R.A. Norman: None. **M. Jimenez-Capdeville:** None. **I. Rodríguez-Leyva:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.05/DD17

Topic: I.05. Biomarker and Drug Discovery

Support: 2R44NS065545-03A1

Title: Non-invasive peripheral nerve interfacing platform for reliable and quantitative tracking of nerve function

Authors: A. HARRISON, E. BROWN, A. M. MELEHAN, A. J. PREYER, M. SONNTAG, A. HECKERLING, ***I. P. CLEMENTS**;
BioCircuit Technologies, Atlanta, GA

Abstract: Improved capabilities for sensing and manipulation of nerve and muscle activity would advance clinical diagnostics, including the ability to precisely quantify and reliably track biomarkers of disease. Here we describe a non-invasive, automated platform for targeted monitoring and manipulation of human peripheral nerves and muscles. Flexible arrays of transcutaneous electrodes are coupled to a custom, miniaturized recording platform, providing 32 or more channels of simultaneous stimulation and recording. Array-based stimulation enables on-target measurement and stimulation selectivity accounting for patient-to-patient anatomical differences. Array-based recordings enable 2D mapping of neural propagation and practical, longitudinal tracking of nerve function between sessions. Ultimately, this platform will facilitate advancements in both neuromuscular research and medical device development, with applications in electrodiagnostics, practical tracking of disease-specific biomarkers, neural prosthetics, and bioelectronic medicine.

Disclosures: **A. Harrison:** A. Employment/Salary (full or part-time):; BioCircuit Technologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioCircuit Technologies. **E. Brown:** A. Employment/Salary (full or part-time):; BioCircuit Technologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioCircuit Technologies. **A.M. Melehan:** A. Employment/Salary (full or part-time):; BioCircuit Technologies. **A.J. Preyer:** A. Employment/Salary (full or part-time):; BioCircuit Technologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioCircuit Technologies. **M. Sonntag:** A. Employment/Salary (full or part-time):; BioCircuit Technologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioCircuit Technologies. **A. Heckerling:** A. Employment/Salary (full or part-time):; BioCircuit Technologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioCircuit Technologies. **I.P. Clements:** A. Employment/Salary (full or part-time):; BioCircuit Technologies. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioCircuit Technologies.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.06/DD18

Topic: I.05. Biomarker and Drug Discovery

Title: Sensitivity of the MRI water proton resonance to myelin

Authors: *S. FOXLEY[1], G. WILDENBERG[2], V. SAMPATHKUMAR[2], P. BRUGAROLAS[4], B. J. POPKO[3], N. B. KASTHURI[2];
[1]Radiology, Univ. of Chicago, University of Chicago, IL; [2]Neurobio., [3]Neurol., Univ. of Chicago, Chicago, IL; [4]Radiology, Harvard Med. Sch., Boston, MA

Abstract: Dysmyelinating diseases are characterized by abnormal myelin formation and function; Shiverer mice are a common model used to demonstrate this devastating condition. Microstructural abnormalities in myelin such as this have been demonstrated to produce measurable effects on the MRI signal. How myelin effects the MRI signal has been described using theoretical models that predict its frequency dependence, however empirical evidence supporting spectroscopic results produced with these models have not been shown. This work describes using a high-resolution 3D-multi-gradient echo (3D-MGE) pulse sequence to measure changes in the water spectrum in both postmortem control (n=5) and dysmyelinated (homozygous shiverer, n=4) mouse brain. All brains were perfusion fixed with gluteraldehyde. Prior to imaging, samples were submerged in fluorinert to susceptibility match the tissue with its surroundings and preserve the tissue over long scan durations. All MRI data were acquired using a 9.4T, small bore MRI scanner (Bruker Biospin). 3D-MGE data were acquired with 0.1mm isotropic spatial resolution over 192 echoes with 1.9ms echo spacing. These data were Fourier transformed along the time dimension to produce voxel-wise water spectra with 2.7Hz spectral resolution. High-angular resolution DTI data were also acquired to estimate the principle diffusion direction of white matter. T2* weighted images were made by identifying the voxel-wise peak signal magnitude from the spectra produced from the 3D-MGE dataset. These high fidelity images demonstrate that grey/white matter contrast is significantly mitigated in the shiverer mouse brain relative to that of the control ($p<0.1$, one-way Student's t-test). Voxel-wise spectral shape was quantified by measuring the asymmetry of the resonance about the peak. This is done by integrating the negative frequency half of the spectrum, subtracting that from the integral of the positive frequency half, and normalizing by the total area under the curve. Spectra from white matter in control brains were shown to produce a larger average asymmetry that those from the shiverer mice. Moreover, the asymmetry in control brain was shown to be dependent on the orientation of the underlying axons relative to the main magnetic field (B0). This is consistent with modeling and suggests that the water spectrum shape is sensitive to both myelin concentration as well as its orientation relative to B0 (Xu et al., Magn. Reson. Med.

2018). These results suggest that the water spectra measured with 3D-MGE are sensitive to the presence of myelin and could serve as a potential MRI biomarker of dysmyelinating disease.

Disclosures: S. Foxley: None. **G. Wildenberg:** None. **V. Sampathkumar:** None. **P. Brugarolas:** None. **B.J. Popko:** None. **N.B. Kasthuri:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.07/DD19

Topic: I.05. Biomarker and Drug Discovery

Support: Biogen

Title: An MR tractography-based study of the impaired white matter integrity along medial longitudinal fasciculus in MS patients with internuclear ophthalmoplegia

Authors: *A. GHAYOOR[1], X. WANG[1], K. KANHAI[2], O. R. THON[3], J. HESTERMAN[1], A. VERMA[4], G. J. GROENEVELD[2], K. C. EVANS[5];
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Abstract: BACKGROUND
The medial longitudinal fasciculus (MLF) connects the paramedian pontine reticular formation and abducens nerve to the contralateral oculomotor nerve, enabling horizontal saccades. MLF lesions, that are common in multiple sclerosis (MS), might lead to internuclear ophthalmoplegia (INO), which causes slowed or absent adduction of the ipsilateral eye. Accurate characterization of MLF tissue integrity via diffusion tensor imaging (DTI) holds promise to inform research efforts in MS but has proven to be challenging.
The study objective is twofold: 1) Develop an imaging biomarker of axonal and myelin integrity of the MLF in MS patients with INO using DTI and brain tractography. 2) Test for correlation between DTI findings and INO severity.
METHODS
Twenty-three patients (11 Female/12 Male with a mean age of 49±10.6 years) with MS and unilateral or bilateral INO were enrolled. Versional dysconjugacy index (VDI) was measured by oculography (using Eyelink1000) to grade INO severity.
T1W, T2W/PD, DTI (b=750, 24 directions) were acquired on a 3T GE MR750. Analysis was performed using a DTI tractography pipeline in Nipype. DTI was preprocessed, susceptibility artifacts corrected, then subjected to a two-tensor tractography algorithm to identify the MLF. MS lesions within and adjacent to the MLF were manually segmented based on abnormal

hyperintensity on T2W and PD images.
DTI scalars (fractional anisotropy (FA), mean, and radial diffusivity (MD, RD)) were estimated for entire MLF tract, and lesion/non-lesion MLF segments, and then two-sample t test were performed between the affected (N=36) vs. unaffected (N=10) eyes. Pearson's correlation of DTI scalars with severity (VDI) was performed within the INO group.

RESULTS

Measures of MS lesion length/load were similar between INO and non INO eyes. However, INO-affected eyes showed significantly higher MD and RD values on the ipsilateral MLF compared to the un-affected eyes. FA values were lower on the ipsilateral MLF of INO-affected eyes, but only significantly lower when considering the whole (bilateral) MLF. Though, none of the DTI scalars were significantly correlated with VDI, after controlling for age, and MS duration.

CONCLUSIONS

The DTI profile within the MLF of INO-affected eyes was consistent with diminished white matter integrity, which we speculate was due to demyelination and tract degeneration associated with MS. Although we failed to detect a significant correlation between DTI scalars and VDI, this novel approach to MLF tractography could allow for better characterization of the MLF integrity than previously published DTI reports of INO in MS that had relied upon registration-based approaches.

Disclosures: A. Ghayoor: None. **X. Wang:** None. **K. Kanhai:** None. **O.R. Thon:** None. **J. Hesterman:** None. **A. Verma:** None. **G.J. Groeneveld:** None. **K.C. Evans:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.08/DD20

Topic: I.05. Biomarker and Drug Discovery

Support: The Shockey Family Foundation

Title: Magnetic resonance imaging corresponds to worsening behavior and gross demyelination in MOG_{35-55} induced experimental autoimmune encephalomyelitis

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Abstract: Experimental autoimmune encephalomyelitis (EAE) is a well-established model for multiple sclerosis (MS) that is characterized by spinal cord pathology progressing in a caudal to

cranial direction. Currently, demyelinated lesions are visualized in mice utilizing Luxol fast blue staining. However, in humans, magnetic resonance imaging (MRI) is routinely used to monitor patient progression. Recently, diffusion MRI has come to the forefront because it utilizes a different approach to the traditional anatomical imaging by visualizing the movement of water molecules. In this study, we have combined anatomical and diffusion MRI to ascertain the feasibility and accuracy of using fMRI studies to characterize EAE pathology. C57BL/6J mice were immunized with MOG_{35-55} and received daily intraperitoneal injections of 10 mg/kg Opioid Growth Factor (OGF), ([Met^5-enkephalin) or saline. Daily composite behavior scores were recorded over a 28-day period based on tail tone, gait, righting reflex and limb strength. EAE mice receiving IP saline treatments had composite behavior scores that differed significantly from normal mice ($p<0.05$). OGF mice demonstrated a reduction ($p<0.05$) in clinical severity from EAE-saline mice at peak disease, day 18. *In vivo* and *ex vivo* MRIs were performed at baseline, day 7, day 18, and day 28 using a 7T magnet system. Following humane euthanasia, spinal cords were removed, sectioned and stained with Luxol fast blue. Preliminary diffusion data from day 28 showed an overall decrease in functional anisotropy (FA) in both saline and OGF mice when compared to baseline with caudal regions more affected than cranial regions. Diffusion images on day 28, showed an increase in overall mean diffusion in both OGF and saline treated mice when compared to baseline. Changes in the MRIs were restricted to the caudal aspects of the spinal cord. In conclusion, these studies suggest that changes in both functional anisotropy and mean diffusion in EAE mice can be identified using MRI. In particular, the increased mean diffusion suggests an increased rate of water molecule diffusion through the tissue that could result from either radial demyelination or longitudinal white matter tract damage. The reduction in functional anisotropy suggests a potential reorganization of the spinal cord architecture, and together with staining or immunohistochemistry will facilitate more accurate assessment of EAE progression.

Disclosures: C.L. Patel: None. **M.D. Meadowcroft:** None. **P.J. McLaughlin:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.09/DD21

Topic: I.05. Biomarker and Drug Discovery

Title: Improved experimental autoimmune encephalomyelitis mice recovery by intravenous injection of conditioned culture medium of induced mesenchymal stem/stromal cells derived from human iPSCs

Authors: *R. DENG[1,2,3], A. LAW[2], Q. DU[1], K. R. BOHELER[3], G.-F. CHAN[2], J. SHEN[1]; [1]Sch. of Chinese Med., [2]Dept. of Paediatrics and Adolescent Med., [3]Stem Cell & Regenerative Med. Consortium, The Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Multiple sclerosis (MS) is a progressive autoimmune disease of the CNS. Conditioned culture medium of mesenchymal stem/stromal cells (MSCs-CM) was reported to be a potential therapeutics for MS. MSCs are multipotent cells, which not only can differentiate into various cell types but also have modulation functions on immune response. However, *ex vivo* expansion of human primary MSCs is limited due to senescence. Therefore we generated induced MSC-like cells (iMSCs) from human iPSCs. We investigated these iMSCs on surface specific markers, differentiation related gene transcriptional levels and cytokine release levels *in vitro*, and immunomodulating effects *in vivo* on an experimental autoimmune encephalomyelitis (EAE) mouse model. We found iMSCs were the same as primary human MSCs by flow cytometry analysis, which are $CD44^+$, $CD90^+$, $CD73^+$ and $CD105^+$ and $CD11b^-$, $CD19^-$, CD45-, $CD14^-$, $HLA\text{-}DR^-$. The RNAseq results also showed these iMSCs were closely similar to primary human MSCs. Furthermore, we compared the protein profiles of secreted cytokines and cell lysates between primary MSCs and iMSCs using Human XL cytokine array. Cells from the same donor were used to reduce variants caused by individual differences. Results showed that secretion profiles were similar between the primary MSCs and iMSCs. At last, we tested the immunomodulating effect of iMSCs-CM and MSCs-CM by intravenous injecting the conditioned medium into EAE mice at the peak time of disease progress (17, 19 and 21 dpi). We found that both iMSCs-CM and MSC-CM improved EAE recovery compared to EAE control mice while the blank culture medium induced EAE mice death (n=5-6). CM treated EAE mice had significantly reduced demyelination and inflammatory infiltrations. The clinical score was below 0.5 after treatments compared to the EAE control maintained at around 1.5 after 30 dpi. In conclusion, we propose these iMSCs can be considered as *ex vivo* cultured MSCs which have potential to be used for therapeutic purposes for MS.

Disclosures: R. Deng: None. **A. Law:** None. **Q. Du:** None. **K.R. Boheler:** None. **G. Chan:** None. **J. Shen:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.10/DD22

Topic: I.05. Biomarker and Drug Discovery

Support: NIH Grant 3U42 OD011158-28S3

Title: Advancing Alzheimer's disease and related dementias research via a multiple-pronged human biospecimen collection initiative

Authors: *M. W. VONDRAN[1], S. SHAD[1], Z. MOURELATOS[2], G. KOPEN[1], T. J. BELL[1]; [1]Natl. Dis. Res. Interchange, Philadelphia, PA; [2]Univ. of Pennsylvania, Perelman Sch. of Med., Philadelphia, PA

Abstract: Human biospecimens are essential to advance our understanding of pathogenesis and treatment of neurological disease, including Alzheimer's disease and related dementias (AD/ADRD). AD/ADRD are multi-factorial, genetically complex and heterogeneous diseases that progress over approximately two to three decades of life. Access to a diverse range of human biospecimens and donors is essential to support the escalating nature of scientific questions and experimental techniques that investigators are pursuing. More comprehensive AD/ADRD human tissue resources suitable for a wide range of experimental analyses are needed. To address this gap, here we report our results on providing human biospecimens for AD/ADRD research. The National Disease Research Interchange (NDRI) is a non-profit organization that specializes in using a project-specific approach to provide scientists with experimental-specific human biospecimens for their studies. Using this approach, NDRI is developing a new, NIH-funded resource, AD/ADRD Human Biospecimen Resource (ADBR). The ADBR is a comprehensive human biospecimen resource that provides biospecimens from two distinct AD/ADRD cohorts, patients and post mortem donors. ADBR's methods to provide human biospecimens for rigorous experimental methods such as RNAseq is presented along with the supporting neuropathological case report data. The advantages of the ADBR's multi-pronged approach are 3-fold. 1) The post mortem donations permit the collection of AD/ADRD and control (non-diseased) human biospecimens with a neuropathological review and case report to confirm the presence or absence of AD/ADRD pathology. 2) The living patient collection enables acquisition of biospecimens that could capture unique time points, such as different stages of the disease or the patients' responses to given treatment protocols. 3) Standardization of donor eligibility and biospecimen collections will yield more accurate and reproducible data. Collectively, ADBR will provide the AD/ADRD research community an unmatched resource to advance basic research evaluating the etiology of AD/ADRD, as well as translational research assessing effective diagnostics and therapies.

Disclosures: M.W. Vondran: None. **S. Shad:** None. **Z. Mourelatos:** None. **G. Kopen:** None. **T.J. Bell:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

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Program #/Poster #: 614.11/DD23

Topic: I.05. Biomarker and Drug Discovery

Support: RO1AG042178

RO1AG47812
RO1NS105473

Title: Structure based design and molecular docking studies for phosphorylated tau inhibitors in Alzheimer's disease

Authors: *J. PRADEEPKIRAN, P. HEMACHANDRA REDDY;
Intrnl. Med., Texas Tech. Hlth. Sci. Ctr., Lubbock, TX

Abstract: The purpose of our study is to identify phosphorylated tau (p-tau) inhibitors In Alzheimer's disease (AD). P-tau has recently received great interest and alternative potential therapeutic target in AD. The continuous failure of Aβ-targeted therapeutics recommends an alternative drug target to treat AD. There is an increasing evidence of tau, which plays a central role in AD pathophysiology, including neurofibrillary tangles, paired helical filaments formation in AD neurons. Abnormal activation, imbalanced phosphatases/kinases, is initiated by p-tau aggregation in AD neurons. In the present study, we performed computational pharmacophore models, molecular docking, and simulation studies for p-tau in order to identify kinase regulated hyperphosphorylated sites in AD. We found multiple serine/threonine sites that altered the R1/R2 repeats flanking sequences in the tau protein, affecting the microtubule stability of tau. The proposed ligand molecules exhibited the p-O ester scaffolds with inhibitory and/or blocking actions against serine/threonine residues of p-tau. Molecular docking studies showed high docking scores and optimal protein-ligand interactions of p-tau. Our docking results revealed that five ligands binds at major tau phosphorylated kinases like glycogen synthase kinase-3beta (GSK-3β), cyclin-dependent kinase-5 (CDK5) positions. These ligands showed the best pharmacokinetic properties, including good absorption, distribution, metabolism, and excretion (ADME) and non-toxic with admetSAR tests. The p-tau pharmacophore based drug discovery models provide the best comprehensive and rapid drug interventions in AD, and tauopathies. We are expected to be the prospective future therapeutic approach in AD.

Disclosures: J. Pradeepkiran: None. **P. Hemachandra Reddy:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.12/DD24

Topic: C.08. Ischemia

Support: NSFC Grant 81771147

Title: Apelin reduces amyloid β generation by attenuating endoplasmic reticulum stress-induced BACE1 expression

Authors: *Y. WU[1], X. WANG[2], H. LU[1], Q. ZHAO[1], Y. ZAI[1];
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Abstract: Neuritic plaques are the major pathological hallmark of Alzheimer's disease (AD). Amyloid β (Aβ) is the major component of neuritic plaques, and BACE1, a β-secretase, mainly contributes to Aβ generation. Increased Aβ plays a major role in the pathogenesis of AD. Growing evidence showed that ER stress constantly exists in AD brains, which promotes Aβ generation and BACE1 upregulation. Our recent work showed that apelin protects neurons from apoptosis by attenuating ER stress in ischemic stroke. However, the role of apelin in Aβ generation remains elusive. Here we showed that constant ER stress exists in AD models, whereas apelin attenuates ER stress. Moreover, apelin markedly reduces Aβ generation and BACE1 expression. Our work indicates that apelin might inhibit Aβ generation by attenuating ER stress-induced BACE1 expression.

Disclosures: Y. Wu: None. **X. Wang:** None. **H. Lu:** None. **Q. Zhao:** None. **Y. Zai:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.13/DD25

Topic: I.05. Biomarker and Drug Discovery

Support: FEDER/MCIU/AEI Grant SAF2017-87349-R)
ISCIII Grant PIE14/00034
Marató de TV3 Grant 20152031)
Catalan government Grant 2017 SGR 1604
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Title: Cerebrospinal fluid ecto-GPR37 in Parkinson's disease

Authors: *F. CIRUELA[1], X. MORATÓ[1], P. GARCIA-ESPARCIA[1], V. FERNÁNDEZ-DUEÑAS[1], I. FERRER[1], P. SVENNINGSSON[2];
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Abstract: In Parkinson disease (PD) management, reliable diagnostic and prognostic biomarkers are needed. GPR37, also known as parkin associated endothelin-like (Pael) receptor, is an orphan G protein-coupled receptor, which suffers a defective parking ubiquitination in autosomal recessive PD that promotes its endoplasmic reticulum aggregation and stress, neurotoxicity and neuronal death. In addition, aggregated GPR37 species have been identified in Lewy bodies (LBs) from sporadic PD or LB dementia postmortem brains. Importantly, this orphan receptor is

a partner of dopamine D_2 and adenosine A_{2A} receptors (D_2R and $A_{2A}R$, respectively). Accordingly, GPR37 has emerged as an important modulator of dopaminergic and adenosinergic transmission in the striatum. Here, we revealed the presence of the N-terminal domain of GPR37 (ecto-GPR37) in human cerebrospinal fluid (CSF). Thus, we engineered a nanoluciferase-based ELISA to evaluate ecto-GPR37 in CSF from healthy and PD subjects. First, by means of immunoblot and mRNA determinations we confirmed an increased GPR37 expression in postmortem substantia nigra from PD subjects. Next, we demonstrated the presence of ecto-GPR37 in CSF from wild-type, but not from $GPR37^{-/-}$, mice, thus validating our homemade ELISA system to monitor ecto-GPR37 expression in biofluids. Subsequently, we assessed the relative abundance of ecto-GPR37 in CSF from healthy controls (n=42) and PD (n=42) subjects. Interestingly, we found that ecto-GPR37 was significantly increased ($P = 0.0002$) in the CSF from PD patients, with no differences between male and female subjects. Importantly, CSF immunoprecipitation mass spectrometry results supported the analytical validity of our ELISA to measure ecto-GPR37 in human CSF. Overall, these results open exciting perspectives and encourage further systemically studies to confirm the clinical validity and utility of ecto-GPR37 as a potential PD diagnostic/prognostic biomarker.

Disclosures: **F. Ciruela:** None. **X. Morató:** None. **P. Garcia-Esparcia:** None. **V. Fernández-Dueñas:** None. **I. Ferrer:** None. **P. Svenningsson:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.14/DD26

Topic: I.05. Biomarker and Drug Discovery

Support: CONACYT Grant 599497
DGAPA Grant IN-111216
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Title: Identification of dopamine and 5-S-cysteinyl-dopamine as Parkinson's disease biomarkers in complex simulated body fluids and their detection by surface enhanced Raman spectroscopy

Authors: *I. BADILLO-RAMÍREZ[1], J. M. SANIGER[1], A. MÜHLIG[2,3], D. CIALLA-MAY[2,3], J. POPP[2,3];
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Abstract: Parkinson´s disease (PD) is the second most common neurodegenerative disorder. Researching in PD biomarkers may open the access to accurate diagnosis of the disease.

Dopamine (DA) metabolism, through the formation of oxidized metabolites, has been related to contribute in the physiology of PD. 5-S-Cysteinyl-Dopamine (5SCDA), a thio-catecholamine product in the dopamine oxidative pathway, induces cell vulnerability and neural death. 5SCDA has been detected in increased concentration in brain samples and fluids of PD patients, indicating that 5SCDA might be a suitable biomarker for PD. Accurate biomarker detection with high sensitivity is highly desirable in routine diagnosis. Surface Enhanced Raman Spectroscopy (SERS), combining the advantages of Raman spectroscopy with plasmonic enhancement of the vibrational signal, allows for the detection of molecules at very low concentration with high sensitivity in a very short time frame, in comparison with standard chromatographic methods. The aim of this study was to show the feasibility of SERS for the detection of DA and 5SCDA in simulated complex body fluids. For this purpose, colloids of silver nanoparticles (AgNPs) were mixed with DA or 5SCDA, at different concentrations, in pure water and in two prepared simulated body fluids, cerebrospinal fluid (CSF) and simulated urine (SU). SERS measurements were performed in cuvette through a Raman microscope with an excitation wavelength of 488 nm. In this investigation we show that SERS is suited very well for the reliable detection of DA and 5SCDA in pure water and simulated CSF. However, only 5SCDA could be detected in SU. The limits of detection (LOD) for DA in pure water and CSF were $1x10^{-6}$M and $1x10^{-7}$M, respectively, while the LOD for 5SCDA in water, CSF and SU were at $1x10^{-7}$M, $5x10^{-11}$M and $1x10^{-6}$M, respectively. 5SCDA was detected in lower concentration than DA. This variation in the detection sensitivity, was attributed to the different Raman cross sections of the two analytes, the molecular orientation relative to the surface of the AgNPs and the type of ions and their concentration in the different simulated fluids. It was found that the composition of CSF improves the SERS detection sensitivity of both analytes DA and 5SCDA. In conclusion, in this work we show that 5SCDA has a lower LOD, in comparison to DA. In simulated complex fluids the SERS sensitivity becomes higher than in pure water. Therefore, as proposed by other authors [Goldstein et al. 2016], 5SCDA might be a better biomarker for PD than DA. Furthermore, it was shown that SERS as a simple, fast and accurate strategy might be a powerful tool for the detection of 5SCDA and other physiological biomarker metabolites.

Disclosures: I. Badillo-Ramírez: None. **J.M. Saniger:** None. **A. Mühlig:** None. **D. Cialla-May:** None. **J. Popp:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.15/DD27

Topic: I.05. Biomarker and Drug Discovery

Support: R44-OD024615-01 Office of Director
The Branfman Family Foundation

Title: Development of a novel positron emission tomographyradioligand for neuroimaging in preclinical Parkinson's disease

Authors: *S. SUBBURAJU[1], A. W. SROMEK[2], P. SEEMAN[3], J. L. NEUMEYER[2]; [2]Medicinal Chem. Program,Division of Basic Neurosci., [1]McLean Hospital, Harvard Med. Sch., Belmont, MA; [3]Departments of Pharmacol. and Psychiatry, Univ. of Toronto, Toronto, ON, Canada

Abstract: The dopaminergic system, especially the D_2 receptor, is affected in various neurological disorders, including Parkinson's disease (PD). Here, the loss of dopaminergic neurons causes a shift of D_2 receptors into the high affinity state (D_2^{high}), the functional or active form of the receptor to which dopamine (DA) binds. Medications for the treatment motor dysfunction, a hallmark symptom of PD, specifically target the D_2^{high} receptor. Unfortunately, PD is difficult to diagnose in early, preclinical stages. Thus, the availability of a selective D_2^{high} agonist as a diagnostic tool could enable early diagnosis and ensure timely onset of treatment. Recently, we described the synthesis and pharmacological evaluation of a series of fluorinated aporphines and identified several high affinity D_2^{high} ligands, which have potential for development as a ^{18}F PET radiotracer. We evaluated two lead radioligands, [^{3}H] MCL-524 and [^{3}H] MCL-536, in saturation and competition binding studies to human D_{2long}. In a competition binding assay between [^{3}H] MCL-536 and the agonist R-(-)-N-n-propylnorapomorphine (NPA), NPA had a *K*i binding affinity of 0.16 nM. When [3H] MCL-524 was used, NPA was found to have a Ki value of 0.9 nM. Co-incubation with guanylylimidodiphosphate abolished binding to D_2^{high}. Next, we evaluated radioligands [^{3}H] MCL-524 and [^{3}H] MCL-536 for biodistribution in brain and peripheral tissues in rats. Peak radioactivity levels were detected in the striatum vs. cerebellum between 15-30 minutes post-administration. In the periphery, binding was highest in liver and kidney, and elimination from the brain and peripheral organs evident at 60 min. *Ex vivo* brain autoradiography with [^{3}H] MCL-524 or [^{3}H] MCL-536 in controls and amphetamine-sensitized rats (a model for elevated D_2^{high}) showed elevated binding in regions of interest (striatum, substantia nigra pars compacta, nucleus accumbens and olfactory tubercules) vs. controls. Replication studies in rhesus monkey confirmed and extended earlier results from cynomolgus monkeys that ^{18}F MCL-524 selectively label the striatum, with a peak ratio of striatum vs. other brain tissues at 30-45 min post administration. Metabolic stability in liver microsome was reasonable for both ligands. In summary, [^{3}H] MCL-524 and [^{3}H] MCL-536 show high selectivity and affinity for the D_2^{high} receptor, ability to cross the blood-brain barrier, fast on and off kinetics and low non-specific binding to tissues, indicating they are suitable D2 receptor ligands for development as an ^{18}F PET tracer. The first proof-of-concept studies in human volunteers are planned in the near future.

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Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.16/DD28

Topic: I.05. Biomarker and Drug Discovery

Support: Charles Dana Foundation
Pennsylvania Tobacco Settlement Biomedical Research Fund
Penn State University Brain Research Funds

Title: Assessment of disease progression in early onset Parkinson's disease (EOPD) patients using transcranial sonography (TCS) and hemisphere specific neuropsychological testing

Authors: *S. RAVI[1], **B. MULLEN**[2], V. SHIVKUMAR[6], D. WAGNER[3], D. DANG[3], M. P. SUBRAMANIAN[4], T. GILMOUR[7], J.-L. WANG[3], P. ESLINGER[3], K. VENKITESWARAN[5], T. SUBRAMANIAN[4];
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Abstract: Early onset Parkinson's disease (EOPD) is defined by the onset of motor symptoms between the ages of 40 to 60. EOPD detection and monitoring for disease progression is critical since these patients are at an increased risk for developing motor and non-motor complications. Neuropsychological testing has revealed subclinical, cognitive deficits in PD that can lead to mild cognitive impairment (PD-MCI) and possibly Parkinson's disease associated dementia (PDD). In our previous research, data indicated the MRT as a valid neuropsychological test to distinguish visuospatial deficits between left and right-onset EOPD (MLPD and FLPD n = 19, MRPD and FRPD n = 24; p = 0.040). Within the same cohort, left-onset EOPD patients scored significantly better (p = 0.021) on the Total Repetitions of the Delis Kaplan Executive Function Verbal Fluency (DKEFS-VF) Test compared to right-onset EOPD patients. To compare these subclinical differences to clinical assessments of PD, we correlated MRT and DKEFS-VF Total Repetition scores to the UPDRS (Parts I-III Total Score). The findings were weak, negative correlations in both neuropsychological tests (MRT, r = -0.210 ; DKEFS VF Total Repetitions, r = -0.121). Transcranial Sonogrpahy (TCS) has been indicated to monitor disease progression in PD, which precedes the onset of motor symptoms between stage I and stage II based on Substantia Nigra Hyperechogeneceity (SN+). SN+ has been shown to remain stable with an area >0.2cm^2 in advanced PD patients (≥H&Y stage II). 44 EOPD patients in Hoehn and Yahr (H&Y) Stage I as determined by the UPDRS were followed every 6 months. A video z-stack of each SN was obtained and largest area of SN+ was quantitated on de-identified clips by a blinded

technologist. SN+ >0.2cm^2 were classified as significant on each side. At V1, SN+ that met >0.2cm^2 was found exclusively on the contralateral SN of all 44 subjects. Mean contralateral and ipsilateral SN+ was 0.268 ± 0.0582 cm^2 and 0.146 ± 0.0493 cm^2, respectively. By 540 days after V1, 67.57% of the patients (n=37) displayed SN+ >0.2cm^2 ipsilaterally and 13.51% of the patients (n=37) were classified as Stage II. Of the 37 individuals who have attended follow-up visits through 720 days from V01, we report bilateral SN+ in all subjects, whereas only 17 of the 37 subjects had clinically progressed to stage II via H&Y Scoring. Our current study aims to associate SN+ with performance on the MRT and DKEFS-VF Total Repetitions measurement. We plan to associate the MRT, DKEFS-VF Total Repetitions, and SN+ to observed PD subtypes such as akinetic-rigid, tremor dominant and equivalent. These subtypes have been shown to have a varied disease progression of motor and non-motor symptoms.

Disclosures: S. Ravi: None. **B. Mullen:** None. **V. Shivkumar:** None. **D. Wagner:** None. **D. Dang:** None. **M.P. Subramanian:** None. **T. Gilmour:** None. **J. Wang:** None. **P. Eslinger:** None. **K. Venkiteswaran:** None. **T. Subramanian:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Adamas, Teva, Acadia, US World Meds. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Taylor Francis Publishing. F. Consulting Fees (e.g., advisory boards); Adamas, Teva, Acadia, US World Meds.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.17/DD29

Topic: I.05. Biomarker and Drug Discovery

Support: NIH grant T32-NS082128
NIH grant R01-NS052318
NIH grant R01-NS075012

Title: Longitudinal magnetic resonance imaging of an alpha-synuclein pathology mouse model

Authors: *W. T. CHU[1], J. C. DESIMONE[2], C. J. RIFFE[3], H. LIU[4], P. CHAKRABARTY[5], B. I. GIASSON[5], D. E. VAILLANCOURT[2];
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Abstract: Background and Purpose: Aggregation of alpha-synuclein (aSyn) is the hallmark pathology for multiple neurodegenerative diseases such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB). The objective of this study was to test how MRI-based biomarkers relate to aSyn pathology progression in a mouse model. **Methods:** 37 human A53T

transgenic M83$^{+/-}$ mice were given bilateral intra-muscular (IM) injections of either 10μg of aSyn fibrils or phosphate buffered saline (PBS). Multi-shell diffusion MRI scans were collected for each mouse at 4 time points: pre-injection, 1 month, 2 months, and 3 months post-injection. The Neurite Orientation Dispersion and Density Imaging (NODDI) model was applied to the diffusion MRI scans to estimate bulk neurite morphology characteristics such as neurite density (NDI), orientation dispersion (ODI), and isotropic volume fraction (ISO). Maps of diffusion metrics such as fractional anisotropy (FA) and mean diffusivity (MD) were also calculated. Average values of each metric were calculated within anatomical regions of interest (i.e. cerebellum, vermis, medulla, posterior pons, thalamus, and striatum). Between-group t-tests (aSyn-injected vs. PBS-injected) were performed with a p-value threshold of 0.05. **Results:** It was confirmed that, pre-injection, no significant between-group differences existed for any of the metrics in all the examined regions. At 1 month post-injection aSyn-injected mice had reduced FA in the cerebellum, vermis, medulla, and posterior pons, reduced MD in the cerebellum, medulla, posterior pons, and striatum, increased NDI in the posterior pons, thalamus, and striatum, and increased ODI in the cerebellum, vermis, medulla, posterior pons, thalamus, and striatum compared to controls. No significant differences in ISO were found. At 2 months post-injection aSyn-injected mice had increased ODI in the thalamus compared to controls, however, no significant differences were found for the other metrics in the examined regions. At 3 months post-injection the aSyn-injected group had reduced FA in the vermis, reduced MD in the medulla, and reduced ISO in the medulla, however, no significant differences were found for the other metrics in the examined regions. **Conclusion:** Our results show that multi-shell diffusion MRI combined with the NODDI diffusion model can resolve subtle longitudinal changes in brain tissue microstructure that result from alpha-synuclein pathology. These findings have direct applications in pre-clinical drug-screening and has the potential to inform future applications of NODDI to human PD and DLB populations.

Disclosures: W.T. Chu: None. **J.C. Desimone:** None. **C.J. Riffe:** None. **H. Liu:** None. **P. Chakrabarty:** None. **B.I. Giasson:** None. **D.E. Vaillancourt:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.18/DD30

Topic: I.05. Biomarker and Drug Discovery

Support: Team Parkinson/Parkinson Alliance
MSA Coalition Grant 2017-10-007
pilot grant from the UCLA American Parkinson's Disease Association Center

Title: Development of a novel ELISA methods for quantification of phosphorylated S^{129}-α-synuclein in biological samples

Authors: *K. BIGGS[1], S. HORNUNG[1,4], S. DUTTA[1], G. BITAN[1,2,3];
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Abstract: Synucleinopathies are a group of neurodegenerative diseases including Parkinson's disease (PD), multiple system atrophy (MSA) and Dementia with Lewy bodies (DLB). They are characterized by the aggregation and deposition of the protein α-synuclein (α-syn) in Lewy bodies (LBs). In healthy brains only ~4 % of α-syn is phosphorylated at Ser^{129} (pS^{129}-α-syn), whereas over 90% pS^{129}-α-syn is found in LBs. There is currently no ELISA available to measure pS^{129}-α-syn. The development of a robust biochemical method to reliably measure low pg/mL levels of pS^{129}-α-syn addresses an urgent need for research and clinical applications. We evaluated different combinations of capture antibodies and detection antibodies on two different platforms, an electrochemiluminescent ELISA platform (Meso Scale Discovery) as well as a traditional chemiluminescent sandwich ELISA using a biotinylated detection antibody. Semisynthetic pS^{129}-α-syn and unphosphorylated α-syn (as a negative control) standards were measured in a concentration range from 0.76 pg/mL to 100,000 pg/mL. Further, mouse brain lysate, human serum, cerebrospinal fluid (CSF), saliva, and brain-derived exosomes were tested in this assay. Using the biotinylated monoclonal antibody EP1536Y and the SULFO-Tag anti-human α-syn antibody (MSD) resulted in the most sensitive measurement of pS^{129}-α-syn standards in the MSD platform. Whereas using EP1536Y capture antibody and biotinylated MJFR1 detection antibody resulted in the most sensitive measurement in the traditional sandwich ELISA. The assays show a wide dynamic range from single pg/mL to tens of ng/mL and does not detect unphosphorylated α-syn up to a concentration of 50 ng/mL. pS^{129}-α-syn could be detected in all the mouse and human tissues tested. Our results demonstrate that these novel ELISAs are highly sensitive and specific for pS^{129}-α-syn. The MSD platform can detect pS^{129}-α-syn at low pg/mL level and the traditional ELISA at a slightly higher minimum concentration but at a lower cost. Both assays achieve these results with high intra- and inter-experimental reproducibility. The traditional ELISA will be useful for high throughput animal studies and other situations where the sensitivity of the MSD platform is not required. The MSD platform assay will be useful for detecting pS^{129}-α-syn in limited volumes of patient samples and can offer new opportunities for diagnostic biomarkers, monitoring disease progression, and quantifying outcome measures in clinical trials.

Disclosures: K. Biggs: None. **S. Hornung:** None. **S. Dutta:** None. **G. Bitan:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.19/DD31

Topic: I.05. Biomarker and Drug Discovery

Title: A mobile platform to assess cognition in amyotrophic lateral sclerosis

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Abstract: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease characterized by the death of upper and lower motor neurons. These motor neurons degenerate over time and result in muscle atrophy, and thus a majority of the research in ALS focuses primarily on the functional consequences of this process on respiratory and movement symptoms. However, ALS patients often face marked cognitive impairment, especially in aspects of executive control. However, evaluations in the clinic to assess cognitive decline are performed infrequently using screening tests (e.g., ALS-CBS) rather than functional psychological tests. To this end, we developed a mobile application to enable self-administration of objective psychological tests in ALS patients at home and at the point of care that can be used to supplement data collected via current screening tools. The application was developed in iOS for the Apple iPhone to assess cognition (Trailmaking A/B and Digit-Symbol-Substitution Test) in patients with ALS and age-matched healthy comparisons. Participants completed two in-clinic visits spaced one week apart in which they performed the cognitive battery on the app. During the one-week period between clinic visits patients completed the cognitive tasks at-home at least twice. Data collection is ongoing and results of the cognitive tests versus standard in-clinic screening assessments will be discussed.

Disclosures: **T. Kangarloo:** A. Employment/Salary (full or part-time):; Biogen. **A. Gupta:** F. Consulting Fees (e.g., advisory boards); Biogen. **S. Paganoni:** None. **S. Chew:** F. Consulting Fees (e.g., advisory boards); Biogen. **E. Collins:** None. **A. Steinman:** A. Employment/Salary (full or part-time):; Biogen. **J. Severson:** A. Employment/Salary (full or part-time):; Digital Artefacts. **J. Berry:** F. Consulting Fees (e.g., advisory boards); Biogen. **J.D. Cosman:** A. Employment/Salary (full or part-time):; Biogen.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.20/DD32

Topic: I.05. Biomarker and Drug Discovery

Support: NIH R21-NS093222

Title: RNA sequencing of cerebellar white matter reveals a potential role of APP and endothelial cell genes in cerebellar multiple system atrophy pathogenesis

Authors: *I. S. PIRAS[1], C. BLEUL[1], I. SCHRAUWEN[2], J. S. TALBOOM[1], M. DE BOTH[1], M. NAYMIK[1], G. M. HALLIDAY[3], J. HOLTON[4], G. E. SERRANO[5], L. I. SUE[5], T. G. BEACH[5], M. J. HUENTELMAN[1];
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Abstract: Multiple System Atrophy (MSA) is a rare adult-onset neurological disorder that is pathologically typified by α-synuclein inclusions in glial cells. MSA clinically presents as either Parkinsonian (MSA-P) or Cerebellar-type (MSA-C). Little is known about the molecular mechanisms associated with MSA or what may distinguish the two subtypes. To address this, we performed RNA sequencing of the cerebellar white matter (CWM) from two independent cohorts of MSA patients (n = 66) and healthy controls (HC; n = 66). RNA samples from bulk brain and from oligodendrocytes (Od) obtained by laser capture microdissection (LCM) were sequenced . Differentially expressed genes (DEGs) were determined using DESeq2 and classified according to their expression in brain using an informatics approach developed by the co-authors.
We detected the highest number of DEGs in the MSA-C group (n = 747), and only a single gene in the MSA-P patients, highlighting the much larger transcriptional change in the MSA-C patient's CWM. The LCM study yielded 187 DEGs in Od, with the top genes involved in myelination. The PPI network revealed enrichment for "collagen genes" (in MSA patients as a whole, adj $p < 0.01$), "cytoskeleton organization" and "cell death" (MSA-C patients, adj $p < 0.01$), and "chaperone folding" (in LCM Od from 6 patients, adj $p < 0.05$). The APP gene (amyloid precursor protein, downregulated in MSA-C) was identified as a top ranked hub gene in both MSA-C and the LCM Od networks. The cell-classification of MSA-C DEGs revealed a downregulation of Od genes and upregulation of microglia (M), astrocyte, endothelial cell (Ec), and neuron genes. M genes were enriched for "NF-kappaB signaling" (inflammation, adj $p < 0.01$). Finally, Ec genes were enriched for angiogenesis (adj $p < 0.01$), a process also reported to be dysregulated in other neurodegenerative diseases.

This is the largest RNA profiling study ever conducted in MSA patients. We were able to define specific transcriptional signatures for MSA-C and detect several candidate genes that may shed additional light onto possible therapeutic approaches. We also report the association of Ec specific transcriptional changes that may affect angiogenesis in the CWM. Several results point to a β-amyloid (Aβ) independent role for APP in MSA. An analogous mechanism has been proposed in Alzheimer's disease and is related to altered metabolism of APP and accumulation of APP C-terminal fragments rather than the more typical Aβ production. This suggests that these two diseases may share a common molecular origin.

Disclosures: I.S. Piras: None. **C. Bleul:** None. **I. Schrauwen:** None. **J.S. Talboom:** None. **M. De Both:** None. **M. Naymik:** None. **G.M. Halliday:** None. **J. Holton:** None. **G.E. Serrano:** None. **L.I. Sue:** None. **T.G. Beach:** None. **M.J. Huentelman:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.21/DD33

Topic: I.05. Biomarker and Drug Discovery

Support: BGIA27250263 (Stamova)
NS106950 (Sharp, Stamova, Ander, Jickling)
NS075035
NS097000
NS101718
NS079153

Title: Immune response in ischemic stroke and intracerebral hemorrhage in neutrophils and whole blood

Authors: *P. CARMONA-MORA, B. P. ANDER, G. JICKLING, X. ZHAN, B. KNEPP, F. HAMADE, H. HULL, E. FERINO, H. AMINI, F. R. SHARP, *B. STAMOVA;
Univ. of California, Davis Sch. of Med., Sacramento, CA

Abstract: Differentiating intracerebral hemorrhage (ICH) from ischemic stroke (IS) can be challenging when imaging is not available. Ruling out ICH is essential for early thrombolytic or endovascular IS therapy to be initiated. Understanding transcriptome differences between both and between IS etiologies, can lead to a better knowledge of the molecular and cellular pathways involved in the response to acute brain injury caused by ICH and IS. In this study we sought to characterize the transcriptomic profiles in blood from cases with ICH and different IS etiologies to identify acute molecular changes in isolated neutrophils and in whole blood.
Peripheral blood was drawn from cases with diagnosed ICH (6) and IS (33) (cardioembolic,

large vessel disease and lacunar) in the first 30 ± 20 hours after the onset of symptoms. We performed whole-genome RNA sequencing of whole blood (WB), and of isolated neutrophils. Control cases (10) with vascular risk factors (diabetes and/or hypertension and/or hypercholesterolemia) were included (VRFC). A linear regression model including diagnosis, sample subtype and their interaction with FDR<0.05 or p<0.05 overlap with FDR<0.2, and |fold-change|>1.2 was used for identifying differentially expressed (DE) genes. Gene ontology and pathway enrichment were performed for investigating their biological context. In addition, we delineated gene networks significantly associated with each diagnosis using Weighted Gene Co-expression Network Analyses (WGCNA). The significant co-expression modules were further studied to provide more insights in the pathways associated to ICH and IS. Transcriptional changes are distinguishable between both diagnoses in neutrophils and WB and also between stroke etiologies. For example, ICH vs VRFC 549 were DE in neutrophils, and 672 in WB. 389, 378, 694 genes were DE between cardioembolic IS, large vessel IS and lacunar IS compared to VRFC in neutrophils. Most of the changes are cell-type specific and involve cell-specific pathways, along with different signal transduction and immune response pathways. For ICH compared to VRFC, about half of the over-represented pathways were unique to neutrophils. 65% of the pathways over-represented in WB were not over-represented in neutrophils. Additional analyses will also allow us to demonstrate alternative splicing differences between to further refine the molecular signatures of both diseases. The unique molecular signatures in neutrophils underscore their involvement in IS and ICH pathophysiology. The large number of unique pathways in whole blood not detected in neutrophils signifies the contribution of other cell types to the ICH and IS responses.

Disclosures: **P. Carmona-Mora:** None. **B.P. Ander:** None. **G. Jickling:** None. **X. Zhan:** None. **B. Knepp:** None. **F. Hamade:** None. **H. Hull:** None. **E. Ferino:** None. **H. Amini:** None. **F.R. Sharp:** None. **B. Stamova:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.22/DD34

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH R01NS082283
Charles Rivers Laboratories

Title: Development of a quantitative approach for comprehensive analysis of rare disease biomarkers and progression in a preclinical model for CLN2 Batten disease

Authors: ***L. LANGIN**[1], K. LEHTIMÄKI[5], T. BRAGGE[5], J. BRUDVIG[1], T. B. JOHNSON[2], D. TIMM[3], A. J. NURMI[5], D. A. PEARCE[6], J. T. PUOLIVALI[5], J. M. WEIMER[4];

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Abstract: With new therapies being regularly developed for pediatric neurodegenerative disorders, there is a critical need to longitudinally track the progression of these diseases through utilization of noninvasive methods in both clinical and animal studies. Using a similar platform that was developed utilizing an animal model of CLN6-Batten disease, a multifaceted approach tracking relevant biomarkers of disease progression was performed on a preclinical mouse model for CLN2 Batten disease. Having accelerated disease advancement including visible, hyperactive tremors and early death, the *Cln2*$^{R207X/R207X}$ nonsense point mutation mouse model is ideal for testing a platform that incorporates the findings of noninvasive testing into one, comprehensive "disease score." Using a range of conventional neuroimaging tests and kinematic gait analysis, this approach tracks 144 parameters over the course of the model's lifespan to ultimately quantify key factors that contribute to disease progression and behavioral deficits. The tangible and quantifiable benefit of an application of this type has both clinical and therapeutic relevance.

Disclosures: L. Langin: None. **J.M. Weimer:** None. **J. Brudvig:** None. **K. Lehtimäki:** None. **T.B. Johnson:** None. **T. Bragge:** None. **D. Timm:** None. **A.J. Nurmi:** None. **J.T. Puolivali:** None. **D.A. Pearce:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.23/DD35

Topic: I.05. Biomarker and Drug Discovery

Support: OpenMinds (Grant # 620229)

Title: Exogenous flupirtine and flupirtine aromatic carbamate derivative as a potential treatment for CLN3 disease

Authors: *J. MAKOUKJI[1], K. MAALOUF[1], S. SAAB[1], B. VAIDYA[2], A. CARMONA[2], P. C. TRIPPIER[2], R.-M. BOUSTANY[1];
[1]American Univ. of Beirut, Beirut, Lebanon; [2]Texas Tech. Univ. Hlth. Sci. Ctr., Amarillo, TX

Abstract: Objective: Neuronal Ceroid Lipofuscinoses (NCL) are fatal, childhood neurodegenerative diseases characterized by seizures, blindness, cognitive and motor decline. CLN3 disease is the most common form. Hallmarks include brain atrophy, retinitis pigmentosa, accelerated apoptosis and ceramide elevation. Treatment regimens are symptomatic, disease-modifying drugs are urgently needed. Flupirtine and its novel aromatic carbamate derivative

(compound 6) exert anti-apoptotic and neuroprotective effects, *in vitro,* in neuronal precursor PC12 cells and human NCL cell lines. This study aims at investigating, *in vivo*, beneficial effects of orally supplied flupirtine and its allyl carbamate derivative (compound 6) in *Cln3*$^{\Delta ex7/8}$ knock-in mice. **Methods**: Flupirtine and compound 6 were tested by establishing growth curves, in neuronal precursor PC12 cells following siRNA knockdown of *CLN3* gene, and in patient-derived NCL lymphoblasts, using trypan blue and JC-1 staining. Ceramide levels were determined in human NCL lymphoblasts before and after treatment. Expression levels of *BCL-2, Caspases 3/8/9,* and ceramide synthesis enzymes (*CERS2/CERS6/SMPD1/DEGS2*) were compared in treated vs. untreated CLN3-deficient PC12 cells by quantitative real-time PCR (qRT-PCR). As a next step, 80 WT and *Cln3*$^{\Delta ex7/8}$ mice (40 males and 40 females) received flupirtine, compound 6 or vehicle for a period of 15 weeks. Effect of flupirtine or compound 6 on *Cln3*$^{\Delta ex7/8}$ mice is determined by performing behavioral tests (open field, pole climbing, Morris water maze, rotarod, wire suspension test), measuring ceramide in brains and sera, assessing impact on longevity, subunit C storage, astrogliosis and neuronal cell counts. Impact of flupirtine and compound 6 on apoptosis markers (BCL-2, caspases...) and ceramide synthesis/degradation enzymes levels is also investigated by qRT-PCR and Western Blot. Global gene expression patterns in *Cln3*$^{\Delta ex7/8}$ mouse brain treated with flupirtine or compound 6 is identified. **Results**: Flupirtine and compound 6 were neuroprotective in CLN3-defective PC12 cells and rescued human NCL lymphoblasts from accelerated apoptosis. Flupirtine and compound 6 decreased ceramide level in human NCL lymphoblasts. Increased *BCL-2,* decreased *Caspases 3/8,* and decreased ceramide synthesis enzyme expression were established in CLN3-deficient PC12 cells treated with flupirtine or compound 6. Based on these results, *in vivo* experiments were conducted to assess their effect on *Cln3*$^{\Delta ex7/8}$ mice. **Conclusion**: These findings establish that compounds analogous to flupirtine demonstrate anti-apoptotic activity with potential for treatment of NCL disease.

Disclosures: J. Makoukji: None. **K. Maalouf:** None. **S. Saab:** None. **B. Vaidya:** None. **P.C. Trippier:** None. **R. Boustany:** None. **A. Carmona:** None.

Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.24/DD36

Topic: I.05. Biomarker and Drug Discovery

Support: 2018 Penn State MDBR Grant

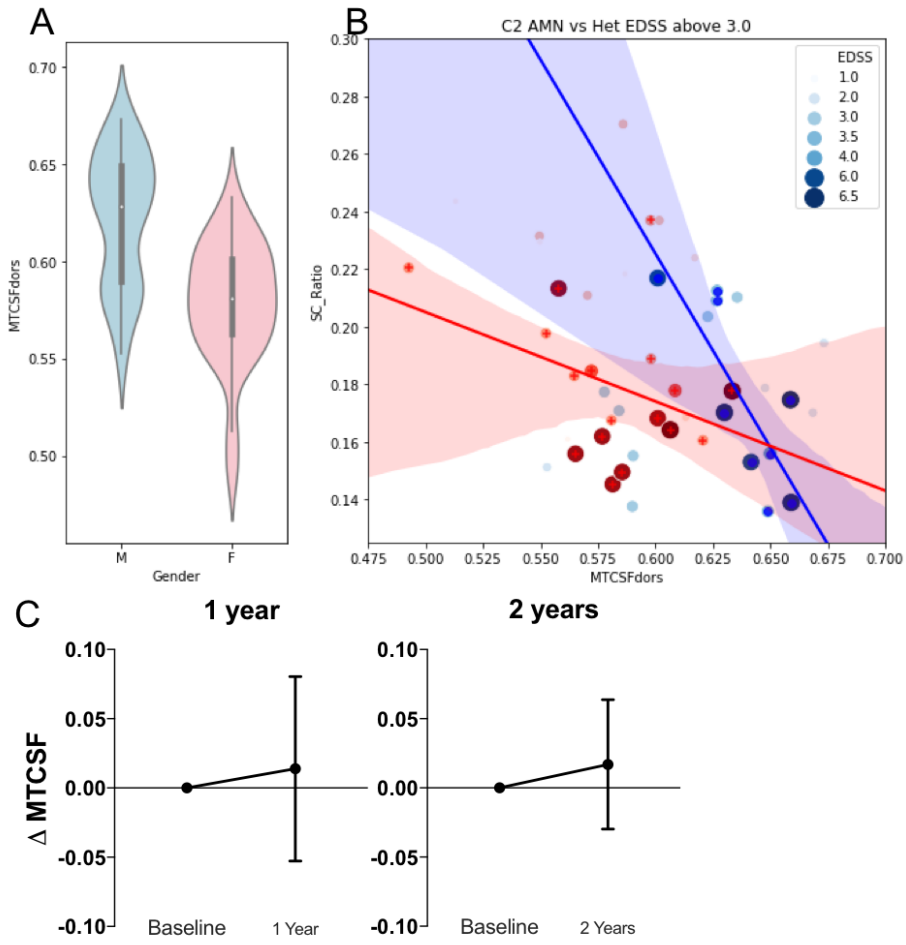
Title: Magnetization transfer imaging in the adrenomyeloneuropathy spinal cord shows potential suitability as a longitudinal biomarker for clinical trial

Authors: *B. R. TURK[1], R. LAWLESS[2], M. KAUFMAN[1], J. L. KELLER[1], K. M. ZACKOWSKI[1], G. V. RAYMOND[3], A. J. BASTIAN[1], A. FATEMI[1], S. A. SMITH[2]; [1]Kennedy Krieger Inst., Baltimore, MD; [2]Vanderbilt Inst. of Imaging Sci., Nashville, TN; [3]Penn State Children's Hosp., Hershey, PA

Abstract: Adrenomyeloneuropathy (AMN) is the non-fatal phenotype affecting ~60% of patients with Adrenoleukodystrophy (ALD), an X-linked inborn error of metabolism due to a mutation of the ABCD1 gene. MRI of the AMN spinal cord shows atrophy at all cervical levels, due to a dying-back axonopathy in long tracts. Our group has previously shown that magnetization imaging (MT) normalized to patient's own CSF levels (MTCSF) shows significant increase in dorsal column signal, and that MTCSF correlates to clinical and sensory motor measurements.

Currently, there is no FDA approved therapeutic compound for AMN. However, multiple therapeutic compounds are in different stages of the development pipeline. One main challenge is a lack of a longitudinal imaging marker for the AMN spinal cord. This study explored secondary imaging outcomes the longitudinal potential of MT as a biomarker from an ALD clinical trial from 2005-2009. Analyses were performed on the spinal cord vertebral level C2. Mirroring our previous findings in other populations, MTCSF was cross-sectionally significantly higher in the dorsal column of the AMN spinal cord versus heterozygote female carriers (Fig A) (n=147, AMN=74,Het=73). Interestingly, cross-sectionally, atrophy measured by spinal cord/column ratio and MTCSF showed a significant linear correlation only in AMN patients with further disease progression, stratified by the expanded disability status scale (EDSS) above 3.0 (Fig B). Longitudinally, MTCSF in AMN shows progression after one year and further progression after 2 years (Fig C). These data indicate that MT may be a suitable biomarker for clinical trial.

Figure caption: A) Violin plot depicting distribution (wings) and quartiles (center) of MTCSF of the spinal cord C2 dorsal column between Males (AMN) and female heterozygote carriers. B) MTCSF vs spinal cord/column ratio, by EDSS (point size and hue) and gender (Male = Blue, Red = Female), with linear regression on data points for EDSS above 3.0 C) Longitudinal delta change of MTCSF in AMN C2 dorsal column over one and two years



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Poster

614. Biomarker and Drug Discovery: Neurodegenerative Diseases

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 614.25/DD37

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Bruteforcing hard targets in neuroscience with computational immuno engineered SuperHuman 2.0 and Tungsten 1.0 VHH

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Abstract: New advances in synthetic and data driven immune engineering antibody discovery are enabling new neuroscience antibody therapeutics to be discovered and engineered in weeks rather than years. Here, we review ten years of progress in computational optimization of antibody discovery libraries through the lens of high-throughput data collection technologies, with specific case studies of modern repertoire design principles applied to neuroscience targets. We emphasize the case studies of TfR, CD19, and amyloid-beta, where computationally optimized libraries generated thousands of unique anti-brain target antibodies, including picomolar binders, mouse/cyno/human triple cross-reactive epitopes, antagonists, agonists, and saturated epitope coverage of the neuroscience target.

Disclosures: **S. Youssef:** A. Employment/Salary (full or part-time):; Distributed Bio. **S. Ives:** A. Employment/Salary (full or part-time):; Distributed Bio. **D. Maurer:** A. Employment/Salary (full or part-time):; Distributed Bio. **V. Chiou:** A. Employment/Salary (full or part-time):; Distributed Bio. **C. Pettus:** A. Employment/Salary (full or part-time):; Distributed Bio. **R. Newland:** A. Employment/Salary (full or part-time):; Distributed Bio. **S. Daraeikia:** A. Employment/Salary (full or part-time):; Distributed Bio. **C. Jones:** A. Employment/Salary (full or part-time):; Distributed Bio. **K. Hervold:** A. Employment/Salary (full or part-time):; Distributed Bio. **G. Day:** A. Employment/Salary (full or part-time):; Distributed Bio. **C. Smith:** A. Employment/Salary (full or part-time):; Distributed Bio. **C.S. Peritore:** A. Employment/Salary (full or part-time):; Charles River Labs. **I. Waddell:** A. Employment/Salary (full or part-time):; Charles River Labs. **J. Glanville:** A. Employment/Salary (full or part-time):; Distributed Bio.

Poster

615. Neuronal Models of Activity and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 615.01/DD38

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSF/CRCNS Grant 1516235

Title: Improved multi-objective optimization for large-scale neuron models

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Abstract: Today's rapid growth of open source neural modeling tools, data sharing platforms, and computational resources presents rich opportunities for in silico hypothesis generation and testing to support experimental findings. However, large-scale neuron models with realistic dendritic morphologies can require extensive tuning to match data. Previous work has shown that multi-objective evolutionary algorithms (MOEAs) can help to partially automate the task, but specific difficulties arise when these methods are applied to neural models. We address these shortcomings with a new technique that substantially improves the performance of such methods.
One difficulty is that neural models often have a large number of parameters, and properly determining them requires multiple experimental recordings. As a result, the number of objective functions required to constrain the model can be large. However, it is well-documented that some of the most commonly used MOEAs fail to converge on problems with more than two or three objective functions, making them ill-suited for use on neural models.
Secondly, due to the highly nonlinear dynamics associated with spiking, errors in these objective functions can be large, even within a bounded parameter range. Tests reveal that most MOEAs also perform poorly when the range of objective function values is not bounded.
We show that these challenges can be overcome by projecting objective values into a bounded space. The resulting method substantially improves the fitting of neural models with multi-objective evolutionary algorithms.

Disclosures: A. Abouzeid: None. **W. Kath:** None.

Poster

615. Neuronal Models of Activity and Disease

Location: Hall A

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Program #/Poster #: 615.02/DD39

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSF IGERT 0903622
College of Engineering, University of Illinois at Urbana-Champaign

Title: Minimum number of voltage-gated channels in a biophysical conductance-based model that can predict spike-timing in neurons with short-term adaptation

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Abstract: In a spike-time code, the time of occurrence of a spike is assumed to carry information about its input. This has led to computational models that can predict the time of each spike, with the most successful model being the adaptive or moving threshold model. With few exceptions

(e.g., Abarbanel and co-workers) nonlinear biophysical conductance-based models (Hodgkin-Huxley or H-H type) have been poor at predicting spike-times because of the difficulty in estimating the large number of model parameters. There is thus a significant gap in exploring biophysical models of spike-timing which have predictive power, i.e., which can be used to predict the spike-times from experimental data. At the biophysical level, it is know that outward potassium currents regulate spike-timing. Further, they are responsible for the adaptive or moving threshold that persists from ten to hundreds of milliseconds causing firing-rate adaptation. This work has two goals: 1) determine a conductance-based model with the smallest number of ion channels that can predict the spike-times observed experimentally, 2) establish the role of outward potassium currents in adaptation. Using publically available intracellular data from L5 pyramidal neurons in the rat somatosensory cortex (the INCF Spike Time Prediction Challenge, 2009), and a parameter estimation procedure developed by Abarbanel and co-workers, we show that only five ion channels are needed to obtain a good fit to the membrane potential and to predict spike times: the three classical H-H type channels (a leak channel, a transient Nav, and a Kv delayed rectifier but with inactivation), a non-inactivating outward M-current (Kv7), and a persistent Na+ current. The predicted spike-time coincidence with experimental data is 0.47 (about 63% of the experimentally reported coincidence). In comparison, the best-fit obtained using a multiscale adaptive threshold model (Kobayashi and co-workers) was about 0.57 (or 76%). Increasing the number of channels does not improve the fit. We verify that the estimated parameters are within the biophysically plausible range, and show that the M-current produces the adaptation observed in the data, and that this adaptation is not long-lasting (10-30 ms). The model mimics the spike-initiation region (the axonal initial segment or AIS) as it does not include voltage-gated channels found elsewhere in the soma or dendrites. Finally, we show that the M-current, but not the delayed rectifier, regulates the spike-rate (proportional to energy consumption). These results support the idea that the AIS may be critical for regulating spike-timing, spike frequency adaptation, and the neuron's energy consumption.

Disclosures: **A.R. Asilador:** None. **R. Ratnam:** None.

Poster

615. Neuronal Models of Activity and Disease

Location: Hall A

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Program #/Poster #: 615.03/DD40

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Automating development of biophysical single cell models

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Engin. and Computer Sci., [4]Electrical & Computer Engin., Univ. of Missouri Columbia, Columbia, MO

Abstract: Neuronal models are of different types spanning the range from phenomenological to detailed biophysical types. These models attempt to capture the key signatures of neuronal responses, depending on the application. Such neural signatures include resting membrane potential, input resistance, membrane time constant, subthreshold oscillations, threshold potential, and frequency-current (F-I) curves. Biophysical models of neurons typically include either simplified or detailed morphology of soma and dendrites modeled as cylinders into which are embedded different current channels, and synapses.
Several approaches have been proposed to develop biophysical models ranging from hand-tuning to automated algorithms that can search large databases. Here we propose automated approaches to construct biophysical models of neurons with different numbers of neural signatures, using both analytic and machine learning components. In the first category, we consider a biophysical model structure for simple spiking neurons with only a few signatures: resting potential, input resistance, membrane time constant and F-I curve. In the second category, we consider neurons with additional signatures such as low- and high- threshold oscillations and bursting. Such approaches are important to speed up the development of network models and also free up the neuroscientist from having to devote time away from science to learn complex technical details.

Disclosures: **Q. Wei:** None. **T. Banks:** None. **B. Latimer:** None. **Z. Chen:** None. **S.S. Nair:** None.

Poster

615. Neuronal Models of Activity and Disease

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Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH Grant F32 DC016775
NSF Award 1622977

Title: Combined biophysical and statistical modeling pipeline for investigating roles of ion channels in stimulus encoding

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Abstract: To understand single neuron computation, it is necessary to know how specific ion channel conductances affect neural integration and output. Knowledge of these relationships is

critical in understanding how changes in biophysical properties affect stimulus encoding. Here we present a computational pipeline combining biophysical and statistical models to provide a link between variation in functional ion channel expression and changes in single neuron stimulus encoding. Biophysical models provide mechanistic insight, whereas statistical models provide insight into what spiking actually encodes. We used published biophysical models of two morphologically and functionally distinct projection neuron cell types: mitral cells (MCs) of the main olfactory bulb, and layer V cortical pyramidal cells (PCs). We first simulated MC and PC responses to pink noise stimuli while scaling individual ion channel conductances and then fit point process regression models (generalized linear models; GLMs) to the resulting spike trains. This provides both stimulus effects (the stimulus filter) and spike-history effects (the history filter). Although we find interesting differences for several channel types in each model, we focus here on high-voltage-activated Ca^{2+} channels (Ca_{HVA}) as an example of our pipeline. Changing Ca_{HVA} conductance converts our MC and PC models from regular firing to burst firing or vice versa. These changes are reflected predominantly in changes of the GLM history filter and early components of the stimulus filter. Through stimulus reconstruction, we find that increasing Ca_{HVA} conductance in MCs reduces coherence of low and medium frequency stimulus components, but not high frequency components. In contrast, varying Ca_{HVA} conductance in PCs has moderate effects on coherence of low and medium frequency components, but substantial reductions in coherence of high frequency components. Thus, we can predict how differences in individual conductances affect encoding of specific stimulus features. Our computational pipeline provides a way of screening all channel types to identify those channels that most strongly influence single neuron computation in any cell type of interest.

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Poster

615. Neuronal Models of Activity and Disease

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Support: R01 AA027023
R01 DA034913
R01 MH122729
R21 MH112117
Department of Energy (LDRD):Funding Number: DE AC0205CH1123

Title: Using convolutional neural networks to predict ion-channels densities in single neuron biophysical models

Authors: *R. BEN-SHALOM[1], J. BALEWSKI[3], V. BARATHAM[4], A. SITHTHARANJAN[4], H. KYOUNG[4], K. KIM[4], K. J. BENDER[2], K. E. BOUCHARD[2];
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Abstract: Conductances generated by ion channels distributed along neuronal membranes contribute markedly to neuronal activity. To better understand the underlying mechanisms of neuronal activity, we need to model single neurons accurately, including spatial densities of different ion channels along the membrane. Currently, it is quite difficult to accurately measure these densities. This makes it difficult to constrain these parameters in compartmental models. Instead, a common approach is to treat these ion channel densities as unknown parameters that are then estimated to allow for accurate recapitulation of *in vitro* recordings from target neuronal datasets. This is traditionally done using optimization algorithms like Multi Objective Optimization (MOO), which seeks to minimize differences between model output and target data using defined criteria - the objectives of the optimization. One central shortcoming of this approach is that MOO often returns different parameters depending on the chosen objectives. Recently, CNNs, which have been applied in a range of dynamical systems fields, have been shown to be advantageous for such complex systems. Here we ask whether CNNs can predict ion channel densities from membrane potentials across a spectrum of neuronal models. We trained CNNs with a simulated dataset of known ion channel densities and their resultant voltage outputs in response to a stimulus. Following training, we tested CNNs with novel voltage outputs generated from a new complement of ion channel densities and asked whether the CNN could determine these densities from the voltage outputs alone. In contrast to MOO-based fitting, where each optimization fit one voltage trace to one set of parameters, a trained CNN was able to provide channel density predictions for all voltages created by the neuronal model, albeit with varying prediction errors. After CNNs are trained, we generate a report for how well each parameter can be constrained and how individual parameters correlate with each other. For simple models, CNNs were able to accurately predict all parameters with relatively small error (less than 4%). For more complex models, we found that some parameters were well predicted, whereas for others CNN predictions were poor. This is presumably because those parameters with higher error had little influence on overall voltage output, at least at the soma. We are currently exploring whether these parameters could be better fit by simultaneous recordings from the soma and other neuronal sites (e.g., axon or distal dendrite). Finally we discuss several ways to reduce the dimensionality of the free parameters to increase accuracy of the predictions.

Disclosures: R. Ben-Shalom: None. **J. Balewski:** None. **V. Baratham:** None. **A. Siththaranjan:** None. **H. Kyoung:** None. **K. Kim:** None. **K.J. Bender:** None. **K.E. Bouchard:** None.

Poster

615. Neuronal Models of Activity and Disease

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Program #/Poster #: 615.06/DD43

Topic: I.06. Computation/ Modeling/ and Simulation

Support: National Defense Science and Engineering Graduate Fellowship
LBNL-internal LDRD "Neural Systems and Engineering lab" (PI, Kristofer Bouchard)

Title: Identifying and mitigating statistical biases in neural models of tuning and functional coupling

Authors: *P. SACHDEVA[1], M. DOUGHERTY[2], S. BHATTACHARYYA[3], K. E. BOUCHARD[2];
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Abstract: Neural activity is a function of factors in the external world (i.e., tuning) and other neurons, some of which may be simultaneously measured and analyzed (i.e., functional coupling), while others are not observed and contribute both shared variance and private noise. Statistical models (e.g., generalized linear models) have been used to describe neural responses using tuning and functional coupling with high predictive accuracy and a set of interpretable parameters. These fitted parameters provide insight into which internal and external factors are important and their relative importance. For example, past studies have demonstrated that the inclusion of coupling greatly improves predictive performance while decreasing the magnitudes of the tuning parameters. Thus, the implication is that neural activity, while shaped by tuning, is largely determined by coupling. However, extracting conclusions about neural activity from model parameters requires that their estimates are unbiased. We demonstrate that correlated variability can introduce the simultaneous equations bias (a phenomenon studied in econometrics) in statistical models of coupling and tuning, potentially biasing parameter estimates and jeopardizing past conclusions about neural computation. We present a novel method, Iterated Two-Stage Factor Analysis (ITSFA), that alleviates the simultaneous equations bias in a common model of neural activity. We show that ITSFA consequentially corrects tuning curves in both single-unit recordings from monkey motor cortex and micro-electrocorticography recordings from rat auditory cortex. We highlight a connection between the increase or decrease of tuning and the distribution of noise correlations. Together, our results shed light on how noise correlations can result in adversarial statistical biases, and provide a novel algorithm to mitigate that bias.

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Poster

615. Neuronal Models of Activity and Disease

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Program #/Poster #: 615.07/DD44

Topic: I.06. Computation/ Modeling/ and Simulation

Support: CHDI

Title: Striatal population models of ionic conductances reveal mechanisms for conversion among healthy, disease, and drug-treated phenotypes

Authors: *S. ALLAM, T. RUMBELL, T. M. HOANG TRONG, J. KOZLOSKI;
IBM Res., Yorktown Heights, NY

Abstract: The variability in electrophysiological signatures of neurons describe phenomena characteristic of the neuron's physiological states. The principal neurons of the striatum, responsible for motor co-ordination and cognition exhibit varied active and passive properties in healthy and Huntington's disease phenotypes. While the manifestation in electrophysiological properties due to disease or drug treatment is an outcome of underlying biochemical pathway modifications, it is difficult to quantify the causation and correlation of these outcomes through single experimental models alone owing to the heterogeneity of the cell population divergent across species, wild-type and disease phenotypes. Here we show, by constructing large populations (using evolutionary algorithms and parameter optimization) of such heterogenous striatal projection neuron models comprising of Hodgkin Huxley type ion channel and non-linear leak conductances constrained by trans-membrane ionic concentrations, robust linear controllers of these active and passive properties of neurons could be revealed. With cannonical correlation analysis, we then provide insights into how the landscape of specific potassium and sodium channel conductances are oriented in healthy population, altered in disease phenotypes and partially restored though drug treatment of the sub-cellular pathways. Our methods provide a way to linearly characterize the effects of various drugs aimed at multiple downstream targets of the dopamine receptor pathways within the striatal principal neurons and predict the effects of such drugs on the disease states within the striatal network

Disclosures: **S. Allam:** A. Employment/Salary (full or part-time):; IBM Research. **T. Rumbell:** A. Employment/Salary (full or part-time):; IBM Research. **T.M. Hoang Trong:** A. Employment/Salary (full or part-time):; IBM Research. **J. Kozloski:** A. Employment/Salary (full or part-time):; IBM Research.

Poster

615. Neuronal Models of Activity and Disease

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Program #/Poster #: 615.08/DD45

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NRF-2015M3C7A1028392
NRF-2018M3C7A1024736
NRF-2018R1C1B6002210

Title: Investigation of factors affecting burst firing patterns of a thalamocortical neuron: Computational NEURON model study

Authors: *S. PARK, S. LEE, J. CHO, Y. HUH;
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Abstract: The thalamus is a structure which relays and modulates sensory information before reaching the cortex. The unique ability of a thalamocortical (TC) neuron to switch between the high frequency firing (burst firing) and single spike firing (tonic firing) have been implicated to be involved in pain modulation. Of the two firing modes, previous studies demonstrated that the properties of TC burst firing, e.g. intervals between burst spikes in a burst, are key components in modulating behavioral nociceptive responses. Therefore, investigating the factors that influence the temporal dynamics of thalamic bursts would offer important insight into understanding the mechanism of sensory modulation. In this study, using full-morphology thalamocortical NEURON model, we investigated how the balance, timing, and intensity of excitatory and inhibitory inputs influences the dynamics of TC bursting patterns. We found that burst firing patterns changed more dynamically under weak inhibitory input conditions compared to strong inhibitory input conditions. To reflect a more realistic condition, we repeated the same analysis with excitatory inputs delivered at different dendritic locations: proximal, intermediate, or distal. Interestingly, we found that an excitatory input into a distal dendrite had the strongest influence on shaping the temporal pattern of TC bursts than the closer intermediate or proximal dendrites. Overall, our results demonstrate that several factors interplay to model the temporal dynamics of a burst firing pattern and provide insight into understanding the factors that contribute to sensory modulation.

Disclosures: S. Park: None. **J. Cho:** None. **Y. Huh:** None.

Poster

615. Neuronal Models of Activity and Disease

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Program #/Poster #: 615.09/DD46

Topic: I.06. Computation/ Modeling/ and Simulation

Support: CHDI Foundation

Title: Dopamine neuron population modeling and intracellular pathway modulation in a nigrostriatal model

Authors: *T. RUMBELL[1], T. M. HOANG TRONG[1], S. ALLAM[1], J. KOZLOSKI[2];
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Abstract: Dopaminergic neurons (DAs) of the rodent substantia nigra pars compacta (SNc) display varied electrophysiological properties *in vitro*. Despite this, projection patterns and functional inputs from DAs to other structures are conserved, so *in vivo* delivery of consistent, well-timed dopamine modulation to downstream circuits must be coordinated. Here we show robust coordination by linear parameter controllers, discovered through powerful mathematical analyses of data and models, and from which consistent control of DA *in vitro* spontaneous firing patterns emerges. We used evolutionary unbiased parameter search and dimensionality reduction to produce a unique population of models that show good generalization to channel blockade and compensatory intracellular mechanisms, and blanket the empirically observed range of electrophysiological profiles. Incorporating these heterogenous models of this neural population into a previously published striatopallidal circuit model (Corbitt et al., J. Neuroscience, 2016), and in combination with similar population modeling of striatal projection neurons (SPNs), we model the reciprocal connection between dopamine release in striatum and GABAergic input onto nigral DAs. We also incorporate existing canonical systems biology models of the intracellular pathway linking dopamine receptor activation to SPN excitability through the DARPP-32 biochemical pathway. This multiscale approach facilitates investigation of the role of both dopamine and drugs in modulating striatonigral circuit activity patterns and basal ganglia oscillations in health and disease.

Disclosures: T. Rumbell: A. Employment/Salary (full or part-time):; IBM Research. **T.M. Hoang Trong:** A. Employment/Salary (full or part-time):; IBM Research. **S. Allam:** A. Employment/Salary (full or part-time):; IBM Research. **J. Kozloski:** A. Employment/Salary (full or part-time):; IBM Research.

Poster

615. Neuronal Models of Activity and Disease

Location: Hall A

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Program #/Poster #: 615.10/DD47

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH Grant MH086638

Title: Efficient *in silico* 3D intracellular neuron simulation

Authors: A. J. H. NEWTON[1], C. CONTE[2], L. EGGLESTON[2], E. BLASY[2], M. L. HINES[3], W. W. LYTTON[4], ***R. A. MCDOUGAL**[2];
[1]Yale Ctr. for Med. Informatics, Yale Sch. of Med., New Haven, CT; [3]Neurosci., [2]Yale Univ., New Haven, CT; [4]SUNY Downstate, Brooklyn, NY

Abstract: The activity patterns of neurons are governed by nonlinear interactions of their internal state and synaptic inputs; these interactions can be predicted using quantitative models. Since NEURON 7.4, the NEURON simulator has supported models coupling 3d intracellular -- necessary for understanding microdomains near spines or the morphology variations where dendrites meet the soma -- and electrophysiological kinetics, however computational overhead imposed practical limits on models that can be studied this way. The recently released NEURON 7.7 features completely redesigned 3D voxelization and parallel simulation algorithms, drastically reducing the compute time -- expanding the set of simulatable models -- without requiring changes to model implementation code. We are able to run a 4-thread 300ms simulation of a propagating wave on approximately 750k voxels near the soma of a virtual neuron with a reconstructed morphology in approximately 258s. Conversion of point-diameter neuron traces to 3D volumes follows the CTNG heuristic (McDougal et al., 2013) but extended so that discretization time scales with the volume of the neuron not the volume of the bounding box. Simulation uses an adaption of the parallel Douglas-Gunn algorithm (Newton et al., 2018) that runs on irregular domains. Reactions are JIT compiled and are exportable to SBML. Currents always enter and are computed based on surface voxels. We demonstrate scaling and simulation using models of the circadian oscillator, propagating calcium waves at the soma, and diffusion near spines.

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Poster

615. Neuronal Models of Activity and Disease

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Program #/Poster #: 615.11/DD48

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH OT2 OD025340

Title: Particle swarm optimization of a nonlinear cable model of an autonomic c-fiber axon

Authors: *B. THIO, N. A. PELOT, D. CATHERALL, W. M. GRILL;
Duke Univ., Durham, NC

Abstract: Computational models of large myelinated somatic axons have been well characterized. However, the vagus nerve is primarily comprised of unmyelinated C-fiber axons, and the responses of small unmyelinated autonomic axons to stimulation have not been modeled. We implemented a non-linear cable model of an autonomic c-fiber axon containing a complement of ion channels with properties derived from voltage clamp data and ionic pumps with Michaelis-Menten kinetics derived from the concentrations of intracellular Na+ and extracellular K+. In addition to non-linear ionic conductances, we implemented ion accumulation mechanisms in a 30 nm-thick periaxonal space. We used multi-objective particle swarm optimization (PSO) to identify an optimal set (i.e., optimal particle) of ion conductances, maximum pump currents, and intracellular resistance (12 dimensions) such that model responses matched characteristics compiled from in vivo recordings in literature. The PSO was initialized with 30 12-dimensional particles set to random values with realistic bounds. At each generation, each particle's performance was evaluated using the conduction velocity, chronaxie, action potential duration, presence of a long-duration (>500 ms) subnormal period (increased threshold during the recovery cycle), and presence of a short-duration (<50 ms) supernormal period (decreased threshold during the recovery cycle). All nondominated conductance sets influenced the update of the conductance sets of all other particles. The PSO converged in 1005 generations which required 10.5 days on 400 cores. The conduction velocity and chronaxie were largely influenced by the NaV1.7 conductance and intracellular resistance, action potential width was most influenced by NaV1.8 channels conductance, and the recovery cycle dynamics were influenced primarily by the ion accumulation dynamics. The optimized c-fiber model had conduction velocities of 0.8 and 1.6 m/s and chronaxies of 1.43 and 1.08 ms for 0.5 and 2 μm fiber diameters, respectively, which are within the literature ranges of 0.45 to 1.76 m/s for conduction velocity and 0.75 to 1.5 ms for chronaxie. PSO enabled optimization of a non-linear cable model of an autonomic c-fiber axon with responses matching those measured in vivo, and the resulting model provides a valuable tool for analysis and design.

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Poster

615. Neuronal Models of Activity and Disease

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Topic: I.06. Computation/ Modeling/ and Simulation

Support: Post-doc grant ULiege

Title: Modulation of slow gating kinetics of ion channels causes a gradual change in neuron excitability

Authors: *J. A. BROEK[1], G. DRION[2];
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Abstract: The physiology of a neuron can exhibit different kinds of spiking behaviour, which are classified as Type I and Type II excitability. Type I has a continuous gain function in the frequency-current (FI) curve and is therefore able to generate low firing frequencies depending on the strength of the applied current. Type II has a non-continuous FI curve, which reflects the threshold behaviour, i.e. the abrupt move from quiescence to fast spiking. The properties of Type I and Type II have consequences for information processing and computational processes such as thresholding and gain scaling. Excitability types have long been classified based on the type of bifurcation associated to equilibrium points: a saddle-node on invariant cycle (SNIC) bifurcation represents Type I excitability and a Hopf bifurcation a Type II excitability. These bifurcations are often related to the shape of the current-voltage (I-V) curve, where Type II excitability reflects a monotonically increasing I-V curve with one equilibrium, whereas a non-monotonically increasing I-V curve reflects Type I excitability and has three equilibriums. Likewise, both excitability types have been associated to specific phase portrait configurations in reduced neuron models. Here, we analyse how excitability types are affected by neural dynamical properties. In particular, we analyse the influence of timescale separation modification on the type of bifurcation in the situation with three equilibriums, without modifying the I-V curve or the phase portrait. We show that increasing timescale separation leads to the occurrence of a Hopf bifurcation before collision with the saddle, hence changing the excitability type from Type I to Type II. As a consequence, in the singular limit, where timescale separation is infinite, no configuration of a classical phase portrait can lead to SNIC bifurcation, and therefore Type I excitability. However, a SNIC bifurcation that persists in the singular limit can be achieved by incorporating the slow regenerative variable in the classical phase portrait.

Disclosures: J.A. Broek: None. **G. Drion:** None.

Poster

615. Neuronal Models of Activity and Disease

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Program #/Poster #: 615.13/DD50

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSF CAREER 1653080

Title: Computational model of neural recordings in dorsal root ganglia

Authors: *M. KADWANI[1,2], R. D. GRAHAM[1,2], Z. J. SPERRY[1,2], S. F. LEMPKA[1,2,3], T. M. BRUNS[1,2];
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Abstract: Dorsal root ganglia (DRG) are neural tissue bulges outside the spinal cord, where the soma of sensory neurons are clustered. DRG are an attractive target for neural interfacing, such as for monitoring organ or limb state for closed-loop neuroprostheses. A greater understanding of this interface may inform the design of new electrodes and lead to less dependence on animal models. Therefore, we developed a computational model of neural recordings from a microelectrode implanted within the DRG. The first model component was a finite element model (FEM) of a microelectrode implanted within the DRG. We also performed simulations for a point electrode placed within an infinite homogeneous medium. To simulate the membrane currents generated by neurons within the DRG, we created a multicompartment model of an Aβ-fiber neuron (80 µm ellipsoid soma diameter; 11.5 µm peripheral axon diameter, 10 µm central axon diameter, 8.7 µm stem axon diameter). We created three versions of this neuron model: one with a straight initial glomerulus (IG) of the stem axon, one with a slightly curved IG, and one with a highly coiled IG to simulate the tortuous path often observed in anatomical studies. We used a reciprocity-based solution to simulate the microelectrode voltage recordings generated by the Aβ-fiber neuron. We calculated the final voltage recording as the sum of the time-dependent voltages generated by each compartment within the neuron model. The model-based intracellular action potentials (APs) matched those reported in the literature. The FEM-based extracellularly-recorded waveforms were similar in shape to recordings with the point electrode, but with smaller amplitudes. APs near the axons were narrower and APs near the soma were wider. The peak-to-peak voltage (V_{pp}) varied from 5 µV to 400 µV for electrode-to-neuron distances of 150 µm to 5 µm, respectively. V_{pp} was larger than 30 µV (typical *in vivo* noise floor) if the microelectrode was within 25 µm of the axon and if within 150 µm from the soma. For the coiled IG neuron, we observed multi-phasic AP waveforms depending on electrode position, similar to *in vivo* observations. In conclusion, our model was able to predict waveforms and amplitudes similar to those observed experimentally. In future work, we will incorporate additional features, such as additional nearby neurons to simulate background noise and

additional neuron types, to better mimic *in vivo* conditions.
Funding: NSF CAREER 1653080

Disclosures: **M. Kadwani:** None. **R.D. Graham:** None. **Z.J. Sperry:** None. **S.F. Lempka:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Presidio Medical Inc.. F. Consulting Fees (e.g., advisory boards); Presidio Medical Inc.. **T.M. Bruns:** None.

Poster

615. Neuronal Models of Activity and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 615.14/DD51

Topic: I.06. Computation/ Modeling/ and Simulation

Support: DARPA ElecTRx

Title: Anatomo-functional description and computer modeling of topographically organized fiber clusters in the rat vagus nerve

Authors: *M. I. ROMERO-ORTEGA[1], M. A. GONZÁLEZ-GONZÁLEZ[2], A. WELLS[3], A. M. CASSARA[4], N. KUSTER[6], E. NEUFELD[5];
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Abstract: The vagus nerve (VN) connects critical periphery organs with different integrative areas in the brain to maintain homeostasis, and electrical stimulation of the VN has been long recognized to have therapeutic effects. However, the origin and fiber type localization in the VN is poorly understood and electrical stimulation is performed in the entire nerve causing undesirable side effects, including hoarseness and voice alterations resulting from off-target activation of large myelinated axons that innervate the recurrent laryngeal nerve (RLN). Current models of the rat VN are limited by the lack of published data on its ultrastructure organization, and the assumption of homogenous random distribution of all axon types. In this study we evaluated the left cervical VN of 12 adult Sprague-Dawley rats using electron microscopy and observed axon clustering of myelinated fibers. We then utilize custom multi-contact electrode cuffs in the left VN of the rat to restrict the volume of depolarizing stimulation to selectively activate afferent axons, while avoiding efferent motor fibers. Electrical stimulation was performed using 50 μsec biphasic pulses at at 1 Hz and variable pulse amplitudes. Electrophysiological recordings of VN and RLN were processed using Matlab. The compound action potentials evoked by electrodes located either in the left (L-E) or right (R-E) side of the

VN, revealed selective activation of A-alpha or A-beta fibers under certain stimulation conditions. Selective depolarization of A-beta, and A-delta afferents in the proximal VN was achieved, without depolarizing A-alpha fibers innervating the laryngeal muscles. DiI labeling was used in some studies to mark the position of the L-E relative to the position of fibers within the nerve, so that the evoked activity was correlated to the anatomical distribution of axon types near the stimulating electrodes. Significant differences in the RLN/VN activation ratio between R-E and L-E configurations were noted. The newly established anatomical, histological, functional, and electrophysiological data allowed the development of sophisticated computational (coupled electromagnetic-neuronal dynamics) models of superior realism, which can be used to gain mechanistic insights and further optimize the electrode design and stimulation protocols. These novel contributions (implant, nerve characterization, computational model) combine to form a powerful platform for neurological investigations.

Disclosures: M.I. Romero-Ortega: None. **M.A. González-González:** None. **A. Wells:** None. **A.M. Cassara:** None. **N. Kuster:** None. **E. Neufeld:** None.

Poster

615. Neuronal Models of Activity and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 615.15/DD52

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Supported by OIST

Title: Agent based modeling of neural development with NeuroMaC

Authors: *E. DE SCHUTTER, M. KATO;
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Abstract: NeuroMaC was initially developed to simulate how interactions between growing neurons shape their dendritic trees (Torben-Nielsen and De Schutter 2014). It implements a stochastic, agent based representation of growth cones - fronts - in a Python multi-core computing environment to efficiently simulate the concurrent growth of hundreds of neurons. An extensive rewrite and expansion of NeuroMaC now offers additional simulation options, a better user interface and improved performance. Extensive documentation combined with examples and exercises help the novel user to discover the rich modeling environment. Model behavior is defined as a Python module that implements several front methods. Models can be run in jupyter notebooks or as Python processes from the terminal. Cell birth, migration and apoptosis combined with a phenomenological approach to attraction and repulsion by chemical cues allow for simulation of the development of complex neural tissues. Synapses can be established between neurons, causing the intracellular release of signaling molecules. Stochastic

diffusion of signaling molecules inside dendrites or axons can promote their extension or retraction.
We are using NeuroMaC to simulate the development of a small volume of murine cerebellar cortex during the first postnatal weeks. The massive downward migration of thousands of granule cells along Bergmann glia and the growth of granule cell axons - the parallel fibers - combined with the early development of Purkinje cell dendritic trees make the cerebellar cortex a very crowded environment. Investigating how evolution has solved these challenges by detailed simulation improves our understanding of this important developmental stage of the cerebellum and suggests additional experiments.
Torben-Nielsen, B. & De Schutter, E. (2014). Context-aware modeling of neuronal morphologies. *Frontiers in Neuroanatomy:* 8, 92.

Disclosures: E. De Schutter: None. **M. Kato:** None.

Poster

615. Neuronal Models of Activity and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 615.16/DD53

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH Grant R01MH086638

Title: Homeostasis and spreading depolarization in multiscale simulation of in ischemic stroke

Authors: *A. J. H. NEWTON[1,2,3], M. L. HINES[1], W. W. LYTTON[3,4,5], R. A. MCDOUGAL[1,2]; [1]Dept. of Neurosci., [2]Ctr. for Med. Informatics, Yale Sch. of Med., New Haven, CT; [3]Dept. of Physiol. and Pharmacol., [4]Dept. of Neurol., SUNY Downstate, Brooklyn, NY; [5]Dept. of Neurol., Kings County Hosp. Ctr., Brooklyn, NY

Abstract: Ionic homeostasis in neurons is essential for maintaining stable electrophysiological properties and a disruption of homeostasis is a characteristic of several pathologies including ischemia and epilepsy. Ionic homeostasis also provides an additional constraint on model parameters. Modeling and simulation of homeostasis with few ions or single compartment neurons can be analyzed mathematically, however for detailed neuronal morphology with multiple charge carrier a numerical approach is required.
Recent developments and performance improvements in the NEURON (neuron.yale.edu) reaction-diffusion module (rxd) allow us to model multiple relevant concentration in the intracellular and extracellular space. We modeled a morphologically detailed hippocampal pyramidal neuron and combine rxd with evolutionary algorithms (BluePyOpt) to obtain parameters that produce realistic electrophysiological responses while maintaining homeostasis of K^+, Na^+, Ca^{2+}, Cl^- and glutamate. We use this model to simulate spreading depression

following ischemic stroke.
We developed multiscale models of spreading depolarization in ischemic stroke, coupling electrophysiology and intracellular molecular alterations and bulk tissue alterations mediated by tortuous extracellular diffusion. We simulated spreading depolarization by placing biophysically detailed models of pyramidal neurons in the penumbrae, with reduced pump conductances. We used this model to explore the hypothesis that individual neurons show a pattern of susceptibility to damage due to morphology and physiology, such as the surface area to volume ratio or the intracellular calcium dynamics. In morphologically simplified cells, excessive intracellular Ca^{2+} produced greater susceptibility in proximal compared to distal dendrites.

Disclosures: A.J.H. Newton: None. **M.L. Hines:** None. **W.W. Lytton:** None. **R.A. McDougal:** None.

Poster

615. Neuronal Models of Activity and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 615.17/DD54

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Bertarelli Foundation
Wyss Center for Bio and Neuroengineering

Title: A multiscale modeling framework to understand and optimize ultrasound neuromodulation

Authors: *T. LEMAIRE[1], E. NEUFELD[2], S. MICERA[1];
[1]Translational Neural Engin. Lab., Ecole Polytechnique Federale De Lausanne, Lausanne, Switzerland; [2]Computat. Life Sci., IT'IS Fndn., Zuerich, Switzerland

Abstract: *Low-Intensity Focused Ultrasound Stimulation* (LIFUS) emerges as an attractive technology for noninvasive modulation of neural circuits, yet the underlying action mechanisms remain unclear.
We recently developed a *multi-Scale Optimized Neuronal Intramembrane Cavitation* (SONIC) model [1], that goes beyond the complex neuronal intramembrane cavitation excitation theory [2] by offering interpretability in terms of effective channel dynamics, for which a wide range of established neuroscientific approaches exist.
Using this model, we systematically explored the LIFUS parameter space to predict cell-type-specific spiking behaviors in cortical and thalamic neurons, and explained transitions between different behavioral regimes (tonic firing, bursting, silencing...) using a phase-plane analysis of differential variables evolving at quasi-steady state.
Moreover, taking advantage of the resulting reduced computational cost, we developed multi-compartmental representations incorporating the SONIC model to predict LIFUS

neuromodulatory effects at various scales in a more reliable manner. (i) A nanoscale model was used to predict how local intracellular currents mediate a synchronized neural response across a cell membrane having a heterogeneous responsiveness to LIFUS; (ii) morphological-scale models of peripheral axons were used to study the fundamental differences in action potential initiation and propagation in myelinated and unmyelinated fibers upon LIFUS.
This computational approach is part of an effort to build a multiscale simulation framework that couples modeling of LIFUS-neuron interaction with that of acoustic propagation in (personalized) anatomical models. The framework is expected to be valuable in supporting mechanistic investigation, device optimization, and personalized treatment planning.
[1]Lemaire T, Neufeld E, Kuster N and Micera S 2019 *Understanding ultrasound neuromodulation using a computationally efficient and interpretable model of intramembrane cavitation* J. Neural Eng.
[2]Plaksin M, Shoham S and Kimmel E 2014 *Intramembrane Cavitation as a Predictive Bio-Piezoelectric Mechanism for Ultrasonic Brain Stimulation* Phys. Rev. X 4

Disclosures: **T. Lemaire:** None. **E. Neufeld:** None. **S. Micera:** None.

Poster

615. Neuronal Models of Activity and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 615.18/DD55

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Modular software for drift diffusion model tested with striatal neuronal populations

Authors: *E. LARA-GONZALEZ[1], M. DUHNE[2], **M. GARCÍA-MATA**[3];
[1]Univ. Nacional Autónoma de México, Ciudad de Mexico, Mexico; [2]Neurociencia Cognitiva, Inst. De Fisiologia Celular UNAM, Mexico DF, Mexico; [3]Facultad de Ciencias, Univ. Nacional Autónoma de México, Ciudad de México, Mexico

Abstract: Motivation: Cellular transmembranal potential mathematical models are a handy tool for analysis of excitable cell behavior. They allow us to perform experiments in silico to explain transmembrane potential dynamics that can not be done *in vitro* electrophysiologic because of physical or technological limitations. Most of the mathematical models have several equations to model different ionic channels making it difficult to reproduce different types of cells with the exact same model. However, the drift-diffusion model (Herrera-Valdez, 2018) proposes a general equation to describe the transmembranal flux, which describes the traffic through ion channels, pumps or exchangers. This will make the modeling of different cellular kinds easier.Methods: We implemented the drift-diffusion model in python using object-oriented programming paradigm. The development has such a structural organization that allows further updates and upgrades as concurrent programming or graph structure implementation.

Additionally, we created a friendly user interface in pyQt. To test the model whole-cell patch clamp recording of striatal neurons *in vitro* was used. Results: We successfully modeled transmembrane voltage dynamics of spiny projection, fast spiking, and cholinergic murine striatal neurons. We compared the action potential width and amplitude. We found no statistical difference between electrophysiologically recorded and the modeled action potentials for all cell types.Conclusion: Object-oriented programming proved to be an adequate paradigm to model different neurons. The drift diffusion model allows the use of a single equation for different channels. This implementation maximizes its versatility by making the modeling of different neuronal types simple.

Disclosures: E. Lara-Gonzalez: None. **M. Duhne:** None. **M. García-Mata:** None.

Poster

615. Neuronal Models of Activity and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 615.19/DD56

Topic: I.06. Computation/ Modeling/ and Simulation

Support: DFG Project 327654276 (SFB 1315)
DFG Research Training Group GRK1589/2

Title: State-dependent effects of electrical stimulation on populations of excitatory and inhibitory neurons

Authors: *C. CAKAN, K. OBERMAYER;
Technische Univ. Berlin, Berlin, Germany

Abstract: Electrical stimulation of neural populations is a key tool for understanding neural dynamics and developing treatments. To investigate the effects of external stimulation on a basic cortical mass model, we analyse the dynamical properties of a low-dimensional mean-field model of two coupled populations of excitatory and inhibitory adaptive exponential integrate-and-fire (AdEx) neurons with biophysically interpretable parameters and validate the results using large network simulations. Bifurcation diagrams establish a close dynamical relationship between predictions from mean-field theory and the underlying ground truth neural network. The dynamical landscape and all attractors are retained in the mean-field approximation. The diagrams reveal asynchronous up- and down-states, bistable regions and limit cycles corresponding to fast excitation-inhibition oscillations in the gamma frequency range and slow adaptation-excitation feedback loops in the delta range. The effect of an external electrical stimulus critically depends on the current dynamical state of the unperturbed system which itself is determined by the mean inputs to the excitatory and inhibitory populations. External stimuli can cause attractor switching such as turning on and off oscillations. Oscillatory stimuli can

frequency-entrain and phase-lock endogenous oscillations to the external input. We show that these effects can be found in the mean-field approximation as well as in the detailed network model, further underpinning the utility of low-dimensional neural mass models.

Disclosures: C. Cakan: None. **K. Obermayer:** None.

Poster

615. Neuronal Models of Activity and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 615.20/DD57

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Intramural Research Program ZIAMH002798 (clinical protocol 02-M-0321, NCT00047853)

Title: Employing support vector machines to identify functionally distinct fMRI resting state networks

Authors: *R. T. PHILIPS[1], S. TORRISI[2], M. ERNST[1], C. GRILLON[1];
[1]NIH, Bethesda, MD; [2]UC Berkeley and Advanced MRI Technologies, LLC., Berkeley, CA

Abstract: Functional connectivity (FC) is defined as the temporal similarity between fMRI signals from distinct brain regions. FC has been shown to reflect anatomical connectivity. However, traditional FC analyses have a few limitations, including: 1. Temporal delays between signals (order of seconds) are ignored; 2. Methods that distinguish important brain regions and networks with distinct FC are inadequate. Here, we propose a new approach to address these limitations, utilizing dynamic time warping (DTW) within a machine learning framework. As a proof of concept, the cortical FC patterns of two spatially nearby but functionally distinct subcortical regions, namely the Substantia Nigra Pars Compacta (SNc) and Ventral Tegmental Area (VTA), are explored. Whole brain resting state fMRI scans from 40 healthy participants, collected using a Siemens Magnetom 7T MRI (32-ch head coil, TR of 2.5s, TE=27ms, 1.2mm isotropic, multiband factor 3), are preprocessed and aligned to a standard template. Two subcortical regions of interests (ROIs) and 360 cortical target parcels are defined based on the CIT168 Atlas and the Glasser HCP Atlas, respectively. The correlations between the each of the 2 subcortical ROIs and the 360 cortical parcels are computed using: 1. standard Pearson correlations (PC), 2. DTW followed by Pearson's correlations (DTW-PC). These correlations serve as inputs to a Support Vector Machine (SVM). The separability of the SNc-cortical and VTA-cortical networks is assessed using Leave One Out Cross Validation (LOOCV). In addition, SVM-Recursive Feature Elimination (RFE) yields the most important features (cortical parcels). Results reveal that the SVM-LOOCV separates the SNc-cortical and VTA-cortical networks with 68.75% and 96.25% accuracy on using PC and DTW-PC, respectively. The top 20

SVM-RFE features (cortical parcels) are sufficient to account for the accuracy levels. Only half of these features survive the Bonferroni-Holm correction with PC inputs; whereas, all the 20 survive with DTW-PC inputs ($p<0.05$). Dynamic time warping based functional correlations in conjunction with recursive feature elimination, within a support vector machine framework, appears to be a viable strategy to separate brain networks and identify important ROIs.

Disclosures: R.T. Philips: A. Employment/Salary (full or part-time):; NIMH/NIH. **S. Torrisi:** A. Employment/Salary (full or part-time):; UC Berkeley and Advanced MRI Technologies, LLC. **M. Ernst:** A. Employment/Salary (full or part-time):; NIMH/NIH. **C. Grillon:** A. Employment/Salary (full or part-time):; NIMH/NIH.

Poster

615. Neuronal Models of Activity and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 615.21/DD58

Topic: I.06. Computation/ Modeling/ and Simulation

Title: A comprehensive biophysical model of substantia nigra pars compacta cells for understanding Parkinsonian neurodegeneration

Authors: *V. R. MUDDAPU, S. V. CHAKRAVARTHY;
Dept. of Biotech., IIT Madras, Chennai, India

Abstract: Parkinson's disease (PD) is the second most prominent neurodegenerative disease around the world. Although it is known that PD is caused by the loss of dopaminergic cells in substantia nigra pars compacta (SNc), the decisive cause of this inexorable cell loss is not clearly elucidated. We hypothesize that "Energy deficiency at sub-cellular/cellular/systems level can be a major cause for SNc cell loss in PD." Here, we propose a comprehensive computational model of SNc cell which helps us to understand the pathophysiology of neurodegeneration in PD. The proposed model includes a rich vein of molecular dynamics related to SNc neurons such as ion channels, active pumps, ion exchangers, dopamine turnover, energy metabolism, calcium buffering mechanisms, alpha-synuclein aggregation, Lewy body formation, reactive oxygen species (ROS) production, levodopa uptake, and apoptotic pathways. The proposed model was developed and calibrated based on experimental data. The influx of glucose and oxygen into the model is controlled, and the consequential ATP variation is observed. Apart from this, the dynamics of other molecular players (alpha-synuclein, ROS, calcium, and dopamine) known to play an important role in PD pathogenesis are also studied. The aim of the study is to see how deficits in supply of energy substrates (glucose and oxygen) lead to a deficit in ATP, and furthermore, deficits in ATP are the common factor underlying the pathological changes in alpha-synuclein, ROS, calcium, and dopamine. The model with its biophysical framework shows four regimes of ATP dynamics by varying glucose and oxygen: (A) Unperturbed (no change in

Basal ATP Concentration (BAC)), (B) adaptation (initial drop and a subsequent return to initial BAC), (C) no adaptation (initial drop and stabilized at a lower BAC) and (D) oscillating (BAC fluctuates). The model suggests that hypoglycemia plays a more crucial role in leading to ATP deficits than hypoxia. We believe that the proposed model provides an integrated modeling framework to understand the neurodegenerative processes underlying PD.

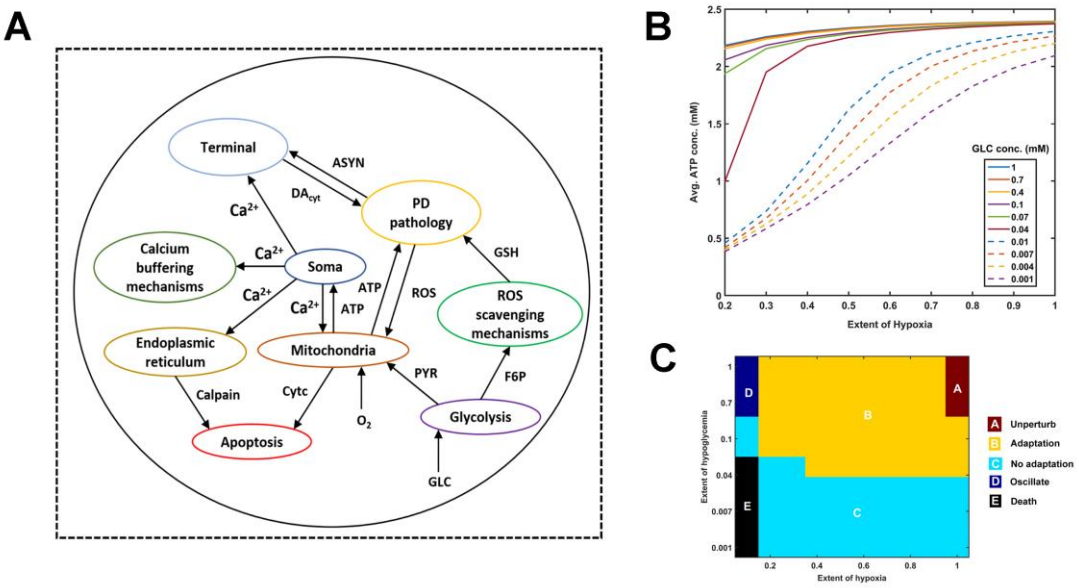

Figure 1 (A) Molecular pathways included in the proposed model of SNc neuron (B) Profile of available ATP for different glucose concentrations across the extent of hypoxia (C) Different model response regimes for the different extent of hypoglycemia and hypoxia.

Disclosures: V.R. Muddapu: None. **S.V. Chakravarthy:** None.

Poster

615. Neuronal Models of Activity and Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 615.22/DD59

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Computational modeling of neural activation during transcranial photothermal stimulation

Authors: *M. BHATTACHARYA, A. DUTTA;
Univ. at Buffalo, Buffalo, NY

Abstract: INTRODUCTION Transcranial Near Infrared Stimulation(tNIRS) has proved to be a powerful tool to modulate cortical excitability. Moreover, photothermal stimulation can be a powerful tool to map brain-wide networks [1]. We developed a computational model to investigate photothermal effects of tNIRS. METHODS Tetrahedral mesh was generated through Delauney Tetrahedralization from the MRI-based digital phantom of Colin27 head atlas. The computation of Finite Element Analysis on the tetrahedral mesh of the head model was performed to solve Radiative Transfer Equation by Diffusion Approximation at near-infrared wavelengths (630nm, 700nm, 810nm) coupled with Bioheat Transfer due to absorbed optical power. We stimulated at the Cz position at the scalp surface using a point source of light of power density 0.5mW/cm^2[2]. We derived the temperature profile across the layers of scalp, skull, CSF, Gray Matter, and White Matter along a line through Cz. To understand cortical excitability alterations, Hodgkin Huxley model of the pyramidal neurons needs to be simulated. RESULTS Temperature change at the gray matter did not show any significant increase to cause any neuronal excitability. We see a change of temperature of around 0.04 degree C, whereas, a change of around 1-2 degree C is suggested for changes in excitability [3]. DISCUSSION Longer wavelengths will be better choice for photothermal stimulation due to lower scattering and stronger water absorption.

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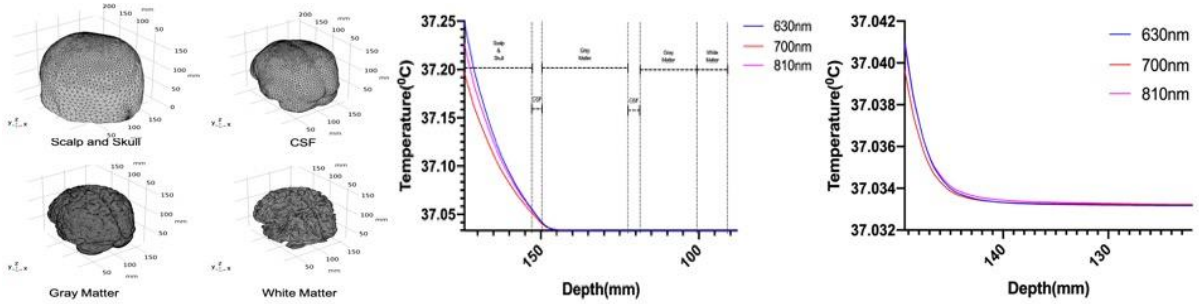

Disclosures: M. Bhattacharya: None. **A. Dutta:** None.

Poster

616. Network Modeling and Application

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 616.01/DD60

Topic: I.06. Computation/ Modeling/ and Simulation

Support: AFOSR FA9550-18-1-0054
Canada Research Chair Program 950-231659

NSERC RGPIN-2016-05352

Title: Multiplicative modulations enhance unique hue representation in V4

Authors: *P. MEHRANI, A. MOURAVIEV, **J. K. TSOTSOS**;
Electrical Engin. and Computer Sci., York Univ., Toronto, ON, Canada

Abstract: Which region in the brain represents unique hues is unknown. We introduce a hierarchical model inspired by neural mechanisms in the visual system for local hue representation and with computational simulations suggest that cells in V4 have the capacity to encode unique hues. Our network of single-opponent color and hue-selective cells differs from that of [1, 2] as it models cells in each of LGN, V1, V2, and V4 areas and explicitly reveals how the contributions of each participating area can lead to a hue encoding. Our network receives cone activations as input and gradually increases nonlinearities in terms of cone responses as observed by [3]. Specifically, single-opponent LGN responses are obtained by linearly combining cone activation. Half-wave rectification keeps V1 tunings similar to those of LGN cells [4] while nonlinear in terms of cone inputs. De Valois et al. [1] suggested that additive/subtractive modulation of cone-opponent cells with S-opponent cell responses rotates the cone-opponent axes to red-green and blue-yellow directions. To achieve this rotation in V2, in addition to single-opponent cells, we propose multiplicative modulations of V1 L- and M-opponent cell activations with V1 S-opponent responses. Multiplicative modulations increase nonlinearities and mix color channels. Moreover, unlike additive/subtractive modulations with little impact on tuning bandwidths, multiplicative modulations reduce tuning bandwidths. Finally, V4 responses are obtained by linearly combining V2 activations with weights determined based on tuning peak distances of V2 cells to the desired V4 neuron tuning peak. Our results indicate that multiplicatively modulated V2 cells play an important role in the representation of hues along intermediate directions in the MacLeod-Boynton diagram [5]. Similarly, these cells have substantial input weights compared to single-opponent V2 cells to V4 neurons selective to unique green and blue hues. Moreover, we observed a gradual decrease in distance of tuning peaks to unique hue angles reported by [6] from our model LGN to V4. Our results show that responses of our network neurons resemble those of biological color cells.
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Disclosures: P. Mehrani: None. **J.K. Tsotsos:** None.

Poster

616. Network Modeling and Application

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 616.02/DD61

Topic: I.06. Computation/ Modeling/ and Simulation

Title: The BEL model, a literature data-based approach with a new concept of target identification

Authors: *K. BORNEMANN[1], M. VON HEIMENDAHL[1], N. LAWLESS[1], T. SCHWEIKARDT[1], A. EMON[2], D. DOMINGO-FERNANDEZ[2], S. SPRINGSTUBBE[2], M. HOFMANN-APITIUS[2], B. HENGERER[1];
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Abstract: Identifying new targets for therapeutic interventions is becoming more challenging. In order to manage an increasing portfolio of biomedical literature based data, we used a big-data approach, tied with an understanding of mechanistic aspects and the molecular basis of depression, a psychiatric disease. We have picked the Biological Expression Language (BEL) model for the identification of new targets and developed a prototype model of a psychiatric condition, focused on anhedonia, a core symptom domain of depression, combined with projection models and DTI/MRI data. We generated a matrix (platform), allowing the identification of new targets via novel interacting neuronal circuits in their functional context and environment. The core of the platform is a connectivity network viewer, consisting of nodes and edges (links, relations), which contains the relevant information from biomedical literature (PubMed) comprising citations, evidence and annotations, thereby revealing the linkage between nodes. The major challenge of this project was to define appropriate key and search terms to handle the huge number of potential abstracts and obtain the most relevant publications to code them as BEL language and integrate to the model. Our platform is composed of two additional modules, a brain projection and human brain connectome viewer, derived from functional neuroimaging of healthy persons. Both modules enable us to link maps of brain projections and connections with neuronal circuit functions from our core module, thereby revealing novel interaction partners that may otherwise have gone unnoticed. Our BEL model relies on the current PubMed knowledge base and requires regular new data entering to keep it up to date. In summary, we have generated a prototype of a combined gene to phenotype network, aimed at modeling a symptom domain, hosted in a matrix tool to identify new targets. The BEL model is also augmentable to other symptom domains and therapeutic indications.

Disclosures: **K. Bornemann:** None. **M. von Heimendahl:** None. **N. Lawless:** None. **T. Schweikardt:** None. **A. Emon:** None. **D. Domingo-Fernandez:** None. **S. Springstubbe:** None. **M. Hofmann-Apitius:** None. **B. Hengerer:** None.

Poster

616. Network Modeling and Application

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 616.03/DD62

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH R01 MH069456
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NSERC PDF
SSHRC Banting PDF

Title: Model-based multivariate mapping of the visual hierarchy with image synthesis

Authors: *J. D. WAMMES[1], D. L. K. YAMINS[3], K. A. NORMAN[4], N. B. TURK-BROWNE[2]; [2]Psychology, [1]Yale Univ., New Haven, CT; [3]Stanford Univ., Stanford, CA; [4]Princeton Univ., Princeton, NJ

Abstract: Given the dramatic individual differences in neuroanatomy, the use of cognitive tasks as functional localizers remains an indispensable tool for neuroscientific inquiry. Localizers allow regions of interest for a particular cognitive function to be identified independent of both the experimental question and anatomical landmarks. Here, we present a novel functional localization approach, which attempts to employ features from convolutional neural networks (CNNs) to exhaustively map levels of complexity along the visual hierarchy. Our approach synthesizes sets of images — using a combination of deep dreaming and feature correlation optimization — wherein the features at all model layers match an experimenter-specified similarity structure, operationalized as the correlations between patterns of unit activity. In preliminary work, our aim was to target higher-order object-selective regions such as lateral occipital (LO) and inferior temporal (IT) cortex, by manipulating higher model layers. Pairs of images were synthesized using a CNN, pre-trained for object recognition. The pairs were matched in similarity at early model layers, while varying in later model layers coding for higher-order visual features. We validated the approach behaviorally by instructing participants to sort the synthesized images according to visual similarity. Model-defined visual similarity was significantly correlated with the resulting pairwise distances. We then selected eight pairs of images, varying parametrically in higher model-layer similarity, and participants viewed the images while being scanned using high-resolution fMRI. Patterns of voxel activity were extracted for each of the 16 images. A searchlight analysis revealed a reliable cluster in LO where neural pattern similarity tracked our predefined model similarity. Together these results

indicate that we were able to synthesize images to elicit a particular representational structure in a higher-order visual region. Although this image set manipulated similarity at only one layer and across only two images at a time, it is possible to synthesize entire representational spaces that are unique at every model layer. We are now conducting follow-up studies using fMRI to determine whether these synthesized representational spaces can be used to localize each consecutive level of visual complexity using just one set of images.

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Poster

616. Network Modeling and Application

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Program #/Poster #: 616.04/DD63

Topic: I.06. Computation/ Modeling/ and Simulation

Title: An ultra-low complexity of the transcriptional profile of the human brain

Authors: *J. HUA, Z. YANG, T. JIANG, S. YU;
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Abstract: The transcriptional profile of the human brain is a complex structure with the orchestrated expression of tens of thousands of genes. Previously we demonstrated that the complexity of genes' expression patterns can be reduced from exponential ($\sim 2^N$) to polynomial ($\sim N^2$). In this work, we aimed to examine if an even lower dimensional space with linear ($\sim N$) complexity can represent the transcription patterns observed in the human brain. To this end, we analyzed microarray transcription data from Allen Institute, obtained from 6 subjects, in over 3000 sites distributed across the human brain cortex. Specifically, three properties of the gene expression pattern were utilized: 1) the mean expression rate of individual genes (MR), i.e., the proportion of brain regions in which a specific gene expresses actively; 2) the distribution of population expression rate (PR), i.e., the proportion of actively expressing genes in a specific brain area; and 3) the coupling of each gene to the whole genome (CG), which measures the correlation between single gene's expression and that of the whole genome. We found that the three properties can accurately predict the transcription profile of the whole genome, which reduced the complexity of the transcriptional profile of human brain to ~N. In addition, we also found that CGs played an important role in predicting the pair-wise interaction between genes and were diverse across different genes. High/low CG genes, i.e., genes strongly/weakly coupled with the whole genome, tended to have different biological functions, with high CG genes more involved in signal transduction and low CG genes more associated with DNA binding. Together, we revealed an ultra-low dimensional space that determines the transcriptional profile of the

human brain, which provides new insights into how transcription of tens of thousands of genes is orchestrated in the human brain.

Disclosures: **J. Hua:** None. **Z. Yang:** None. **T. Jiang:** None. **S. Yu:** None.

Poster

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Conicyt Fellowship 21140603 (SC)
Conicyt Grant FB0008 (PO)
ICM-MINECON P09-022-F

Title: Contribution of noise, chaos and network topology to the emergence of multi-stable dynamics in neuronal networks

Authors: ***P. ORIO**[1,2], C. CORONEL[2], J. PALMA-ESPINOSA[2], M. GATICA[2], S. CASTRO[2]; [1]Inst. de Neurociencia, Univ. De Valparaiso, Valparaiso, Chile; [2]Ctr. Interdisciplinario de Neurociencia de Valparaiso, Univ. de Valparaiso, Valparaiso, Chile

Abstract: Multi-stable behavior of the brain dynamics is actively being studied as a landmark of ongoing ('resting') cerebral activity, reported in both fMRI and M/EEG recordings. This consists on a continuous switching between different partially synchronized states, in the absence of external stimuli. Multi-stability is thought to be an important mechanism for dealing with sensory novelty and to allow for efficient coding of information in an ever-changing surrounding environment. There is some understanding about how network topology, connection delays and noise can contribute to building this dynamic, but a systematic exploration of the interplay between these factors is still missing. We are studying the emergence of dynamical Functional Connectivity (dFC) in simulations of biophysically inspired neurons and neural masses, characterizing how local chaotic and stochastic influences the switching between different network states, and how this interacts with topological features. We calculate the Functional Connectivity (FC) matrices that describe the pair-wise phase synchronization or correlation in a moving window fashion. Then, the FCs are compared by angular distance to obtain the Functional Connectivity Dynamics (FCD) matrix and clustered into states. In deterministic simulations, the networks show multi-stable dynamics in a certain range of global connectivity strength and. When the network is composed of nodes that have chaotic dynamics, we observe a richer dFC with more and more diverse states. We also characterized the multi-stable dynamics when the networks are, in addition to chaotic, subject to ion channel stochasticity in the form of

multiplicative (channel) or additive (current) noise. Moderate noise can enhance the multi-stable behavior that is evoked by chaos, resulting in more heterogeneous synchronization patterns, while more intense noise abolishes multi-stability. In networks composed of nonchaotic nodes, moderate noise can induce multi-stability in an otherwise synchronized, nonchaotic network. Finally, we are studying how the effects of noise and chaos are maintained under different network topologies, including the Structural Connectivity of the Human Connectome. Preliminary results show that Small-World Networks sustain the multi-stability in a larger global coupling range. However, the Human Connectome contains a core of nodes that facilitate the appearance of multiple states, enabling a richer dynamic. Our results aim towards understanding the origins of the dFC, enabling a fine tuning of the dynamics in artificial systems and dealing with neuropathologies associated to the disruption of dFC.

Disclosures: P. Orio: None. **C. Coronel:** None. **J. Palma-Espinosa:** None. **M. Gatica:** None. **S. Castro:** None.

Poster

616. Network Modeling and Application

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Program #/Poster #: 616.06/DD65

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSF Grant DMS-1517828

Title: Semibalanced networks and inhibitory plasticity implement nonlinear computations

Authors: *C. BAKER[1], R. ROSENBAUM[2];
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Abstract: Recent work in modern computational neuroscience has focused on replicating the properties of artificial neural networks (ANNs) using purely biophysical principals. Many of these studies prioritize adapting ANN architectures to account for spiking dynamics and firing rates as a first top-down approach to making biologically realistic ANNs. Instead, we take a bottom-up approach starting from a biologically realistic network of sparse, recurrently connected adaptive exponential integrate-and-fire neurons (AdEx) in an asynchronous irregular state with balanced excitation and inhibition. We show how simple ANN architectures may be explicitly instantiated in terms of subpopulation averaging, and how more complex self-generating activation functions can arise from strong heterogeneous external input patterns. These patterns naturally lead to inflation in the number of non-spiking neurons, but maintain balance within the spiking portion of the population, hence leading to a semi-balanced operational state. We then show how combining these networks with well-established inhibitory synaptic plasticity (ISP) stabilizes the firing rate activity of the network in response to familiar

stimuli, as well as creating a mechanism of surprise detection.
For comparative analysis, we show how to utilize these methods to solve classification problems involving nonlinear computations such as the exclusive OR (XOR) operator, radial basis transformations, as well as their analogues in higher-dimensional spaces. We then hedge the performance of our biological networks against true ANNs with identical numbers of computing units and layer structure. Our comparison shows that such biologically realistic networks can indeed impart high-quality nonlinear computational power on par with fully-connected ANN structures.

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Poster

616. Network Modeling and Application

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Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSFC 31700951
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JCYJ 20170818110022721

Title: Hierarchical levels of predictive coding play different roles in second-language learning

Authors: *Z. TANG[1], K. ZHOU[2], W. HE[3], M. XU[1];
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Abstract: A considerable amount of literature has indirectly investigated the link between language learning and predictive coding accounts through beta and gamma oscillatory neural dynamics. However, it remains unclear as to how predictive coding processing directly affect language learning, and no previous study has investigated the different impact of predictive coding processing between first-language learning (Chinese) and second-language learning (English). To answer these questions, we adopted behavioral measure (associative learning task) and computational modeling in primary school children (n = 67) in the present study. Behavioral measurements indicated that the higher second-language learning level, the bigger the surprise, but the correlation of first-language learning level and surprise were not significant. A hierarchical Bayesian model suggested a positive correlation between the perceptual parameter ω_2 at the second level and second-language learning level, but not first-language learning level. The perceptual parameter ω_3 at the third level were not significantly correlated with those two languages learning level. To further examine the effect of predictive coding processing, the subjects were divided into high and low achievement groups according to their second-language

learning level. We found that the low achievement group updated the learning rate at the third level more than the high achievement group. This result is similar to that of autism study. This study offers insights into the behavioral, algorithmic mechanisms in the relationship between predictive coding processing and language learning and the different impact of predictive coding processing between those two languages learning.

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Poster

616. Network Modeling and Application

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Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 616.08/DD67

Topic: I.06. Computation/ Modeling/ and Simulation

Title: An autoregressive mathematical model for reproducing neuronal responses with respect to various types of spiking

Authors: *S. HIRAI[1], A. MASAOKA[3], T. KOHAMA[2];
[1]Kindai Univ., Wakayama, Japan; [2]Kindai Univ., 930 Nishimitani, Kinokawa, Wakayama, Japan; [3]Tamagawa Univ., Machida, Japan

Abstract: Higher-order brain functions such as visual cognition are extremely complex. Recent studies have shown that constructive approaches help understand such brain mechanisms. Masaoka & Kohama described a neuron network model that reproduces the attentional modulation in several brain regions using an autoregressive mathematical representation (Masaoka & Kohama, 2018). This model is configured with several functional units that correspond to specific brain regions. These regions are constructed by networks of many individual neurons. However, the Masaoka & Kohama model is a macroscopic expression of the regional brain activity and does not include individual neuronal responses. In this study, we proposed a modified Masaoka & Kohama model to reproduce various types of spiking of individual neurons that could share mathematical expressions between macroscopic and microscopic brain functions. We modified the Masaoka & Kohama model for the following three functions: (1) delay in the connection between neurons, (2) self-inhibition to reduce the firing rate of spikes, and (3) spiking probability at a certain time, which controls the firing rate of each neuron. We compared the output of our model to that of the Izhikevich model, which shows high reproducibility of neuronal responses. The results showed that our model sufficiently reproduces the various spiking responses of neurons. The responses of the proposed model were compared to the outputs of the Izhikevich model (Izhikevich, 2003), which showed high reproducibility of neuronal responses with respect to the following types of spiking: regular, fast, low-threshold, intrinsically bursting, and chattering. The results showed that the proposed model reproduced the

outputs of the Izhikevich model, which suggested that our model was also able to reproduce the various types of neuronal responses.

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Poster

616. Network Modeling and Application

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Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH R01 DC014367
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Title: A rapid online learning network derived from biological olfaction

Authors: *A. BORTHAKUR[1], T. A. CLELAND[2];
[1]Computat. Biol., [2]Psychology, Cornell Univ., Ithaca, NY

Abstract: The mammalian olfactory system learns from very few examples, presented in unpredictable online sequences, and then recognizes these learned odors under conditions of substantial interference without exhibiting catastrophic forgetting. Moreover, it achieves this performance despite encountering odorant stimuli at widely differing concentrations and in unpredictable backgrounds. This combination of properties - particularly the capacity for rapid, online, lifelong learning - to date has not been matched by artificial systems. We here present a spike timing-based network model based on the architecture and functionality of the mammalian olfactory bulb that exhibits rapid, online learning of arbitrary high-dimensional input vectors (such as odorants) and, based on very small training sets, recognizes and classifies test inputs across concentrations and in the presence of substantial interference. A limitation of conventional computational neuroscience modeling in this context is that networks typically are presented with problems that are already recognized, thereby neglecting the potential problem of overfitting. To counter this, we tested the network with data gathered from physical sensor systems, including gas sensor arrays (machine olfaction), hyperspectral cameras, and the acoustic features of anuran calls. These datasets include challenges such as sensor drift, hierarchical classifications, unknown within-groups variance, changing environments, and unpredictable odorant concentrations. To enable a single instantiated network to perform well under these diverse conditions - a challenge termed “learning in the wild” - we developed a series of preprocessors and heterogeneities that condition diverse sensory inputs into a regularized statistical structure. Interestingly, one critical signal conditioning step depended on the indirect

afferent excitation of mitral cells via external tufted cells; this network motif may present a solution to a previously unrecognized sensory sampling problem in the biological system. Thus, in addition to its performance characteristics as an artificial system, this multi-layer network serves as a computational model embedded in the wild, enabling assessment of the in vivo utility of fast oscillatory dynamics, spike timing regulation, and the architectures of olfactory bulb network connectivity and plasticity motifs.

Disclosures: **A. Borthakur:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Provisional Patent 8631-01-US. **T.A. Cleland:** 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.; Intel INRC Research Grant. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Loihi access (cloud server, hardware loan). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Provisional Patent 8631-01-US.

Poster

616. Network Modeling and Application

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 616.10/DD69

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Exploring the redundancy of resting-state functional network connectivity

Authors: *K. M. OUDYK, Z. QI, R. MARKELLO, E. DUPRE, B. MISIC, J. POLINE; Neurol. and Neurosurg., McGill Univ., Montreal, QC, Canada

Abstract: INTRODUCTION
Investigating the features of resting state networks can help elucidate the functional organization of the brain. Here, we explore the redundancy of resting state networks, in order to determine whether there is redundancy and if so, what is the nature and location of the redundancy.
METHODS
To this end, we applied the Yeo resting-state functional networks [1] to functional Magnetic Resonance Imaging (fMRI) on 69 subjects [2]. We calculated the mean functional connectivity of each set of within- and between-network connections (from now on, 'connections'), and then explored the predictability and predictive role of each connection using general linear models with leave-one-out prediction on connections.
RESULTS AND DISCUSSION
Within-network connections were generally better predicted by between-network connections than by other within-network connections. Further, we found strong reciprocality in the

predictive roles of pairs of connections, that is, connection AB's role in predicting CD was similar to CD's role in predicting AB. However, this reciprocality decreased with increasing strength of the predictive roles. Further, reciprocality was related to the nature of the pair of connections: to whether the pairs share a network and whether the connections are within- or between-network connections. For example, a network's connection to another network was more predictive of it's within-network connectivity than vice versa. This was particularly the case for some connections between higher- and lower-level networks and connections within lower-level networks. For example, the dorsal attention & visual networks' connection was more predictive of the visual-visual within-network connection than vice versa. This top-down resemblance will be discussed in the context of other known characteristics of the resting state networks.

REFERENCES
[1] Yeo et al. (2011). *Journal of Neurophysiology, 106*(3).
[2] Misic et al. (2015). *Neuron 86*(6).

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Poster

616. Network Modeling and Application

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Topic: I.06. Computation/ Modeling/ and Simulation

Support: NRF grant 2017R1C1B5076731

Title: Deep learning based activity recognition of daily livings with wearable sensors for stroke survivors and non-disabled controls

Authors: *S. KIM[1], Y. SHIN[1], S.-A. CHOI[1], J. LIM[2], Y. OH[3];
[1]Physical Therapy, Jeonju Univ., JeonJu, Korea, Republic of; [2]Dankook Univ., Youngin, Korea, Republic of; [3]Neurosci., Samsung Electronics, Suwon, Korea, Republic of

Abstract: Individuals with stroke often show decreased use of the more-affected arms even if they have capability to use them. Recently, to assess real-world use of the more-affected arm, wearable sensors such as accelerometers or mobile devices have been widely used, and the success of these wearable devices depends on accuracy of recognizing daily activities of individuals with stroke. Previous research on human activity recognition has suffered from inaccuracy and inability to generalize a trained model due to various factors, such as insufficient data and not fine-controlled design of activities that often includes only gross movements, such as walking, jumping, or sitting. Here in this study, we attached five inertia measurement units on

subjects' upper extremity and trunk, and collected data from thirty young non-disabled subjects and ten individuals with stroke while they performed eighty daily activities of living including washing dishes, folding tower, and applying make-up lotions, etc. Each activity was segmented and labeled manually, and then the labeled data was trained in deep-learning based models for activity classification. We applied techniques to improve cross-subject generalization including data augmentation and transfer learning. Our model showed that applying deep learning methods improves accuracy of activity recognition of daily living for both non-disabled subjects and stroke survivors. Our work can be applied to generate a daily and/or weekly activity profile of patients, analyze patterns of habitual use of the upper extremity in post-stroke, and provide online visual or tactile feedback if they do not use their more-affected arms and hands for various daily activities.

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Poster

616. Network Modeling and Application

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Program #/Poster #: 616.12/DD71

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Biophysical model of IL-BLA network to study DBS-induced changes in theta coherence

Authors: *Z. CHEN[1], Z. CHEN[2], F. FENG[1], E. BLACKWOOD[3], M.-C. LO[3], A. S. WIDGE[3], S. S. NAIR[1];
[1]Electrical & Computer Engin., [2]Electrical Engin. and Computer Sci., Univ. of Missouri Columbia, Columbia, MO; [3]Psychiatry, Univ. of Minnesota, Minneapolis, MN

Abstract: Neurostimulation is increasingly used as a treatment for neuro-psychiatric disorders. This direct brain intervention is thought to function at a network level. From invasive deep brain stimulation (DBS) to low-energy interventions such as transcranial electrical stimulation, applying energy to a brain region changes not just that target, but a broad network of regions coupled to the target. Further, a major effect of stimulation appears to be changes in neural synchrony, i.e. the coordinated firing of neural ensembles within and between brain regions. Synchrony is often reflected in the presence of oscillatory activity in the electro-encephalogram or local field potential (LFP), in consistent oscillatory phases (coherence) between regions, and nesting of oscillations (cross-frequency coupling) within regions.
The Widge laboratory recently demonstrated stimulation approaches that specifically affect networks. Electrical pulse sequences were shown to increase or decrease both frequency-limited coherence and broad-band synaptic connectivity between brain regions, without changing oscillatory power or other intrinsic features of the individual regions. The effects are repeatable within and across subjects and lasted for hours after stimulation offset.

We developed a scaled down 1680-cell detailed biophysical computational model of the basolateral amygdala (BLA) and the infralimbic cortex (IL) using biological estimates of connectivity and synaptic neurophysiology. Background input is used to match baseline *in vivo* firing rates and LFP. A module for realistic electrical stimulation is being developed for incorporation into the overall *in silico* framework. As a parallel study, plasticity is selectively 'dialed-in' into suitable model IL and BLA synapses to mimic stimulation effects and explore post-stimulation synaptic weight configurations that might replicate *in vivo* post-LFP data. The model can thus assist with screening of multiple hypotheses related to the contrasting effects of *in vivo* stimulation on synaptic potentiation and on inter-regional theta coherence between IL and BL. Preliminary results indicate that modest changes in synaptic weights between excitatory IL and BLA connections can explain the alteration of *in vivo* single-pulse evoked potential response (ERP) in BLA from stimulation in IL. However, potentiation of solely excitatory model synapses in IL and BL could not reproduce the changes in theta coherence found post-stimulation in *in vivo* studies. This suggests that differential plasticity, including of the inhibitory type may be needed, and a systematic evaluation of such scenarios is the focus of on-going studies.

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Poster

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Topic: D.09. Multisensory Integration

Support: NIH EB000809
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Title: *In vivo* swine model for developing and validating acoustoelectric brain imaging: Towards noninvasive, real-time 4D electrical brain mapping

Authors: C. WILHITE, A. ALVAREZ, A. BURTON, C. PRESTON, D. MUSTACICH, A. FUGLEVAND, K. GOTHARD, S. COWEN, ***R. S. W. WITTE**;
Univ. of Arizona, Tucson, AZ

Abstract: Our vision is to develop a noninvasive technique for electrical mapping of the human brain at higher resolution than electroencephalography. Acoustoelectric (AE) brain imaging (ABI) uses pulsed ultrasound to transiently modulate tissue resistivity and can be used to map current densities in 4D and at high spatial and temporal resolutions (millimeter, millisecond).

This study describes a setup for developing and validating ABI in the somatosensory cortex of swine *in vivo*. Following craniotomy, the right or left snout was electrically stimulated (100 µs pulse at 0.5 Hz, 1-15 mA) using two, horizontally spaced needle electrodes (2-3 cm separation) while evoked activity across the contralateral rostrum somatosensory area was mapped with a 16-channel electrocorticography array. The stimulating electrode pair was repeatedly inserted along the dorsoventral axis of the snout (1 cm increments, 5 sites) to create a somatotopic map of activation across the cortical rostrum area. Surface electrophysiological mappings revealed strong evoked potentials (0.2-0.9 mV peak) that were spatially confined (5-55 mm^2 FWHM) to the area of cortex represented by the receptive field of the stimulation site. Consistent with similar topographic studies, dorsal to ventral stimulation of the snout corresponded to a caudal to rostral progression of activation across the rostrum somatosensory cortex. In a separate experiment, evoked EEG signals were also detected across the skull and scalp. We then integrated our custom ABI platform with ultrasound transducer (0.6 MHz) placed over somatosensory cortex to generate AE signals during snout stimulation for current density reconstruction. ABI displayed concentrated current densities at the rostrum somatosensory area after snout stimulation with spatial and temporal correlations between evoked potentials and AE signals. Using this model, we are capable of evoking robust, scalable, and spatially selective neuronal currents in pigs for quick and reliable *in vivo* testing of ABI in large animals. This initial study (n = 4 pigs) is an important step towards validating ABI for noninvasive, high-resolution electrical mapping of the human brain to help diagnose, monitor, and treat a variety of neurological conditions with electrophysiological signatures.

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Poster

616. Network Modeling and Application

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Program #/Poster #: 616.14/DD73

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Human brain-to-brain entanglement states during eye contact

Authors: *R. LEE;
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Abstract: INTRODUCTION: Human eye contact induces mutual perceptions and mentalization [1]. Such interactions may yield the correlated dyadic brain states. Some of these states may only co-exist in the dyadic minds - the state changes in one brain result in simultaneous changes in another. Although the monadic perspectives of eye contact have been

widely studied, its dyadic perspectives of the co-dependent brain-states just emerged recently [2]. Computationally speaking, these dyadic brain states may or may not be decomposed to two monadic brain states. Borrowing a concept from quantum communication [3], these non-decomposable states may represent bi-partite entanglement states. **METHOD**: To describe a dyadic fMRI experiment [4] in quantum formation, two individual brain's correlation matrices among their activated parcellates can be orthogonalized by PCA and form two Hilbert spaces (A and B) respectively. The Hilbert space C for the coupled brains can be generated from the tensor product of the A and B. Meanwhile, the overall dyadic activation can be further decomposed into independent components which represent different communication channels during eye contact. For each channel, the density matrix of dyadic brains was empirically derived from the distance correlation matrix of the time series of dyadic activation vertices in Hilbert space C. Based on each channel's density matrix, (1) its quantum discord [3] can be computed; (2) its quantum computational circuits can be modeled using Monte Carlo method. **RESULTS:** As the average results from 19 dyadic datasets, the ten channels' quantum discords are 0.0, 0.82, 0.8, 2.3, 0.44, 1.28, 1.16, 1.34, 0.05, and 0.73 qubit respectively. Also, the circuit model in one channel reveals OR-XOR logic. Both results suggest entanglements in some dyadic brain states during eye contact. **CONCLUSIONS**: This is the first experimental evidence that the dyadic brain entanglement states exist during eye contact, which could offer an unprecedented method to quantify human social interaction and communication. **REFERENCES:** [1] Itier, R. et al, Neuroscience and Biobehavioral Review (2009) 33, 843. [2] Schilbach, L. et al, Behavioral and Brain sciences (2013) 36, 393. [3] Wilde, M, Quantum Information Theory, (2017) Cambridge Press. [4] Lee, R. PLoS ONE, (2015) 10(4): e0121791. doi:10.1371/journal.pone.0121791

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Poster

616. Network Modeling and Application

Location: Hall A

Time: Tuesday, October 22, 2019, 1:00 PM - 5:00 PM

Program #/Poster #: 616.15/DD74

Topic: E.09. Motor Neurons and Muscle

Support: NINDS U19 EB025153
NIH DP2 NS083037
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Title: Optimal force production via flexible neural control of motor units

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Abstract: Roughly 10^2–10^3 motor units (MUs) control each muscle, providing myriad ways to generate a particular force profile. Nevertheless, MUs are believed to obey an orderly recruitment process, the 'size principle' (SP), wherein small MUs are recruited before larger MUs. Intriguingly, several studies report deviations from the SP during dynamic movements, but whether such deviations represent instances of a broader phenomenon remains unclear. We used mathematical optimization to develop predictions regarding optimal MU recruitment strategies. We tested those predictions using a new experimental paradigm and novel spike-sorting methods. Finally, we asked whether cortical recruitment of MUs extends beyond the single degree of freedom associated with the SP.

Predictions were derived from the recruitment strategy that best matched actual force to desired force. We modeled an idealized motor pool of five MUs of varying size. As observed empirically, larger MUs had briefer twitch responses. Optimization predicted that recruitment should obey the SP for steady forces, but deviate from the SP for rapidly changing forces. Specifically, there should be preferential recruitment of larger MUs, whose briefer twitch responses are better suited for rapid force fluctuations.

We trained a monkey to generate a variety of force profiles (steps, ramps, sinusoids, and chirps) via isometric contractions of the anterior deltoid, whose activity we recorded using 8 modified percutaneous electrodes. We leveraged Bayesian nonparametrics and optimal filtering to decompose EMG into the spike times of single MUs. For steady forces, MU activity lay on a 1-dimensional nonlinear manifold (as predicted by the SP), but departed from this manifold for higher frequency (>1 Hz) forces. MU activity in both steady and dynamic regimes were consistent with our model.

Our theoretical and empirical results suggest that MU recruitment depends both on instantaneous and future force commands. The need to consider the future suggests supra-spinal structures may play a role in recruitment. To test this, we used microstimulation of sulcal motor cortex, via a 32-channel linear array, combined with simultaneous EMG recordings as described above. Microstimulation produces artificial activation under experimenter control, yielding the potential to reveal degrees of freedom that are available but rarely used, and might be difficult to otherwise observe. We found that stimulation recruited MUs in ways that often deviated from the 1-dimensional manifold observed during steady force production. Thus, MU recruitment is flexible, force-profile specific, and can be influenced by descending control.

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